24 July 2025
EMA/CHM/231085/2025
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Nurzigma

International non-proprietary name: pridopidine

Procedure No. EMEA/H/C/006261/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ADM	Antidopaminergic medication
ADR	Adverse drug reactions
(TE)AE(s)	(treatment-emergent) Adverse event(s)
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0\text{-}24\ (ss)}$	Area under the concentration-time curve from 0 to 24 hours (at steady state)
$AUC_{0\text{-}\infty\ (ss)}$	Area under the concentration-time curve from the time of dosing extrapolated to infinity (at steady state)
bid	Twice daily
BDC	Bile-duct cannulated
BDNF	Brain derived neurotrophic factor
B/P	Blood/plasma
BCRP	Breast cancer resistance protein
BUN	Blood urea nitrogen
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CAG	Cytosine-adenine-guanine (repeats)
CFB	Change from baseline
CI	Confidence interval
$C_{max\ (ss)}$	Maximum concentration (at steady state)
CGI-(C)(S)	Clinical Global Impression of (Change) (Severity)
CHMP	Committee for Medicinal Products for Human Use (EMA)
CL_{tot}	Total body clearance
CMA	Conditional marketing authorisation
CrCl	Creatinine clearance
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
C-QTc	Concentration-QTc
CSR	Clinical study report
(c)UHDRS	(Composite) Unified Huntington's Disease Rating Scale
CYP	Cytochrome P450
DDI	Drug-drug interaction
D2R	Dopamine-2 receptor
D3R	Dopamine-3 receptor
ECG	Electrocardiogram
EC_{50}	Half maximal effective concentration
EC_{90}	90% effective concentration
EMA	European Medicines Agency
EHA	European Huntington Association
EoS	End of study
ER	Endoplasmic reticulum
EU	European Union
FAS	Full analysis set
FDG	Fluorodeoxyglucose
FEED	Fertility and early embryonic development
FT	Finger tapping

Fu	Fraction unbound
GCP	Good clinical practice
GD	Gestational day
GLP	Good laboratory practice
HART	Huntington Disease ACR16 Randomized Trial (ACR16C009)
hERG	ether-a-go-go-related gene
HPLC	High performance liquid chromatography
HD	Huntington's disease
HD-QoL	Huntington's Disease health-related Quality of Life questionnaire
(m)HTT	(mutant) Huntingtin
IC_{50}	Half maximal inhibitory concentration
ICE	Intercurrent events
ICH	International Council for Harmonisation
IEA	Integrated efficacy analysis
IOI	Inter-onset interval
IP	Intraperitoneal
IS	Independence scale
IV	Intravenous
ISA	Integrated safety analysis
(L)(U)LOQ	(Lower) (Upper) limit of quantification
LS(M)	Least squares (mean)
MAA	Marketing authorisation application
MAM	Mitochondria-associated membrane
MATE(1)(2-k)	Multidrug and toxin extrusion protein (1) (2-k)
MDRD	Modification of diet in renal disease
MedDRA	Medical dictionary for Regulatory Activities
MermaiHD	Multinational European Multicenter ACR16 study in Huntington´s Disease (Study ACR16C008)
MI	Multiple imputations
(m)ITT	(modified) intent to treat
MMRM	Mixed model for repeated measures
mMS	Modified motor score
MNAR	Missing not at random
MRHD	Maximum recommended human dose
MRI	Magnetic resonance imaging
MS/MS	Tandem mass spectrometry
NOAEL	No-observed-adverse-effect level
OAT(1)(3)	Organic anion transporter (1) (3)
OATP(1B1)(1B3)(1A2)(2B1)	Organic anion transporting polypeptide (1B1) (1B3) (1A2) (2B1)
OCT(1)(2)	Organic cation transporter (1) (2)
OLE	Open-label extension
PBT	Persistent, bioaccumulative, and toxic
PD	Pharmacodynamics
PET	Positron emission tomography
P-gp	P-glycoprotein
PK	Pharmacokinetics

PMM	Pattern-mixture model
PO	*Per os*, oral(ly)
PP	Per protocol
PPB	Plasma protein binding
PopPK	Population pharmacokinetics
PRIDE-HD	PRIdopidine Dose Evaluation in Huntington's Disease (Study TV7820-CNS-20002)
PROOF-HD	Pridopidine Outcome On Function in Huntington Disease (Study PL101-HD301)
PSW	Propensity score weighing
PT	Preferred term
Q-motor	Quantitative motor
qd	Once daily
QTc	Corrected QT interval
QTcF	QT interval corrected by Fridericia´s formula
S1R	Sigma-1 receptor
rCMRGlc	Regional Cerebral Metabolic Rate of Glucose Consumption
RMP	Risk management plan
(R)SE	(Residual) standard error
RO	Receptor occupancy
ROI	Regions of interest
RP-HPLC	Reversed-phase high performance liquid chromatographic
SAE	Serious adverse event
SAP	Statistical analysis plan
SAWP	Scientific Advice Working Party
SDMT	Symbol digit modalities test
SC	Subcutaneous(ly)
SD	Standard deviation
SmPC	Summary of products characteristics
SPM	Statistical parametric mapping
SOC	System organ class
SWR	Stroop word reading
TEAE	Treatment emergent adverse event
TFC	Total functional capacity
TK	Toxicokinetics
t_{max}	Time of the maximum concentration
TMS	Total motor score
T/p	Tissue to plasma
$t_{½}$	Terminal elimination half-life
TMS	Total motor score
VMAT2	Vesicular monoamine transporter 2
V_{ss}	Volume of distribution at steady state
WoE	Weight of evidence

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Prilenia Therapeutics B.V. submitted on 29 July 2024 an application for marketing authorisation to the European Medicines Agency (EMA) for Nurzigma, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 15 December 2022

Nurzigma, was designated as an orphan medicinal product EU/3/05/288 on 20 June 2005 in the following condition: Treatment of Huntington's disease.

The applicant applied for the following indication

> Nurzigma is indicated in adults for the treatment of Huntington´s disease (HD).

During the procedure, the applicant updated the indication as per below

> Nurzigma is indicated in adults for the treatment of early Huntington´s disease (HD) in adults who are not treated with antidopaminergic medicinal products (ADMs; see section 4.4. and 5.1).

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0496/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0496/2023 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

1.5. Applicant's request(s) for consideration

1.5.1. Conditional marketing authorisation, accelerated assessment

The applicant requested during the procedure consideration of its application for a conditional marketing authorisation (CMA) in accordance with Article 14-a of the above-mentioned Regulation.

The applicant requested accelerated assessment in accordance with Article 14 (9) of Regulation (EC) No 726/2004.

1.5.2. New active substance status

The applicant requested the active substance pridopidine contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.6. Protocol assistance

The applicant received the following protocol assistance on the development relevant for the indication subject to the present application:

Date	**Reference**
21 February 2006	EMEA/H/SA/701/1/2006/PA/III
15 November 2007	EMEA/H/SA/701/1/FU/1/2007/PA/II
19 May 2011	EMEA/H/SA/701/1/FU/2/2011/PA/SME/II
19 November 2015	EMEA/H/SA/701/2/2015/PA/I
19 November 2015	EMA/CHMP/SAWP/737068/2015
12 October 2017	EMA/CHMP/SAWP/645332/2017
23 February 2023	EMA/SA/0000105622

The protocol assistance pertained to the following *quality, non-clinical, and clinical* aspects:

Carcinogenicity programme; Proposed ERA study.

Design of a proposed phase 3 study to support benefit-risk assessment and in particular on: population (including inclusion and exclusion criteria), primary and secondary endpoints (including motor symptoms, Unified Huntington's Disease Rating Scale (UHDRS) motor score, cognitive function assessment, affective symptoms assessment, functional assessment and safety assessment), dose and dosing schedule, treatment duration, safety assessment, sample size, stratification criteria, statistical considerations, use of co-medications and post-authorisation follow-up; approach to establish bioequivalence between tablets strengths; clinical pharmacology programme; pharmacokinetics programme and in particular on: impaired hepatic function, impaired renal function, potential drug-drug interactions and food effect; use of the modified motor score (mMS) as primary endpoint; Design of a confirmatory phase 3 study (ACR16C019) to support benefit-risk assessment and in particular on: primary endpoint and magnitude of effect, patient population and study duration; overall clinical development plan and safety database to support a conditional marketing authorisation; design of a proposed phase 3 study (PRIDE-HD) to support benefit-risk assessment based on this single pivotal

trial, and in particular on: population, primary and secondary endpoints, cardiac (QT effect) evaluation, sample size treatment duration, statistical considerations (including method of analysis and sensitivity analyses); adequacy of the clinical development program; clinical programme; Population to be used for the primary efficacy analysis; mixed model repeated measures (MMRM) approach.

1.7. Steps taken for the assessment of the product

The application was received by the EMA on	29 July 2024
The procedure started on	15 August 2024
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 November 2024
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	4 November 2024
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	18 November 2024
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	12 December 2024
The applicant submitted the responses to the CHMP consolidated List of Questions on	21 March 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	30 April 2025
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	08 May 2025
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	22 May 2025
The applicant submitted the responses to the CHMP List of Outstanding Issues on	24 June 2025
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	13 July 2025
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	22 July 2025
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a marketing authorisation to Nurzigma on	24 July 2025
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	24 July 2025

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

2.1.2. Epidemiology

Huntington's disease (HD) is a rare, genetic, chronic progressive and fatal neurodegenerative disorder.

The estimated prevalence of HD in North-Western Europe, North America, and Australia ranges from 5.96 to 13.7 cases per 100,000 people (Baig et al 2016; Fisher et al 2014). HD is more common in people with European ancestry. In the EU, ~ 40,000 people live with HD (Medina et al 2022).

HD leads to gradual impairment of a function and introduction of a variety of psychiatric symptoms including depression and aggressiveness. This results in heavy reliance and eventually total dependence on care. As such caregiver burden is widely recognised in HD. (Youssov et al., 2022)

2.1.3. Aetiology and pathogenesis

HD has an autosomal dominant mode of inheritance. (Quinn and Schrag 1998; Walker 2007). HD results from cytosine-adenine-guanine (CAG) trinucleotide repeat expansion in the Huntington (HTT) gene, which encodes for the HTT protein. Without a curative treatment available the pathophysiology has not been fully confirmed, but is currently thought to be primarily due to toxicity of mutant HTT (mHTT).

2.1.4. Clinical presentation, and stage/prognosis

CAG repeat length is inversely correlated with disease onset. Unaffected individuals have <35 CAG repeats; HD carriers have 36+ CAG repeats, although those with 36-39 repeats may or may not eventually develop HD. Patients with 36-55 CAG repeats usually have adult-onset HD where patients with >60 CAG repeats often have juvenile-onset HD by showing symptoms before the age of 20. (Medina et al., 2020; Serranilla et al., 2022)

HD is characterised by variable disease manifestation but includes movement-, psychiatric, and cognitive problems that worsen over-time. Chorea is a key sign of HD; others often reported are abnormal eye movements, irritability, depression and suicidal behaviour (McAllister et all., 2021). Following onset, symptoms steadily worsen over the ensuing 15 to 20 years, leading to an overall decline in ability to function and perform activities of daily living, ultimately leading to a state of immobility, severe cognitive and global functional impairment and death (Ross et al 2014; Ross and Tabrizi 2011).

In this marketing authorisation application (MAA), for HD disease classification, the Shoulson and Fahn system was used (i.e., based on total functional capacity (TFC) scores) (Shoulson and Fahn, 1979). Scores range from 0 to 13, with 13 being unaffected, and score of 0 as complete incapacity. The TFC assesses five functional domains, i.e., occupation (0-3 pts.), ability to take care of finances (0-3 pts.), perform domestic chores (0-2 pts.), activities of daily living (0-3 pts.), and required care level (0-2 pts). Score for TFC stage 1: 11–13, stage 2: 7–10, stage 3: 3–6, stage 4: 1–2, and stage 5: 0.

2.1.5. Management

Currently only symptomatic treatments are approved. In the EU, tetrabenazine and haloperidol are approved for symptomatic management of chorea in HD. In addition, a variety of therapies are used (on- and off-label) to treat motor, cognitive, behavioural and psychiatric symptoms.

Pharmacological therapies used include antipsychotics as haloperidol, tricyclic antidepressants as clomipramine, and selective serotonin reuptake inhibitors as sertraline and citalopram. Often also a speech therapist, dietician, physiotherapist and/or occupational therapist aids in symptom management.

There is no approved therapy that modifies HD disease progression, indicating an unmet medical need.

2.2. About the product

Pridopidine is a selective sigma-1 receptor (S1R) agonist. Its mode of action in HD specifically is not fully elucidated; pridopidine is proposed to have neuroprotective effects through S1R, such as protecting neurons from mHTT (Eddings et al., 2019).

The initially proposed indication was

> Nurzigma is indicated in adults for the treatment of Huntington´s disease (HD).

The latest proposed indication is

> Nurzigma is indicated in adults for the treatment of early Huntington´s disease (HD) in adults who are not treated with antidopaminergic medicinal products (ADMs; see section 4.4. and 5.1).

Proposed treatment regimen is 45 mg twice daily, following 45 mg once daily for two weeks (as titration step).

2.3. Type of application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on uncertainties and limitations regarding efficacy data (i.e., efficacy only in a subgroup that appeared to have been defined *post hoc*, concerns on extrapolation towards a broad population, concerns on maintenance of effect).

The applicant requested during the procedure consideration of its application for a CMA in accordance with Article 14-a of the above-mentioned Regulation, based on the following criteria:

The benefit-risk balance is positive. The applicant claimed that efficacy has been demonstrated in the population of adults with early HD who are not treated with ADMs prior enrolment and while on trial (off-ADMs group). The applicant claimed that results across various clinical outcome measures that cover different disease domains were numerically in favour in the pridopidine-treated off-ADM group compared to off-ADM placebo group in the pivotal trial PROOF-HD (consistency claim). Additionally, the applicant claimed that these favourable effects were maintained during the open label extension (OLE) phase (maintenance claim). Furthermore, the applicant claimed that safety profile is acceptable and manageable. Thus, the applicant considers that the benefit-risk balance is positive for adults with early HD who are not treated with ADMs.

It is likely that the applicant will be able to provide comprehensive data. The applicant is proposing a randomised, double-blind, placebo-controlled confirmatory study followed by an OLE, for a total duration of 3 years. The first period will be a 6-month placebo-controlled study in which patients will

be off-ADMs. The primary objective of the confirmatory study is to confirm meaningful and lasting benefits of pridopidine on overall clinical progression (composite UHDRS (cUHDRS)) over time in patients with HD. The applicant is confident that this study design will allow for an adequate treatment effect size for cUHDRS at 6 months as well as provide supportive data for its individual components and finger tapping Inter-onset interval (FT-IOI) in the off-ADM population. The second period will be a 2.5-year OLE phase, with in-clinic assessments performed every 6 months, during which endpoints will be evaluated in comparison to propensity score-matched external natural history cohorts (ENROLL-HD and TRACKHD). The OLE part of the study will provide further longitudinal data to support persistence of efficacy over time. Based on this, the applicant considers this criterion to be fulfilled.

Unmet medical needs will be addressed. The applicant claimed that the treatment for HD is currently only symptomatic to treat behavioural and movement disorders and that there are no approved effective therapies that can alter disease progression. In the target population of adult patients with early HD who are not taking ADMs, the applicant claimed that efficacy has been demonstrated globally in different domains including global progression. Thus, the applicant considers this criterion to be fulfilled.

The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. In the view of the high unmet medical need in the condition and based on the favourable effects in the target population, the overall acceptable and manageable safety profile and a convenient oral administration twice a day (bid), the applicant considers this criterion to be fulfilled.

2.4. Quality aspects

2.4.1. Introduction

The finished product is presented as hard capsules containing pridopidine hydrochloride, corresponding to 45 mg pridopidine free base.

Other ingredients are:

Capsule content: microcrystalline cellulose, colloidal anhydrous silica, magnesium stearate (E470b);

Capsule shell: gelatine, titanium dioxide (E171), red iron oxide (E172), yellow iron dioxide (E172);

Printing ink: shellac (E904), black iron oxide (E172), propylene glycol (E1520), concentrated ammonium solution (E527) or potassium hydroxide (E525) for pH adjustment.

The product is available in a blister sealed with coated lidding foil.

2.4.2. Active Substance

2.4.2.1. General information

The chemical name of pridopidine hydrochloride is 4-[3-(methylsulfonyl)phenyl]-1-propylpiperidine hydrochloride corresponding to the molecular formula C15H23NO2S·HCl. It has a relative molecular mass of 317.87 and the following structure:

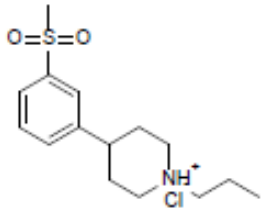


Figure 1: active substance structure

The chemical structure of pridopidine hydrochloride was elucidated by a combination of elemental analysis, UV, IR, 1H and 13C NMR and mass spectrometry (MS). The solid-state properties of the active substance were measured by differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), thermogravimetric analysis (TGA) and gravimetric vapor sorption (GVS).

The active substance is a white to almost white powder. It is non-hygroscopic and photostable.

Pridopidine has a non-chiral molecular structure.

Polymorphism has been observed for the active substance: pridopidine hydrochloride form I and form II. The two forms have been properly characterised and studied, and it was found that form I is the most thermodynamically stable form under ambient conditions. The applicant demonstrated that the active substance is consistently manufactured to Form I, which is supported by active substance batch data. Furthermore, an identification test of the polymorph by XRPD is included in the active substance specification for pridopidine hydrochloride.

2.4.2.2. Manufacture, characterisation and process controls

The active substance is manufactured at one site for which satisfactory information with respect to GMP standards have been provided.

Pridopidine hydrochloride is synthesised using commercially available and well-defined starting materials with acceptable specifications.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances.

Potential and actual impurities were well discussed with regards to their origin and characterised.

The commercial manufacturing process for the active substance was developed in parallel with the clinical development program. The quality of the active substance used in the various phases of the development is considered to be comparable with that produced by the proposed commercial process.

The active substance is packaged in double low-density polyethylene (LDPE) bags within a high-density polyethylene (HDPE) drum. The LDPE bags material complies with Commission Regulation (EU) 10/2011, as amended.

2.4.2.3. Specification

The active substance specification includes tests for description (visual), identification (IR, HPLC, XRPD), identification of chloride (Ph. Eur.), water content (Ph. Eur.), sulfated ash (Ph. Eur.), elemental

impurity (ICP-SFMS, Ph. Eur.), formic acid (IC), related substances (HPLC), residual solvents (HS-GC), benzene (HS-GC), assay (HPLC), microbial quality (Ph. Eur.) and particle size (Ph. Eur.).

The active substance specification parameters and limits are in line with relevant guidelines and are acceptable.

During the procedure, a second identity test (by HPLC) has been included, as requested by CHMP. In addition, it was requested to demonstrate that the polymorphic identity test (by XRPD) is sufficiently specific. This was properly addressed, and the method was considered sufficiently specific. Following the request from the CHMP the applicant committed to set acceptance criteria for the characteristic 2θ peaks; this issue should be addressed by the applicant in case of a future MA application. Limits for solvents, elemental and genotoxic impurities have been set according to the relevant ICH guidelines. In response to a major objection during the procedure a test for benzene, in line with ICH Q3C was included. Impurities present at higher than the ICH Q3A guidelines were qualified by toxicological and clinical studies and appropriate specifications have been set.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the active substance and related substances reference standards has been presented.

Batch analysis data from multiple batches from development to proposed commercial scale) of the active substance are provided. The results are within the specifications and consistent from batch to batch.

2.4.2.4. Stability

Stability data from at least three commercial scale batches of active substance from the proposed manufacturer stored in the intended commercial package under long term conditions (25 ºC / 60% RH), under intermediate conditions (30 ºC / 65% RH) and under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided.

The following parameters were tested: description, identification by XRPD, assay, related substances, water content and microbial enumeration. The analytical methods used were the same as for release and were stability indicating.

All tested parameters were within the specifications, with no significant trend. In addition, stability data demonstrated that the polymorphic form does not change during storage.

Photostability testing following the ICH guideline Q1B was performed. Results on stress conditions under acidic, basic, oxidative, light exposure and heat conditions were also provided.

It was demonstrated that the active substance is photostable, and it was therefore agreed that no special storage conditions are required.

The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period. No special storage conditions are required.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is presented as hard capsules containing pridopidine hydrochloride, corresponding to 45 mg pridopidine free base together with the standard excipients silicified microcrystalline cellulose and magnesium stearate. The hard capsules have the following appearance: size 2 hard gelatine capsules, approximately 18 mm in length, with a coloured opaque cap imprinted with black ink and a white opaque body imprinted with black ink.

All excipients are well known pharmaceutical ingredients, and their quality is compliant with Ph. Eur. standards, except certain excipients used in inks, which are either compliant with EU Regulation 231/2012, or comply with US National Formulary. There are no novel excipients used in the finished product formulation. The list of excipients was provided in the dossier and in section 2.4.3.1. of this report.

A risk evaluation of the silicified microcrystalline cellulose co-processed excipient has been provided in line with the *EMA document Questions and Answers regarding co-processed excipients used in solid oral dosage forms (EMA/CHMP/CVMP/QWP/422493/2024).*

Two excipients are of animal origin: gelatine (including bovine sourced), used for the hard capsules shell, and shellac (from insects), used in the printing ink. TSE/BSE safety certificates have been provided.

Pharmaceutical development

The aim of the pharmaceutical development was to develop an immediate release hard gelatine capsule, that meets the relevant quality standards, and is packaged in a suitable container to allow achievement of the targeted shelf life. The quality target product profile (QTPP) and critical quality attributes (CQAs) were defined in the dossier.

Pridopidine hydrochloride exists in one stable polymorphic form, form I, which is used in the finished product. The applicant sufficiently demonstrated that the manufacturing process does not affect the polymorphic form, PSD and morphology of the active substance.

The formulation development studies have been described in detail. The initial formulation used in early clinical studies consisted of a blend of the active substance with microcrystalline cellulose that used a manual mixing and encapsulation process for a range of dose strengths. As the product progressed into pivotal clinical studies, the formulation was modified to support the manufacture of larger batch sizes. For the final proposed commercial formulation, the target dose of 45 mg pridopidine was selected, and an imprinted, dual-coloured capsule shell was implemented.

The formulation changes during development did not impact the dissolution profile of the finished product, which was demonstrated by the provided data. The clinical formulation was found to be equivalent to the commercial formulation based on data generated in accordance with ICH M13A. A bioequivalence study has not been performed, which was found acceptable since in-vitro bioequivalence was demonstrated. The proposed dissolution method is in line with the Ph. Eur. 2.9.3. The discriminatory power of the dissolution method has been demonstrated.

Manufacturing process development

The manufacturing process development was aimed at: the improvement of the blending properties of the bulk product, the scaling up of the batch size, the use of an automatic encapsulation system and

the optimisation of manufacturing parameters. The information provided was considered adequate and properly justified.

The primary packaging is a blister sealed with coated lidding foil. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

2.4.3.2. Manufacture of the product and process controls

The finished product is manufactured at one manufacturing site. Primary packaging is performed at a separate manufacturing site. Satisfactory information with respect to GMP documentation has been provided.

The manufacturing process consists of the following main steps: mixing of the active substance with excipients and blend formation, encapsulation of the blend in hard gelatine capsules, transfer of the bulk and primary packaging.

Upon request from CHMP, the applicant defined a holding time for the bulk capsules, which was found acceptable as supported by stability data. In addition, the applicant committed to further investigate whether the proposed bulk holding time can be shortened; this issue should be addressed by the applicant in case of a future MA application

The process is considered to be a standard manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. Process validation will be performed after approval, which is acceptable as the process is standard. The provided validation scheme is considered acceptable. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

The identified CPPs have been mentioned in module 3.2.P.3.3 and the target/NOR and Proven acceptable ranges (PAR) values have been added for all process parameters. The available development data, the proposed control strategy and batch analysis data from commercial scale batches fully support the proposed PARs.

2.4.3.3. Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form: description (visual), identification (HPLC, UV), water content (Ph. Eur.), uniformity of dosage units by content uniformity (Ph. Eur. and in-house), dissolution (Ph. Eur. and in-house), microbiological quality (Ph. Eur.), assay (HPLC), related substances (HPLC).

The release and shelf-life specifications for the control of the finished product have been adequately justified and are found acceptable.

The initially proposed specification acceptance criteria for dissolution of was not found acceptable and a MO was raised. During the procedure, in response to the MO, the dissolution limit was tightened, which is acceptable as it is in line with the dissolution of relevant clinical batches.

As requested by CHMP the initially proposed limits for total related impurities at release and shelf life have been tightened in line with batch data.

A justification for not including a test for polymorphism and residual solvents in the specification of the finished product has been provided and found acceptable.

The proposed skip testing for the microbiological quality test and its frequency have been adequately justified.

The potential presence of elemental impurities in the finished product has been assessed following a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Upon request, the elemental impurities risk assessment has been completed with further information on those elements which the applicants declare as intentionally added during the synthesis of the active substance. The additional information provided was found acceptable. In addition, further information has been provided regarding the lack of risk of presence of elemental impurities in the excipients used in the formulation of the finished product. Based on the risk assessment it can be concluded that it is not necessary to include any elemental impurity controls.

A risk assessment concerning the potential presence of nitrosamine impurities in the finished product has been performed as requested considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). During the procedure a MO was raised with respect to the risk of nitrosamine formation during the manufacturing process. Also, additional information has been requested in relation to the risk of nitrosamines formation linked to finished product excipients. Based on the information provided in the applicant's response to the MO, it is accepted that there is no risk of nitrosamine impurities in the active substance or the related finished product. Therefore, no specific control measures are deemed necessary.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards of the active substance and related substances have been presented.

Batch analysis results are provided for at least three commercial scale batches of the finished product confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

2.4.3.4. Stability of the product

Stability data from at least three pilot scale batches of finished product stored under long term conditions (25 ºC / 60% RH) and under intermediate conditions (30 ºC / 65% RH), and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The initially proposed shelf-life was not found acceptable due to insufficient stability data and MO has been raised. Additional data was requested to allow extrapolation of the shelf-life. The supportive data which were initially provided were not considered representative of the product proposed for marketing, as the product was presented in a different packaging. Additional data from representative batches was therefore requested. In response to the MO, the applicant provided sufficient data, as per above time and storage conditions, from batches of medicinal product which are identical of those proposed for marketing and were packed in the primary packaging proposed for marketing, thus MO was resolved.

Additional supportive stability data has been provided for one representative commercial scale batch used in clinical studies stored under long term conditions and intermediate conditions and under accelerated conditions.

Samples were tested for description, assay, related substances, dissolution, water content and microbial quality. The analytical procedures used are stability indicating.

All tested parameters were found to be within the proposed specifications. No trends were observed under long term or intermediate storage conditions. Under accelerated storage conditions, an increase in water content was observed, but it was within the specification limits.

MO was also raised to request the applicant to demonstrate compliance with the new specification limit for dissolution requested by CHMP (see product specification section above) also at shelf life. Compliance was demonstrated for the batches provided under all three stability conditions.

In addition, one commercial scale batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. The results showed that the finished product is not sensitive to light even when exposed to light outside the blister.

Based on available stability data, the proposed shelf-life with no special storage condition is also acceptable.

Bulk stability data have also been provided for the product packaged as bulk. The proposed holding time was considered justified and was accepted.

2.4.3.5. Adventitious agents

Gelatine obtained from sources including bovine, is used in the product. Valid TSE CEP from the suppliers of the gelatine used in the manufacture of the finished product is provided.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner.

During the assessment there were a number of quality MOs raised. These concerned the control of benzene in the active substance specification, the finished product release and shelf-life specification limits for dissolution, the evaluation of potential nitrosamine impurities in the active substance and finished product, and the initial proposal for the finished product shelf life. To resolve these MOs, the applicant added a benzene control test to the active substance specification, provided further information concerning the dissolution method and tightened the finished product dissolution release and specification limits, provided further information on potential nitrosamine impurities with a revised risk assessment, and provided further evidence with respect to compliance with the updated dissolution specification limits for stability batches and additional stability data supporting the finished product shelf life.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

At the time of the CHMP opinion, there were a number of minor unresolved quality issues having no impact on the Benefit/Risk ratio of the product, pertaining to the active substance specification (polymorphic identity) and holding time for bulk capsules.

Product information (PI)

At the time of CHMP opinion, there was a remaining concern on the proposed PI, specifically the proposed text in section 4.2 regarding potential administration with other substances. In case patients have difficulty using pridopidine hard capsules (e.g., due to dysphagia) the applicant proposes that pridopidine hard capsules ‘should be ‘swallowed whole with water or swallowed whole with substances of other consistencies as appropriate.’ However, the applicant should provide further justification that

the administration with substances of other consistencies (e.g. apple sauce) would not impact the quality of the finished product before the text would have been acceptable in the PI. In addition, should the applicant propose manipulation of the capsule to ease administration, then appropriate stability should be demonstrated. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

2.4.5. Recommendation(s) for future quality development

Not applicable.

2.5. Non-clinical aspects

2.5.1. Introduction

Pridopidine is a small molecule intended for the treatment of HD with a novel mechanism of action.

Pridopidine is a potent and a selective S1R agonist. Currently there are no approved selective S1R agonists. The clinical route of administration is the oral route. Pridopidine, as a 45 mg capsule, will be taken by patients. The strength refers to the free base rather than the pridopidine hydrochloride salt.

The S1R is an endoplasmic reticulum (ER) protein located mainly at the mitochondria-associated membrane (MAM). Activation of the S1R by pridopidine enhances protective pathways essential for neuronal cell health and survival. Positron emission tomography (PET) imaging studies in human brain show that at the clinically relevant dose of 45 mg bid, pridopidine has a selective and robust occupancy of the S1R (>90%) with negligible occupancy of the dopamine D2/D3 receptors (~3%).

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

In vitro

In vitro binding studies showed that pridopidine acts as an agonist at the human S1R (half maximal effective concentration (IC_{50}) 0.14 µM, Ki 0.057 µM). Main metabolite (TV45065) exhibited lower binding affinity for the human S1R (IC_{50} 5.80 µM, Ki=2.44 µM) compared to pridopidine. Available literature provided by the applicant indicates that pridopidine has a binding affinity for rat S1R (Ki= 0.069 µM) in a similar range as reported for humans in the initial dossier (Ki=0.057 µM). A newly submitted report on a competitive radioligand binding assay using two high-affinity radiolabelled S1R ligands ([3H]SA4503 and [3H]fluspidine) further indicates comparable S1R binding affinity across human, mouse and rat species. No binding affinity for monkey and dog S1R were presented as these assays were not commercially available. However, the applicant performed amino acid sequence alignment of the S1R orthologs in species used in toxicology studies. The protein sequences of S1R share high level of alignments across these species. The highest identity can be seen between the human and monkey sequences (100%). The human sequence also shares a high level of identity with dog (97.76%), rabbit (96.41%), rat (93.72%) and mouse (90.13%). The regions important for ligand binding were 100%

identical across species. Overall, sufficient evidence was provided that suggests similar affinity of pridopidine for the S1R across the used toxicology test species.

The applicant states that the importance of the S1R in HD is demonstrated by studies in which S1R deletion in HD cells causes a significant increase in the levels of mHTT aggregates and subsequent toxicity, while overexpression of the S1R reduces mHTT aggregates. As a protein primarily located at the MAM, the S1R functions as a molecular chaperone in the ER, facilitating the proper folding of newly synthesised proteins and preventing the accumulation of misfolded proteins. In HD, MAM function is disrupted, resulting in aberrant Ca2+ homeostasis, impaired mitochondrial function and enhanced ER stress, leading to neurodegeneration. The applicant provided a comprehensive package of *in vitro* experiments, mainly based on literature, investigating the effect of pridopidine on neuroprotection via downstream effects following activation of the S1R.

In vitro data suggest that pridopidine restores the MAM integrity in HD YAC128 mouse striatal neurons and restored ER Ca2+ levels, while in neurons lacking the S1R, pridopidine had no effect on ER Ca2+ levels. Pridopidine significantly reduced ER stress, as demonstrated by reduced expression of H2a-green fluorescent protein in Htt96Q transfected murine striatal cells, and by a S1R-dependent reduction in p-eIF2α and the late UPR markers CHOP and GADD34 in Htt96Q transfected HEK293 cells. In human HD lymphoblasts, pre-treatment with pridopidine rescued the mitochondrial membrane potential in the presence of hydrogen peroxide as oxidative insult. This effect was abolished when the S1R where knocked down in these cells. Also in YAC128 neurons, pre-treatment with pridopidine improved the mitochondrial membrane potential. In both H2O2 challenged YAC128 mouse striatal neurons and human neural stem cells differentiated from patient-derived induced pluripotent stem cells, pridopidine restored mitochondrial respiration, while adenosine triphosphate production was only significantly improved in YAC128 neurons. In addition, pridopidine restored levels of reactive oxygen species.

In multiple neurodegenerative diseases, including HD, autophagy is disrupted, resulting in toxic intracellular protein aggregation leading to neuronal dysfunction and death. The nucleocytoplasmic transport of the transcription factor EB from the cytosol into the nucleus via the nucleopore complex is important during autophagy. In the NCS-34 motor neuron-like cell line overexpressing plasmids encoding GFP fused to the HRE (G4C2)31, pridopidine or the overexpression of S1R rescued the reduced levels of nuclear transport of the transcription factor EB and increased autophagy.

In HD, diminished brain derived neurotrophic factor (BDNF) transport leads to reduced BDNF delivery to the striatum, contributing to striatal and cortical neuronal death. In rat B104 rat neuroblastoma cells, pridopidine significantly enhances BDNF secretion, an effect that was eliminated in the presence of a S1R antagonist. In HD cortical neurons seeded on a microfluidic device, pridopidine improved axonal BDNF transport.

Neuropathological features of HD also include disrupted stability of synaptic spines resulting in impaired corticostriatal synaptic function and connectivity, eventually leading to degeneration of striatal neurons. In YAC128 neurons, pridopidine restored spine density in a S1R dependent manner and rescued synaptic plasticity.

Finally, in both mice and human cell models expressing mHTT, pridopidine prevented cell death, which was shown to be S1R dependent.

Literature indicates that S1R agonists activity appeared characterised by the biphasic dose response curve. In general, in the presented non-clinical *in vitro* studies, optimal pridopidine concentrations were 100 nM to 5 µM while lower (1 and 10 nM) and higher (10 and 100 µM) concentrations were less efficacious and is therefore mechanistically in line with other S1R agonists. These concentrations (28 – 1407 ng/ml) will likely be reached in the central nervous system (CNS) at clinically relevant exposures, considering the clinical maximum concentration (C_{max}) at the MRHD (618 ng/ml) and the comparable

fractions in brain and plasma. More comments on the translatability of the bell-shaped response curve to pridopidine efficacy are made in section 3.3 of the clinical AR.

In vivo

Pridopidine *in vivo* pharmacodynamic (PD) studies included a PET imaging target engagement/receptor occupancy study in Wister rats, the evaluation of motor, cognitive, and behavioural outcomes in YAC128 HD mice and the potential effects on neuronal protection and motor performance in R6/2 HD mice. The R6/2 HD mouse model expresses exon 1 of the human HTT gene with ~150 CAG repeats, exhibits rapid disease progression, and was discussed to be useful for studying early-stage intervention and therapeutic effects. The YAC128 model carries the full-length human huntingtin gene with ~ 128 CAG repeats, exhibits a more protracted disease course, making it suitable for exploring long-term treatment strategies and investigating pathogenic mechanisms. The brains of both animal models reveal shrinkage/atrophy of cortical and striatal regions, similar as in human patients.

Notably, pridopidine was previously mainly known as dopamine stabiliser and by acting as dopamine D2 receptor (D2R) antagonist or weak partial agonist, it can exhibit inhibitory or stimulatory effects on dopamine-dependent behaviour depending on the prevailing dopamine tone. Later, pridopidine appeared to display nanomolar affinity for the S1R (Sahlholm et al. 2013). Therefore, the occupancies of both S1R and D2R by pridopidine in the living rat brain were examined using PET imaging in rats. Pridopidine selectively occupied the S1R receptor occupancy (RO) at doses of 3 and 15 mg/kg, while D2/D3 RO was observed at 60 mg/kg. Thus, it was indicated that significant D2R occupancy was only observed at a dose 20-fold higher than was required for S1R occupancy.

In the publication on YAC128 HD mice, pridopidine (at 10 and 30 mg/kg) was administered prior to (early treatment) the onset of disease-related phenotypes and in advanced disease stages (late treatment), and its efficacy was assessed by behavioural and neuropathological analyses. In the early treated mice, pridopidine improved motor learning at 2 months of age and motor coordination at 2 until 10 months of age, based on the latency to fall in the rotarod tests (fixed speed for motor learning, accelerating speed for motor performance). In addition, improvements were seen in the climbing test at 2 months of age. No effects were seen on spontaneous activity tested at 12 months. At the later tested time points, the effects of pridopidine on climbing and motor coordination decreased. YAC128 HD mice treated with pridopidine spent more time in the centre of the arena in the open field as well as in the open arms of the elevated plus maze compared with vehicle-treated YAC128 HD mice, indicative of a reduced anxiety-like phenotype. In addition, both doses of pridopidine reduced depressive-like behaviour in the forced swim test. In general, the effects of early pridopidine treatment on motor function and anxiety were seen at the high dose of 30 mg/kg. In the late treatment cohort, pridopidine did not improve motor function, had no effect on anxiety-like phenotypes, but only improved depressive-like phenotypes. Despite improved HD symptoms, no effect on striatal or corpus callosal atrophy was observed. Early pridopidine treatment did reverse striatal transcriptional deficits, related to synaptic changes and the cholinergic system.

In the R6/2 transgenic HD mouse model (Squitieri et al, 2015), pridopidine (5 mg/kg, intraperitoneal (IP)) administration significantly increased survival in pre-symptomatic mice. Pridopidine initially improved motor function for about 4 weeks, after which mice consistently showed a slight worsening in performing the motor function tasks. Since the study ended after 11 weeks, it is not known whether the motor capacity would return to levels of vehicle treated R6/2 mice. In symptomatic R6/2 mice, responsivity to pridopidine was transient and an additional dose was necessary to keep a sustained improvement in motor function over 11 weeks of treatment. On a molecular level, pridopidine at a dose adjustment to 6 mg/kg, enhanced the expression of both BDNF and cAMP-regulated neuronal phosphoprotein (DARPP32) in the striatum of R6/2 mice. In addition, pridopidine significantly reduces the size of mHTT aggregates in both the striatum of R6/2 mice as in HD striatal-derived cell lines.

Antagonism of S1R reduced pridopidine-mediated anti-apoptotic effects as well as the pridopidine-induced reduction in the size of mHTT aggregates in HD cells, further supporting that the mechanism of action of pridopidine is mediated through S1R.

2.5.2.2. Secondary pharmacodynamic studies

The selectivity of pridopidine was evaluated in several binding screens of receptors, ion channels, and enzymes.

After the highest affinity for S1R (Ki 0.057 µM), pridopidine showed low affinity for the human adrenergic α2C (Ki 1.58 µM), dopamine D3 (Ki 1.63 µM), serotonin (5-Hydroxytryptamine) 5-HT1A (Ki 3.63 µM) and dopamine D2L (Ki 29.5 µM).

In an additional panel of various CNS targets, pridopidine showed weak activities as an antagonist at the dopamine D2L receptors (half maximal effective concentration (EC_{50}) =77.5 µM) and D2S (EC_{50} =94.5 µM). No binding affinity or enzymatic activity observed for additional ~30 CNS targets tested.

Pridopidine has low affinity for the human S2R (Ki = 9.0 µM or 5.45 µM (study DPR-2017-097 and AB32866, respectively)), weak activity on the muscarinic M4 receptor (EC_{50} = 14 µM) and no activity on histone deacetylase 6. Pridopidine has low affinity for the rat S2R (Ki 3.32 µM). Main metabolite TV-45065 has low binding affinity for the human S1R (Ki 2.44 µM).

No meaningful binding affinity or activity to various receptors, enzymes and channels was observed. Inhibition rates of pridopidine (at 10 µM) to ~70 receptors, ion channels, transporters, and enzymes were less than 50%, including sodium, potassium and calcium channels which are of importance because S1R is expressed in the heart.

Inhibition rates of pridopidine (up to 10 µM) to ~20 receptors, ion channels, transporters, and enzymes were less than 50%, except for 51% inhibition at the human M4 receptor. However, an IC_{50} was not calculated and at 1 µM, the inhibition was less than 10%, indicating that it is not likely that pridopidine affects the M4 receptor at clinically relevant concentrations. Pridopidine caused no stimulation of adenylate cyclase.

Pridopidine (1 µM) and TV-45065 (1 µM) had no meaningful binding affinity for transporters (norepinephrine and dopamine) in rat tissues. There was no binding of metabolite TV-45065 on the D2, 5-HT1A receptors. Unfortunately, pridopidine binding was not evaluated for the rat D2/D3 receptor.

Lastly, upon request, the applicant has performed a binding screen of pridopidine hydrochloride and its major metabolite TV-45065 against a usual panel targets including most of standard investigated targets. The highest recommended concentration was appropriately assessed. Each target was only assessed in duplicate, but no high divergence occurred between tests and values for CNS-related targets were within a similar range to that identified in previous studies. The study did not highlight concern against standard non-CNS transporter, ion channels, enzymes and receptors. The study summarised concentration response curve to determine IC^{50} and Ki values for (CNS) targets identified in the former study, confirming highest activity and selectivity against S1R among CNS targets.

2.5.2.3. Safety pharmacology programme

The safety pharmacology package comprised separate good laboratory practice (GLP)-compliant cardiovascular (dogs), CNS (rats), respiratory (rats) safety studies, a combined GLP-compliant safety pharmacology study (dogs) and non-GLP cardiovascular safety (dogs and rabbits) studies. *In vitro* studies comprised a GLP-compliant hERG inhibition assay. No stand-alone studies were performed concerning renal function/urinary parameters, but these were evaluated in the general toxicity studies.

In the GLP-compliant *in vitro* human ether-a-go-go-related gene (hERG) inhibition study, significant hERG suppression was observed from 3 µM and higher in a concentration-dependent manner. The calculated IC_{50} was 12.6 µM, which is approximately 5.7-fold the clinical exposure at the MRHD (C_{max}: 2.2 µM, 618 ng/ml).

In the GLP-compliant CNS rat study, there were no effects on neurobehavioural, neurovegetative, psychotropic or neurotoxic effects as well as no effect on body temperature at pridopidine (free base) doses up to 35.4 mg/kg. At the highest dose (141.6 mg/kg) pridopidine induced a decrease in body temperature and sedative and neurovegetative effects characterised by a decrease in spontaneous locomotor activity, a passivity to finger approach and when touched on the head and an increase in incidence of ptosis. The no-observed-adverse-effect level (NOAEL) of 35.4 mg/kg corresponds to an estimated plasma C_{max} of 3093 ng/mL, which is 5-fold higher than the C_{max} in humans (618 ng/mL) at the maximum recommended human dose (MRHD). In the combined safety pharmacology dog study, pridopidine affected general behaviour from the low dose (4.4 mg/kg) onwards evidenced by tremor and twitch, salivation, oral mucosal flush and abnormal stool. At the high dose, this led to incidences of clonic and tonic convulsion and enophthalmos The applicant considers that mild to moderate effects occurred at 13.3 mg/kg. However, due to the dose-related incidence of these CNS effects it is considered that there is no NOAEL. The lowest dose corresponds to a C_{max} of 508 ng/ml, which is lower than the anticipated clinical C_{max}.

In the GLP-compliant cardiovascular safety study in dogs, there were no effects on QT interval duration at doses up to 2.2 mg/kg. From the mid dose onwards, a dose-dependent and short onset hypotension occurred, followed immediately by a transient hypertensive action and a late onset hypotension. Further, pridopidine dosed at ≥ 0.44 mg/kg had a negative chronotropic action and caused increases in pulmonary and end-diastolic arterial pressure, vasoconstriction of several arteries, prolongation of ventricular conduction duration and a modification in the T wave morphology. The low dose of 0.09 mg/kg was therefore considered the NOAEL. In the combined safety pharmacology study, the administered doses were higher and at doses of ≥ 13.3 mg/kg QTc interval prolongation was observed. At the high dose (44 mg/kg), a shortened the R-R interval, increased QRS duration and prolongated QT interval were observed. In addition, there was an increased blood pressure, heart rate and body temperature, which were considered related to the symptoms of convulsion. This suggests that the NOAEL in this study is 4.4 mg/kg, where no effects on the electrocardiogram were observed, corresponding to a C_{max} of 508 ng/ml. In the non-GLP study in Mongrel dogs, increased QTc prolongation, the major finding of this study, was observed at ≥ 3 mg/kg. At the NOAEL of 1 mg/kg, the plasma concentration was 8 µM, which is 3.6-fold above the clinical C_{max}.

In a GLP-compliant respiratory rat study, there were, apart from a transient respiratory stimulant action, no apparent effects of pridopidine up to doses of 35.4 mg/kg. At the high dose (141.6 mg/kg) there was a delayed decrease in peak inspiratory and peak expiratory flows associated with long-lasting decreases in tidal volume and minute volume, suggesting a respiratory depressant action, followed by a late onset increase in airway resistance, suggesting a bronchoconstrictor effect. Therefore, the NOAEL for respiratory effects is 35.4 mg/kg, corresponding with estimated plasma levels of is 3093 ng/mL, which is approximately 5-fold the clinical C_{max}. In contrast to the stand alone respiratory safety study, in the combined safety pharmacology study, no notable pridopidine-related effects were observed up to the highest dose of 44.3 mg/kg.

2.5.2.4. Pharmacodynamic drug interactions

No dedicated non-clinical studies on PD drug-drug interactions (DDI) were provided. Any potential interactions are covered in the clinical overview and in the product information.

2.5.3. Pharmacokinetics

2.5.3.1. Methods of analysis

Bioanalytical methods were developed to support the analyses of pridopidine and its main metabolite TV-45065 in rat, mouse, dog, rabbit and monkey plasma (heparin or EDTA). Plasma concentrations of pridopidine and TV-45065 were determined using a reversed-phase high performance liquid chromatographic (RP-HPLC) assay procedure with MS/MS detection (LC-MS/MS method) after protein precipitation or solid phase extraction for sample preparation and adding an internal standard.
The analytical method validations were performed for the same matrices at different laboratories at which alternate codes were used (for pridopidine: PL101, TV-7820, ASP2314, ACR16, FR310826; for TV-45065: ASP1904513, ACR30, FR609814;). Non-GLP as well as GLP methods were validated with respect to intra- and inter-day accuracy, precision, sensitivity, linearity, reproducibility, matrix effect and stability. Preventive measures were taken to mitigate the carryover impact for rat and dog plasma measurement.
There were no major differences between the methods and the results of the different methods appear comparable and therefore relevant for the current development. The analytical range for pridopidine and metabolite TV-45065 in the method used in the pivotal rat and dog repeated-dose toxicity studies were lower limit of quantification (LLOQ) 1 ng/mL to upper limit of quantification (ULOQ) 1000 ng/mL.

To measure pridopidine and TV-45065 in brain homogenates and plasma from mice, non-validated LC-MS/MS methods, similar to method JCL076261, were developed. The sensitivity of these methods ranged over the studies, i.e. in plasma 2-25 ng/ml up to 3000-20000 ng/mL for pridopidine and 1-5 ng/mL up to 1000-4000 ng/mL for TV-45065. In brain homogenates sensitivity ranged from 2-75 ng/mL to 3000-6000 ng/mL for pridopidine and from 1-7.5 ng/mL to 1000-6000 ng/mL for TV-45065.

The toxicokinetic evaluation of plasma from pivotal repeated-dose toxicity rat study (A86365) and dog study (A95185) does not seems to be within the reported long-term -20°C stability period. However, based on the measured exposure data it is unlikely that the lack of appropriate stability data had a relevant impact on the results.

2.5.3.2. Absorption

After a single oral dose of pridopidine (3 10, 30 mg/kg) to male Sprague Dawley rats (n=3 per time point), absorption was fast yielding a time of maximum concentration (t_{max}) at 0.5 h, whereafter it declined quickly in a bidirectional fashion with an terminal elimination half-life (t½) of 0.6 – 1.2 hrs. Over this dose range the C_{max} was dose proportional while the exposure (AUC_{∞}) was 2-fold more than dose-proportional. Upon intravenous (IV) dosing (3 mg/kg) in the same experiment, total body clearance (CL_{tot}) and volume of distribution at steady state (V_{ss}) were 3.9 L/h/kg and 3.5 L/kg, respectively. Oral bioavailability was found to be from 82% up to 183%. In addition, also the concentrations of the metabolite TV-45065 were measured, which reached a C_{max} at 0.5 – 2 hrs after dosing, declining with a t½ of 1.3 – 2 h. Metabolite-to-parent ratio (AUC) ranged from 0.38 to 0.20 (po) and was 0.24 for the IV route.

In a second single dose experiment pridopidine was administered to SD rats orally (PO), subcutaneously (SC) and IV using the same dose (15 mg/kg). Bioavailability was found to be 53%, when given orally and 56% subcutaneously. TV-45065 to parent ratio (AUC) was found to be 0.11, 0.15 and 0.23 when given IV, SC or PO, respectively.

After a single IP or SC dose of pridopidine (0.27 mg/kg) to male B6/SJL mice (n=24 per group), a similar plasma exposure of pridopidine and TV-45065 was seen. The absorption was fast yielding a

tmax at 0.25 h, whereafter it declined quickly (t½ 1.0 – 1.3 h) with remaining less than 5% of Cmax exposure at 6 hrs after dosing.

After a single oral dose of pridopidine (1, 3, 10 mg/kg) to male Beagle dogs (n=3), absorption was fast yielding a tmax at 0.7 – 0.9 h, whereafter it declined quickly in a bidirectional fashion with an t½ of 2.0 – 3.0 hrs. Exposure (Cmax and AUC∞) values increased up to 2-fold more than dose-proportionally. Upon IV administration (1 mg/kg) CLtot and Vss were found to be 1.3 L/h/kg and 4.5 L/kg, respectively. Oral bioavailability increased from 65% up to 122%.

The pharmacokinetics (PK) of [14C]-pridopidine (2.794 MBq/mg) was studied using adult male and female Beagle dogs (n=3/sex) following single PO (3 mg/kg) and IV (1 mg/kg) dosing. Oral absorption was fast yielding a tmax at 0.5 - 3 h, whereafter the radioactivity was eliminated quickly displaying an t½ of 2.7 hrs. In addition, also the concentrations of pridopidine and the metabolite TV-45065 were measured. The t½ in plasma were 1.6 and 2.9 hrs, for pridopidine and TV-45065, respectively. Oral bioavailability of pridopidine was found to be 60%.
Following IV administration, total plasma clearance of pridopidine was 1.3 L/h/kg. Volume of distribution (Vss =2.4 L/kg) was larger than plasma volume, indicating distribution into extravascular tissues.

In three multiple dose studies, the exposure of pridopidine and TV-45065 was determined in plasma and brain (homogenate) of mice. Male C57Bl/6 mice were given once-daily oral administrations of pridopidine for seven days (0.27 2.7, 26.8, 35.7 mg/kg) or for twenty-one days (26.8, 53.1 88.5 mg/kg). In addition, female FVB mice received once-daily oral or SC administrations of pridopidine (26.8 mg/kg) for seven days. Following 7 or 21 days of dosing, a similar plasma and brain PK profile was seen for SC or PO administration to mice. Oral absorption of pridopidine to plasma and brain was fast, yielding tmax at 0.25 h, followed by a fast decline (t½ 1-2 h). Exposure of pridopidine in brain was higher but paralleled that of plasma and, generally, increased dose proportional. Pridopidine's brain-to-plasma exposure ratios were about 2 to 3.5. Plasma TV-45065 levels parallelled pridopidine exposure having a metabolite-to-parent ratio of 0.4 – 1. TV-45065 was detected in mouse brain around Cmax but at a very low level, having a brain-to-plasma Cmax ratio <0.07.

Multiple dose Toxicokinetics (TK) in rats and dogs was assessed in the repeat-dose toxicity studies up to 26 weeks and 52 weeks of daily oral dosing, respectively. Exposures generally increased proportionally or slightly greater than proportionally with dose. Accumulation upon multiple dosing in the rat was up to 2.7-and 4.4-fold after 13 or 26 weeks of dosing, respectively, while in the dog it was generally less than 2-fold after 13, 26 or 52 weeks. No marked sex difference in exposure was noted in either rat or dog.

2.5.3.3. Distribution

The blood/plasma (B/P) ratio was only studied in vivo, using the male Sprague Dawley rat after 14C-pridopidine administration 3 mg/kg (5.73 MBq/kg), and found to be 1.2, 1.1 and 0.9 at 0.25h 1 & 4 hrs after dosing, indicating that 14C-pridopidine is evenly distributed between plasma and blood cells ((51%, 46%, 37%).

The B/P ratio was also investigated in male and female beagle dogs (n=3/sex) after a single oral dose of 14C-pridopidine (3 mg/kg, 2.794 MBq/mg salt) and found to be 0.9 - 1.1 using total radioactivity exposure (AUC0-12h) indicating that, as in the rat, that drug-derived material was evenly distributed across plasma and blood cells.

The in vivo tissue distribution of 14C-pridopidine was investigated after an oral (gavage) dose of 3 mg/kg (5.73 MBq/kg) using quantitative whole-body autoradiography at 0.25h 1, 4 & 24 hrs post

dosing in the male albino Sprague Dawley rat (n=3/time point) and, in a separate experiment at 1h up to 672 hrs in Long Evans rats (pigmented, n=7, 1 animal/time point). Following oral administration, radioactivity was quickly distributed to all tissues studied. The highest 14C-related radioactivity in tissues was found at 0.25 to 1 hour post dose. At 1 h post dose, Tissue to Plasma (T/P) ratio was generally found to be >1 for all tissues except for fat (0.6), meaning that tissue exposure levels were above plasma levels. Thereafter, radioactivity decreased quickly (t½ ~2h) and was low but still present in most tissues at 24 hrs after administration. Apart from the digestive track, the highest T/P levels were found in the excretory organs (liver (21x), kidney (13x), small intestinal (38x)), in mandibular and harderian gland (11x) , pancreas and pituitary gland (10x), spleen, adrenal and bone marrow(7x). In brain T/P ratio was maximal (3x) at 15 min post-dosing, 2x at 1 hour and 0.4x at 4 and 24 hrs after dosing.

In the Long Evans rat, radioactivity was present up to 672 hrs after dosing in eyeball (uveal tract) and in skin (pigmented and non-pigmented), while in blood up to 504 hrs and in plasma up to 72 hrs after administration. Melanin binding of pridopidine is evident from the pigmented tissues which were studied, as radioactivity in pigmented skin was higher and longer retained than in the non-pigmented skin and eye. At 24 hrs post-dosing, the T/P ratio of the eye was 0.7 in the albino SD rat and 415 in the Long Evans rat, while maximum tissue radioactivity was 586 ng eq/g at 1 h and 12,700 ng eq/g at 168 hrs post dosing, respectively. A possible risk for phototoxicity, however, is considered low due to low UV absorption of pridopidine (see toxicology section).

No information on placental transfer, foetal exposure or milk transfer was provided but this is expected to occur given the nature of the compound and the extended tissue distribution.

In mice, distribution of pridopidine to brain and plasma was measured following 7 or 21 days of oral daily dosing. A similar plasma and brain PK profile was seen after pridopidine administration to mice. Brain absorption was fast having a similar tmax as of plasma for all dose levels. Exposure in brain was higher but generally paralleled that of plasma. Pridopidine's brain-to-plasma exposure ratios were generally 2 to 3.5.

Distribution of pridopidine to brain and plasma was measured using a 90 min PET scan in conscious male rhesus macaques monkeys (n=4) treated with 11C-pridopidine (6, 20 mg/kg, sc). Pridopidine penetrated the brain and exposure followed plasma level. Brain-to-plasma ratio was 2 to 4 for both dose levels. Brain Cmax of pridopidine lagged ~15 minutes after plasma Cmax. The pridopidine concentrations in the different brain regions were similar.

Plasma protein binding (PPB) studies were performed in vitro using ultrafiltration of 14C-pridopidine with plasma from male mouse (B6C3F1), rat (SD), dog (beagle), monkey (Cynomolgus), human and female rabbit (New Zealand White (NZW)). PPB was low across all species and the mean percentage bound was found to be 17.1% to 22.4% in mice, 18.6% to 23.9% in rats, 12.4% to 14.7% in rabbits, 12.6% to 16.0% in dogs, 15.1% to 19.5% in monkeys, and 26.0% to 32.2% in humans at 0.03, 0.3, 3 and 30 µg/mL. The fraction unbound (Fu) of pridopidine was about 1.2-fold higher in plasma from preclinical species than human plasma (Fu ~0.7).

The PPB for the major metabolite TV-45065 (0.024 - 1.2 µg/mL) was determined in human plasma using an equilibrium dialysis method and PPB was found to be lower than for pridopidine ranging from 3.8% to 6.7%, indicating a 1.4-fold higher free plasma concentration for TV-45065 (Fu 0.95) than for pridopidine. This concentration range encompasses the Cmax of TV-45065 at steady state in the clinic of 36 ng/mL at 45 mg bid.

In addition, the binding of pridopidine (0.028, 0.28, 2.8, 14 and 28 µg/mL) to rat and mouse brain homogenates was evaluated in vitro using equilibrium dialysis (3h at 37°C). The protein binding ranged from 52.8% to 74.3% in rat and from 50.9% to 78.3% in mouse, respectively. On average, for

both rat and mouse, the binding to brain homogenate protein was ~58% meaning Fu of ~0.42. As the Fu in plasma was about 0.8 this means that the free pridopidine concentration in brain homogenate is about 2-fold lower than in plasma.

2.5.3.4. Metabolism

The *in vitro* metabolite profile was assessed by an incubation of ^{14}C-labelled pridopidine (10 and 100 µM) with liver microsomes or cryopreserved hepatocytes from mouse (B6C3F1 and CD1), rat (SD), rabbit (New Zealand White), dog (beagle), monkey (Cynomolgus), and human. After incubation and acetonitrile extraction, the supernatants were analysed by HPLC-RAD and LSC.

Upon a 2 hour incubation (10 µM) with liver microsomes, the percentage of ^{14}C-pridopidine slightly decreased to 86% - 94% remaining except for dog (72%) and monkey (46%). The metabolite TV-45065 was formed in all species examined but <10% except for dog (25%) and monkey (51%). Using hepatocytes, upon a 6 hour incubation, a similar pattern was seen, with the highest metabolism and TV-45065 formation in monkey and dog, followed by rabbit, mouse and rat, while human had the lowest metabolism. TV-45065 was the only metabolite observed *in vitro* in human hepatocytes. Although in mice, rats, rabbits, dogs and monkeys in total six other metabolites were observed, these were, except peak1 (rat, 8.6%), less than 5%.

In vitro, metabolism studies showed that human CYP2D6 is the main enzyme responsible for the N-dealkylation of pridopidine to TV-45065 (to a lesser extent also by CYP2C19 and 3A4). However, pridopidine is also a time-dependent, irreversible inhibitor of CYP2D6 thus inhibiting its own metabolism in humans.

Pridopidine metabolite fingerprinting in plasma, brain, urine, and bile was assessed following a single oral dose of ^{14}C-pridopidine (3 mg/kg, 6.475 MBq/kg) to fasted male Sprague-Dawley rats (n=3). Unchanged ^{14}C-pridopidine was detected in plasma at 15 min, 1, and 4 hrs post-dose at 85%, 57%, and 6% of the total radioactivity, respectively. At the same time points, the N-de-alkyl metabolite TV-45065 was found at 7.5%, 12% and 15%. In addition, eight other HPLC peaks were detected, of which Peak1 (27%) and Peak3 (13%) were above 5% at 4 h post-dose.
In brain, however, only unchanged pridopidine was detected at 15 min, 1 and 4 hour post-dose. The ratios of pridopidine in the brain compared to that in plasma at each time point were 3.4, 3.2, and 6.6.
In urine (0-24 h), about 58% of the oral ^{14}C-dose was recovered, which consisted of unchanged pridopidine (14%), TV-45065 (14%), Peak1 (9%), Peak3 (8%) and Peaks 6, 7 and 8 each for less than 3%.
In bile samples collected from 0-24h after dosing 48% of the oral ^{14}C-dose was recovered. In bile, however, no unchanged pridopidine or TV-45065 was found but Peak3 (22%), Peak1 (12%), Peak2 (1.3%) and Peak5 (0.4%) were detected.
As it was found that Peaks 1 and 3 disappeared by the enzyme treatment of urine and bile, and that the hydrolysis was inhibited by the addition of a β-glucuronidase inhibitor, it is suggested that they are glucuronides.

In an additional study plasma, pooled urine and bile samples were extracted to yield metabolites for structural identification. In this study, unlabelled pridopidine (50 mg/kg) was administered orally to intact and bile-duct cannulated (BDC) Sprague Dawley (SD) rats, from which plasma samples were collected at 1- and 2-hours post-dose, urine and bile were collected up to 24-hours post-dose.
A total of 8 metabolites (R1 to R8) were identified in rat urine samples collected after oral administration of pridopidine and their structures were elucidated. R1 was identified as TV-45065. The proposed metabolic pathways of pridopidine in rats involve aromatic hydroxylation (R2, R3, R4, R5,

and R6), N-depropylation (R1 and R7), aliphatic oxidation to form a lactam (R7), N-oxidation (R8, also referred to as ACR694 in other studies), O-glucuronidation (R2, R3, and R4), and O-methylation (R4 and R6).

The *in vivo* metabolism of pridopidine was also investigated in male and female beagle dogs (n=3/sex) after a single oral dose of ^{14}C-pridopidine (3 mg/kg, 2.794 MBq/mg salt) analysing by HLPC pooled plasma (0-12 h) and faeces (0-48 h) after ACN/H2O extraction and urine (0-6 and 6-24 h) directly. In 0 – 12 hrs pooled plasma, five metabolites were detected, of which the two largest were TV-45065, the de-alkyl metabolite (M1), and the unchanged pridopidine (M2) with 62% and 25% of ^{14}C-label, respectively. The other metabolites were below 5% (4% M4, 2% M3, 1% M5).
In urine (0-24 h) about 88% of the oral ^{14}C-dose was recovered, which consisted for 72% of M1 (TV-45065) and for 12% of M2 (unchanged pridopidine). M3, M4 and M5 were also detected but at <2% of the ^{14}C-dose. In faeces (0-48h), only 3-4% of the ^{14}C-dose was recovered, which consisted for about 60% of TV-45065 and 10% of unchanged pridopidine. M3, M4 and M5 were <5% of recovered ^{14}C-label.

From clinical studies, information on the presence of human metabolites indicates that, as in preclinical species, TV-45065 is the major metabolite present in plasma and urine following a single and repeated dosing with pridopidine. The C_{max} of TV-45065 is ~71 ng/mL following a single dose with 45 mg pridopidine and ~32 ng/mL following twice daily dosing with 45 mg pridopidine. The area under the concentration-time curve from 0 to 24 hours (AUC_{0-24}) of TV-45065 is ~1200 ng × h/mL on Day 1 and 693 ng × h/mL at steady state following twice daily dosing with 45 mg pridopidine.

2.5.3.5. Excretion

The excretion of 14C-pridopidine-related radioactivity was investigated in male Sprague Dawley rats (intact and BDC, n=3) after an oral dose of 3 mg/kg (6.475 MBq/kg) and followed for up to 7 days (168 hrs, intact) and 3 days for BDC. Following oral administration to the rat, 14C-pridopidine-related radioactivity was quickly excreted, through the renal (59.7%) and faecal (36.8%) route, which, when including the carcass (0.4%), amounted to 96.8% of the radioactivity dose after 7 days. The total recovery of radioactivity was high in the rat and 91% was already reached at 24 hours after dosing. In bile duct-cannulated rats, at three days following oral administration, excretion into the bile and urine was 48% and 47% of the radioactivity dose, respectively, indicating an even distribution between urinary and biliary clearance. The low presence in faeces (0.8%) indicate that the fraction absorbed upon oral administration was about 1.

Excretion of 14C-radioactivity was also investigated in male and female beagle dogs (n=3/sex) after a single oral (3 mg/kg, po) or IV (1 mg/kg) dose of 14C-pridopidine (2.794 MBq/mg salt) and followed for up for seven days (168 hrs). Following both PO or IV administration to the dog, 14C-pridopidine-related radioactivity was quickly excreted, predominantly through the renal route, which amounted after seven days to 89-92% (PO) and 91-94% (IV) of the radioactivity dose. Excretion through the faecal (biliary) route was minor and contributed only for 3-4% (PO) and 2-3% (IV). The total recovery of radioactivity after seven days was high in the dog 95-97% (PO) and 97-98% (IV) and 90-93% was already reached at 24 hours after dosing. The excretion data suggest a very high oral absorption of pridopidine in the dog.

In both species excretion to expired air was not studied but this is expected to be low given the high 14C-recovery.

2.5.4. Toxicology

2.5.4.1. Single dose toxicity

Single-dose toxicity of pridopidine was assessed in mice, rats, and dogs. The inclusion of three species exceeded the two mammalian species typically required by the ICH M3(R2) guidelines. In rodents, pridopidine was administered via both IV and oral routes, despite the oral route being used in clinical studies.

In mice, minimal lethal doses were 309.8 mg/kg (oral) and 44.3 mg/kg (IV). In rats, the minimal lethal doses were 221.3 mg/kg (oral) and 44.3 mg/kg (IV). Adverse clinical signs were noted in both species at selected tested doses including subdued behaviour, laboured respiration, flaccid, ataxia, piloerection, and/or tremor.

In dogs, a dose of 66.4 mg/kg led to adverse effects requiring moribund sacrifice, while 22.1 mg/kg caused shaking and subdued behaviour in females. In contrast, no signs of toxicity were observed in the male at 44.3 mg/kg.

2.5.4.2. Repeat dose toxicity

The repeat-dose toxicity of pridopidine was evaluated in mice (2-13 weeks), rats (2-26 weeks) and dogs (7days-52weeks). All dosing was via oral administration in order to comply with the intended route of human exposure. For the rodent species, both oral (gavage) and dietary administrations occurred whereas for the dogs only oral dosing was used. The dose range used in mice was 30-750 mg/kg/day, in rats was 10-300 mg/kg/day, in dogs was 4.4-44.3 mg/kg/day.

The principal AEs of pridopidine identified in non-clinical species were CNS-related clinical signs (all species), changes in reproductive organs (in rodents), significant body weight decrease (in rats) and QT prolongation (in dogs). All relevant non-clinical findings are discussed below.

Body Weight effects:

The applicant has re-evaluated all GLP repeat-dose toxicity studies in mice and rats for effects on body weight and food consumption. The principles for determining a body weight-related NOAEL are appropriate. Body weight reductions exceeding 10% compared to controls are generally considered biologically significant. A decrease in food consumption without accompanying weight loss is typically not regarded as toxicologically significant and does not define the NOAEL. Conversely, significant weight loss (>10%) in the presence or absence of reduced food intake is an indicator of systemic toxicity. If no dose–response relationship is observed across tested doses and no other relevant toxic effects are present, the NOAEL may be set above the highest dose tested. NOAELs were established separately for each sex when differences between males and females were evident.

Mice: In mice, data from three (4-13 weeks) GLP repeat-dose toxicity studies were re-examined. Two of these studies involved dietary exposure and one involved oral gavage exposure. Data show variable results; it is not clear whether it is due to different mice species used. More than 10% decrease in body weight plus food consumption was found in one 13 study at the highest dose of 750 mg/kg/day.

Rats: In rats, data from five repeat-dose toxicity studies were re-examined (13-26 week). Two studies involved dietary exposure and three involved oral gavage exposure. More than 10% decrease in body weight were found in all studies and was more evident in males. In the 26-week study, the male NOAEL was 13.3 mg/kg/day (exposure multiple 1.3), with no body weight effects in females. In contrast, in the 13-week study (PQK0004), more than 10% body weight reductions were observed in both sexes from

60 mg/kg/day, leading to a NOAEL of 20 mg/kg/day and safety margins of 1.8 for males and 1.4 for females.

Dogs: body weight effects were not shown in the 7days and 4 weeks dog studies. In the first 13 week study, individual body weight variation was found sporadically during treatment period. In the 26 and 52-week study, dogs at doses of 13.3 mg/kg/day and above exhibited weight loss and lower food consumption (18%-40%) in the first week, however, body weight stabilised or recovered over time. Although food consumption improved over the course of the study, it remained below pre-dosing levels for the high-dose group. Both males and females showed similar patterns of weight loss and food consumption. The NOAEL for body weight decrease effect is 4.4mg/kg/day from 26 week study, with a AUC of 4259/4777 ng.h/ml, resulting an exposure margin of 0.3 based on AUC, indicating clinical relevance.

In summary, body weight effects were observed across three species during repeat-dose toxicity studies of pridopidine. These effects, primarily involving body weight loss or reduced weight gain, were often linked to decreased food consumption, though not exclusively. In rats, significant dose-dependent body weight loss (greater than 10%) and reduced food consumption were particularly pronounced in males, who showed limited or no recovery. This was often accompanied by alterations in organ weights. In dogs, the effects were transient and reversible, with no notable gender differences. In mice, more than 10% reduction was only found in one 13week study at the highest dose.

Renal effects:

In clinical trials of patients treated with pridopidine, small declines in creatinine clearance (CrCl) were observed, indicating moderate renal impairment.

CrCl is not a general test for assessing renal function in animal studies. Instead, renal function is typically evaluated through blood chemistry (blood urea nitrogen [BUN] and serum creatinine), urinalysis (urine volume, specific gravity and the presence of protein or glucose), as well as histopathological examination of kidney tissues and kidney weight monitoring. Findings regarding these aspects are summarised below.

Mice: Renal function data were collected from the 4-13 week studies, though it should be noted that urinalysis was not performed in any mice studies. In one 13-week study, at highest dose 750 mg/kg/day, plasma creatinine levels remained normal, while reductions in glucose and cholesterol, along with elevated plasma electrolytes (sodium, chloride) and increased plasma urea, were observed. In another 13-week study, slight elevations in creatinine were noted in males at 100 and 300 mg/kg (middle and high dose), but these were minor and within the normal range. Elevated urea nitrogen was recorded in males at 30 mg/kg, along with reductions in total protein and albumin in both sexes, though these lacked dose-dependence. In conclusion, while some changes suggest renal involvement, overall renal effects were subtle, with no evidence of severe toxicity in the mice studies.

Rats: Renal function-related findings in rats were reviewed across studies from 4 to 26 weeks. Changes were primarily noted in the middle- and high-dose groups (≥30 mg/kg/day), though one 13-week study showed renal effects (decreased total protein, absolute kidney weight) even at 10 mg/kg/day with a C_{max} 1036/960 ng/ml, AUC 8850/7983 ng.h/ml. Therefore no NOAEL could be determined in this study, yielding an exposure margin of 0.6 based on AUC at the lowest dose, indicating clinical relevance. Increases in serum creatinine were recorded in one 26-week study and in one out of four 13-week studies, while elevated BUN levels were observed in two out of four 13-week studies. Urinalysis across most studies revealed increased urinary volume, decreased protein levels, and altered glucose, with less frequent changes in electrolyte levels, pH, and specific gravity. Occasional histopathological findings included tubular vacuolation and reductions in kidney weight, particularly at higher doses and with longer treatment duration.

In the 26-week study, urinalysis showed significantly decreased glucose and urine density in high-dose females at 132.8/88.5 mg/kg/day, with no histopathological correlates, and recovery after treatment cessation. Other parameters, including urine osmolality and urine protein, showed no meaningful deviations from historical control data. Clinical chemistry revealed increased creatinine in males and females at the high dose (132.8/88.5 mg/kg/day) at Week 13 and Week 27. Increased urea values were observed at the low and mid doses but not at the high dose, all reversing after treatment cessation and within historical control ranges. Histopathology showed tubular vacuolation and necrosis in high-dose animals that died, indicating agonal effects. A significant decrease in relative kidney weight in mid-dose males was deemed incidental, with no dose-response and no similar findings in females, and was within historical control data.

In conclusion, serum creatinine and BUN levels were not consistently sensitive indicators of early renal function changes in these studies, as elevations were only observed in very few cases. Renal function-related findings were mostly transient, reversible, without histopathological correlates or within historical control ranges in rats.

Dogs: No treatment-related renal changes were seen in any animals.

In summary, in mice, while some changes were observed in urinalysis at the highest dose (750 mg/kg/day), overall renal effects were subtle. In rats, renal function-related findings were mostly transient, reversible, without histopathological correlates or within historical control ranges. No treatment-related renal changes were observed in dogs.

Reproductive organ changes

In the repeat-dose studies involving middle and high dose groups in rodents (>44.3 mg/kg/day), significant changes were observed in reproductive organs. Female rodents exhibited decreased uterine and ovarian weights, hypertrophy of the corpus luteum, epithelial mucous degeneration in the vagina, mucification of the vaginal epithelium, tall columnar epithelium in the uterus, uterine atrophy, and mammary gland hypertrophy. In males, alterations included the presence of cell debris in the lumen of the epididymis, decreased secretion in the prostate and seminal vesicles, focal degeneration of seminiferous tubules in the testis, and increased secretion with microscopic changes in the mammary glands. Besides, in a fertility study, female rats dosed at 132.8 mg/kg/day experienced a reduced frequency of oestrous cycles, with 2 out of 20 females failing to enter oestrus shortly after treatment initiation. Additionally, in a 26-week repeat-dose study at 132.8/88.5 mg/kg/day, anoestrus was noted in the vagina.

CNS effects

Mouse: CNS related effects were seen in one 2 week and one 13 week mouse study. Animals exhibited decreased activity and convulsions as well as prone position only in week 1 or 2 at dose 300 mg/kg/day. The NOAEL in mice for CNS toxicity is 100 mg/kg/day, with Cmax of 5625.1 ng/ml, resulting moderate safety margin of 9.1.

Rats: CNS-related toxicity was observed in most rat studies (2–26 weeks), presenting as convulsions, tremors, lethargy, salivation, and subdued behaviour. These signs appeared with increased incidence and/or severity in the high-dose group, indicating a dose-dependent effect. The symptoms, emerging shortly after dosing and resolving within 1–2 hours post-administration, are characteristic of C_{max}-driven effects. Notably, symptom severity did not increase with prolonged treatment, and no abnormalities were observed during the withdrawal period. In the 26-week studies, the lowest dose associated with these effects was 44.3 mg/kg/day. The NOAEL in rats for CNS toxicity is 13.3 mg/kg/day, with corresponding C_{max} values of 2451/2163 ng/ml and a safety margin of 3.7.

Dog: CNS-related findings were observed in all studies (7d-52w), the clinical signs included tremors, salivation, ptosis, tachypnoea, tonic convulsions, hypoactivity, lacrimation, and muscular hypotonia. In the 26-week study, CNS-related clinical signs were noted at the lowest dose (4.4 mg/kg/day), with a C_{max} of 393/341 ng/mL. No NOAEL was determined. In the 52+8-week study, clinical signs started at the middle dose (13.3 mg/kg/day). The NOAEL in dog for CNS toxicity was 4.4mg/kg/day, with a C_{max} of 403/527 ng/mL, resulting margin of safety of 0.8, indicating clinical relevance. Dogs were the most sensitive species regarding CNS toxicity. The overall margin of safety was low (0.8 in 52 week study), and no NOAEL could be established in the 26-week study. However, no CNS related clinical signs were noted in recovery animals in studies with a recovery period (26+4 week and 52+8 week), and most changes were transient, resolving by the next dosing without worsening upon repeated administration.

Cardiac effects:

Electrocardiograms (ECGs) were not measured in mice or rats during repeat-dose toxicity studies. In dogs, the 13-week study showed slight elevations in QRS duration, heart rate, and QTc in males at 15 and 50 mg/kg/day, along with minor variations in the P-R interval and QTc at Week 13. These changes were considered non-toxicologically significant, as they were mild and fell within the background data range. In the 26-week study, QT prolongation and changes in T-wave polarity were observed at 15 and 40 mg/kg/day, with margin of safety of 1 and 2, respectively. The 52+8-week study revealed QT prolongation, sporadic first-degree AV block, and altered T-wave polarity at doses above 13.3 mg/kg/day (margin of safety of 2.8), but these effects resolved during recovery.

In the combined safety pharmacology study, QTc interval prolongation and alterations in cardiac parameters, including a shortened R-R interval and increased QRS duration, were seen at doses ≥ 13.3 mg/kg, with a NOAEL of 4.4 mg/kg (C_{max} 508 ng/ml), indicating a lack of exposure margin. Additionally, preclinical studies showed binding of pridopidine at high concentrations to the hERG channel.

2.5.4.3. Genotoxicity

Standard GLP-compliant genetic toxicity studies have been conducted including an *in vitro* Ames assay, an *in vitro* mouse lymphoma Tk gene mutation assay, and an *in vivo* micronucleus test in mice.

In the Ames assay, pridopidine was incubated with Salmonella typhimurium strains with or without metabolic activation (S9 mix) at concentrations ranging from 44.3 to 4425 µg/plate. No increase in revertant colonies occurred in any strain, at any dose, with or without metabolic activation. Pridopidine was not considered to be mutagenic in this assay.

In a mouse lymphoma assay, pridopidine was incubated with L5178Y cells for 4 and 24 hours in the absence of S9 mix and for 3 hours in the presence of S9 mix. Concentrations tested ranged from 277 to 4425 µg/mL. No biologically meaningful increase in mutant frequency was noted. Pridopidine was not mutagenic in this assay.

A second mouse lymphoma assay was conducted, comprising both a dose-range finding assay and a confirmatory assay. In the confirmatory mutation assay with metabolic activation (4-hour treatment, 250–1300 µg/mL) and the confirmatory non-activation mutation assay (24-hour treatment, 50–450 µg/mL), no increase in mutant frequency was observed at any concentration. Based on these results, pridopidine was concluded to be not mutagenic in this assay.

Finally, an in vivo micronucleus study was conducted using male Specific Pathogen-Free mice. No biologically or statistically significant increases in the frequency of micronucleated polychromatic erythrocytes were seen at any dose (44.3-177 mg/kg). The estimated Cmax (15,483 ng/mL) and AUC0-24 (59,104 ng·h/mL) values at the high dose are 25.1- and 4.5-fold higher, respectively, than the MRHD. This provides a substantial exposure margin, which is generally considered sufficient to

capture any potential mutagenic or clastogenic effects that might translate to humans. Pridopidine was concluded to exhibit no mutagenic or clastogenic activity in this study.

2.5.4.4. Carcinogenicity

In this GLP study, transgenic rasH2 mice (CbyB6F1/Tg strain) (n=25/sex/group) were administered pridopidine at dietary concentrations targeting nominal doses of 0, 20, 60 and 175mg/kg/day in males and0, 60, 175 and 500mg/kg/day in females for 26 weeks. Pridopidine was associated with a significant increase in the induction of benign adenomas in the Harderian gland of female rasH2 transgenic mice at the 500mg/kg/day dose, with 5 out of 25 animals affected. It can be agreed that humans do not have Harderian glands, suggesting limited human relevance. No other toxicity was found in this study. Although there is a significant deficiency with regard to the lack of intrinsic TK, TK extrapolation from the 4-week repeat-dose oral (dietary) toxicity study performed with the same doses resulted in Cmax/AUC0-24 for pridopidine at least 2.7/1.4-fold (14.3 / 10.2-fold for the metabolite) higher than the Cmax/AUC values in humans at the MRHD. It is agreed the recommended 50-fold exposure ratio for high dose selection that sufficient for detecting carcinogens in this model (ICHS1) cannot be achieved due to limiting toxicities. Based on the absence of general toxicity, the doses of 175mg/kg/day in males and 500mg/kg/day in females were considered the NOAEL. Based on this study, there appears to be an unlikely risk of carcinogenicity in humans.

Weight of evidence approach

The applicant provided a weight of evidence (WoE) approach to support the omission of 2-year rat carcinogenicity study for pridopidine.

2.5.4.5. Reproductive and developmental toxicity

Fertility and early embryonic development

Pivotal, GLP-compliant reproductive studies evaluating fertility and early embryonic development (FEED) in rats have been performed. Separate studies were conducted in which males only or females only were evaluated. All studies involved bid oral (gavage) administration.

In males, pridopidine (≥44.3mg/kg/day) caused adverse clinical signs and body weight, food consumption decrease, but did not affect mating performance, fertility indices, or uterine parameters up to the highest dose. Therefore, the NOAEL for general toxicity was 13.3mg/kg/day, and for FEED, it was 132.8mg/kg/day. At the fertility NOAEL dose level of 132.8mg/kg/day, the Day 91 AUC_{0-24} values of pridopidine in male rats were 11.6-fold higher than the corresponding exposures in humans at the MRHD.

In the female only dosed study, Sprague Dawley (SD) rats were dosed beginning 14 days prior to mating, up to Gestation Day (GD) 7. In the high-dose animals(132.8mg/kg/day), adverse clinical signs (twitching, tremor, clonic convulsion, decreased spontaneous motility, salivation, moist fur around the urethral orifice) and decreased body weight and food consumption were noted. A prolonged dioestrus phase occurred at 44.3mg/kg/day and above, and the group mean frequency of oestrus decreased significantly at 132.8mg/kg/day.

Embryo-fetal development

In the pivotal GLP embryo-foetal development rat study (TX054007), daily oral doses of 13.3, 44.3 and 132.8mg/kg/day pridopidine were administrated to pregnant rats (Sprague Dawley) from GD7 to GD17.

At a dose of 132.8mg/kg/day, adverse pridopidine-related maternal effects included clinical signs (clonic convulsions, decreased spontaneous motility). At 44.3mg/kg/day and higher, there was a decrease in body weight and food consumption, leading to a significant decrease in body weight gain in the high dose group.

In the high dose fetuses group, the incidence of fetuses with external abnormalities significantly increased as observed by cleft palates in 3.2% of all fetuses. All cases were secondary cleft palate due to dysraphia in the secondary palate, with the primary palate closed. In addition, a significantly increased incidence of skeletal variations, observed by short supernumerary ribs, was demonstrated in the high dose group (10.8% vs 3.7% in the control group). However, this incidence was only slightly outside the historical background data (2.6% to 10.6%) and no dose-dependency was observed, with an incidence of 10.4% and 4.8% in the 15 and 50 mg/kg/day groups, respectively.

In the pivotal GLP embryo-foetal development rabbit study (TX054009), daily oral doses of 4.4, 13.3 and 44.3 mg/kg/day pridopidine were administrated to pregnant rabbits (Kbl:NZW) from GD6 to GD18.

In the dams dosed with 44.3mg/kg/day , one animal died after the first dosing. Abortions were observed in seven high dose animals at GD 18 – 21 without apparent necropsy findings but related to a reduction in food consumption which was apparent from the mid dose and higher, since these dams ate little or no food during the treatment for 10 to 15 days before abortion. From the mid dose and higher, animals also had a decrease in body weight (gain). For the dams, it can be agreed that the NOAEL is 4.4mg/kg/day, corresponding to an exposure margin of 0.47-fold the exposure in humans at the MRHD based on AUC, suggesting that the body weight findings are clinically relevant.

In the fetuses, there was one litter of a high-dosed female that was completely resorbed, with post-implantation loss of 12.6%, but this was not significantly different compared to control. Also this female ate little or no food for 10 days from the day after the start of treatment. Regarding skeletal variations, there was a significantly increased incidence of fetuses with junction of sternebrae in the high dose group. However, this finding is a relatively common spontaneous skeletal variation in rabbit fetuses. There were no pridopidine-related teratogenic effects at doses up to 44.3mg/kg/day.

Pre- and postnatal development

In the pivotal pre-and postnatal development study (R-1014), total daily oral doses of 4.42, 13.3, and 44.2mg/kg/day of pridopidine were administered to pregnant SD rats from GD7 to LD20.

In F0 females treated with 44.2mg/kg/day, there was a decrease in body weight gain during the gestation period, in body weight during lactation and in food consumption at several gestational days and at one lactation day. In the live pups of high-dosed dams, a temporal retardation of physical development in offspring of high-dosed dams was noted, which included suppressed body weight and weight gain during the lactation period (and extending into the post-lactation period for the males) and low values for indices of external differentiation (pinna detachment, eruption of the lower incisor, opening eyelid)all confined to the high-dose group and absent in low- and mid-dose pups. The delay in pinna detachment was limited to the offspring of a single dam, and the delays in the other two parameters were limited to three days compared to control group, with minimal overall impact.

It can therefore be agreed that the NOAEL for the dams and growth and physical development of the offspring was 13.3mg/kg/day and for behaviour and reproductive performance of the F1 generation was the 44.2mg/kg/day dose. At the NOAEL for behaviour and reproductive performance of the F1 generation, the margin of exposure was 3.7 based on the AUC in humans at the MHRD. At the NOAEL for growth and development, the AUC values were 0.8-fold the AUC in humans at the MHRD, suggesting that these findings occurred at clinically relevant exposures.

Juvenile toxicity

The applicant applies for the indication treatment in adults with Huntington's disease. Nevertheless, a GLP juvenile toxicity study was conducted.

During the dosing period, administration of 50 mg/kg pridopidine caused a low incidence of clinical signs and reduced body weights, body weight gains, and food consumption. These findings were not considered to be adverse as they were either transient, observed at single days and in a minimal number of animals given the total population of evaluated animals.

In subset 1 females, organ weight observations included lower uterus/cervix weights, correlating to microscopic findings of atrophy of the vagina epithelium observed at ≥20 mg/kg and mucification of the vagina epithelium, follicular degeneration, decreased number of corpora lutea in the ovary and mammary gland hyperplasia at ≥10 mg/kg. These findings were considered related to prolactinaemia and are similar as observed in adult rats. However, apart from a significant decrease in the number of oestrous cycles in subset 3 females dosed at 50 mg/kg, there were no pridopidine-related microscopic findings in the reproductive tract tissue or on the pregnancy rate in Subset 3, nor on microscopic findings in the non-pregnant females in Subset 3 and in the females of Subset 2. In the Morris water maze performed during the recovery period (between postnatal day 126 and 146), there was a significant delay in learning in females dosed at 50 mg/kg during the first two sessions but no effect on memory during the third session (single probe trial).

2.5.4.6. Toxicokinetic data

Toxicokinetic data are provided in the PK section, repeat dose toxicity section as well as developmental and reproductive toxicity section.

Multiple dose TK in rats and dogs was assessed in the repeat-dose toxicity studies up to 26 weeks and 52 weeks, respectively. Exposures generally increased proportionally or slightly greater than proportionally with dose. Accumulation after multiple dosing was up to 2-fold in rat and 1.3-fold or less in dog. No marked sex difference in exposure was noted in either rat or dog.

The applicant has not explained why the 28-day mouse study data was selected for species differences comparison instead of the longer 13-week mouse study data. However, since neither of these studies are considered pivotal, this issue is not further pursued. The NOAEL levels were lower in 3 studies than indicated by the applicant. The NOAEL dose was considered to be 175 mg/kg/day for the 28-day mouse study and 4.4 mg/kg/day for the dog 12 month study, due to the observed CNS and cardiac toxicity at 13.3 mg/kg/day. In the juvenile study, no NOAEL could be determined in rats due to the observed reproductive organ changes at the lowest dose. However, these reproductive organ changes may not be relevant for humans (also see section 4.5.4).

Exposure multiples >1.0 were achieved at NOAEL for the major metabolite TV-45065. However, some exceptions were noted for pridopidine itself: these include the 28-day toxicity study in mice, the 12-month toxicity study in dogs, the carcinogenicity study in female mice, the effects on growth and physical development in rats, and the juvenile toxicity study in rats.

Some pivotal studies (genotoxicity and carcinogenicity) appeared to lack toxicokinetics and were extrapolated from other studies.

2.5.4.7. Local Tolerance

No local tolerance studies are necessary as this is an oral product.

2.5.4.8. Other toxicity studies

2.5.4.8.1. Dependence

To evaluate the dependence potential of pridopidine, GLP-compliant drug abuse liability studies in monkeys/rats were conducted that evaluated self-administration, drug discrimination and physical dependence.

One self-administration study was conducted to evaluate the reinforcing potential of pridopidine (LL07386). Rhesus monkeys were tested in a short (4 days) procedure (for 2-hour/day/dose) and in a long (2 to 4 weeks for 24-hour/day/dose) procedure. Monkeys were divided in groups including positive control pentobarbital (1.0 mg/kg/infusion), negative control saline, or pridopidine at dose levels of 1.0, 0.5, 0.25, 0.125 and 0.06mg/kg/infusion (4 days procedure) or 1.0, 0.5 and 0.25mg/kg/infusion (2-4 week procedure). These doses were selected as they did not induce behavioural, in particular CNS, effects in the dose-range finding phase. Animals did not exhibit active self-administration of pridopidine in the short procedure. In the long procedure, two of four animals exhibited increased self-administration of pridopidine at 0.25 and/or 0.5 mg/kg/infusion as compared to the vehicle level, as reflected by the number of self-administrations that exceeded 10 times per day for 5 consecutive days or more. Overall, these results indicate that at clinically relevant exposures, pridopidine may have weak reinforcing characteristics.

In a drug-discrimination test in rats (Lister Hooded), subcutaneously administered pridopidine at 30 and 45 mg/kg induced a response on the cocaine-trained lever in 45% and 40% of the animals, indicating partial generalisation, suggesting that pridopidine may have some interoceptive effects, similar to cocaine. However, because a dose of 45 mg/kg also markedly decreased the rate of responding, potentially due to non-specific effects on locomotor activity, no definitive conclusion was drawn whether there was a cocaine-like discriminative stimulus with pridopidine.

In a second drug-discrimination test, rats (SD) were tested for generalisation of pridopidine (20 mg/kg, IP) to various compounds from different pharmacological classes. In general, only compounds which evoke a similar subjective state as the training drug will produce consistent responding on the drug-associated lever. None of the tested compounds showed full generalisation to pridopidine (haloperidol, d-amphetamine, 1-(3-Trifluoromethylphenyl)piperazine, phentermine and aripiprazole). Only at the highest tested doses, haloperidol (0.3 and 0.6mg/kg) , d-amphetamine (1.5mg/kg), phentermine (1.25, 2, and 5 mg/kg), 1-(3-Trifluoromethylphenyl)piperazine (1 and 3mg/kg), and aripiprazole (1, 3, 10, and 15mg/kg) induced partial generalisation to pridopidine. There was most overlap in the effects of pridopidine with the antipsychotic haloperidol. Co-administration of d-amphetamine (0.06-0.6mg/kg) with pridopidine induced attenuation of pridopidine effects (pridopidine-lever responding reduced from ~97 to 68%). At 20 mg/kg pridopidine, a maximum plasma concentration of >7-fold the Cmax concentration at steady state in humans at the therapeutic dose was noted. Together the results suggest that pridopidine may have some interoceptive stimulus similar to D2 antagonists and further suggests a lack of stimulant-like properties on lever-pressing behaviour.

In a physical dependence study in rats, pridopidine tolerance to behavioural and withdrawal effects was assessed during a repeated dosing period of 4 weeks and a recovery period of one week, respectively and compared to positive control diazepam. There were no withdrawal signs observed after treatment with pridopidine up to the highest tested dose of 2.4 mg/g in food, as indicated by the absence of gross behavioural observations and of notable changes in food consumption and body weight gain. The high dose plasma levels were in a range of 1.4-fold to 8.5-fold the clinical Cmax.

Therefore, from this study it can be concluded that pridopidine has no physical dependence-producing potential in rats.

2.5.4.8.2. Studies on impurities

The once daily oral gavage administration of two impurities, each at doses up to 315 µg/kg/day to Sprague Dawley rats for 13 weeks was well tolerated and no test-article related toxicity was observed. Based on the proposed clinical dose of pridopidine of 90 mg/day, a 60 kg person and the used conversion factor of 7 from human to rat, it is agreed that these impurities are qualified up to 3%.

The impurities were tested negative in the Ames test and in the chromosomal aberration test, indicating that these impurities are not genotoxic in vitro.

Overall, the proposed limit above the qualification threshold can be accepted from a non-clinical point of view.

2.5.5. Ecotoxicity/environmental risk assessment

Table 1:Summary of main environmental risk assessment study results

Substance (INN/Invented Name): pridopidine hydrochloride			
CAS-number (if available): 882737-42-0, 346688-38-8 (salt-free)			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log D_{ow}: pH 5: -1.8 pH 7: -0.6 pH 9: 1.4	Potential PBT: N
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC_{sw}, unrefined	0.0054	µg/L	≥ 0.01 threshold: N
Other concerns (e.g. chemical class)			N

Conclusions on studies for pridopidine hydrochloride

Pridopidine hydrochloride is not a Persistent, Bioaccumulative, and Toxic (PBT) substance. Considering the above data, pridopidine hydrochloride is not expected to pose a risk to the environment.

2.5.6. Discussion on non-clinical aspects

Pharmacology

In vitro binding studies showed that pridopidine acts as an agonist at the human S1R (Ki 0.057 µM). Main metabolite (TV45065) exhibited lower binding affinity for the human S1R (IC50 5.80 µM, Ki=2.44 µM) compared to pridopidine. Although requested, no in vitro selectivity data of pridopidine for S1R over dopamine D2/D3 receptors in species that were used in the long-term toxicology studies was provided. To address the S1R selectivity over dopamine D2/D3 receptors, the applicant refers to the already presented published data on PET imaging of RO in rats, but no in vitro affinity data were provided. Based on an additionally provided study, higher S1R RO over D2/D3 receptors was also expected in non-human primates, but with an extrapolated occupancy of 10% at clinical concentrations, D2/D3 receptor binding can also not be completely excluded. In addition, given the limited data points in this study, the extrapolation seems inaccurate and no comparison was made with receptor occupancy for S1R itself. No in vitro affinity data on selectivity of pridopidine for the S1R compared to D2/D3 receptors were provided for the dog, the other long term toxicity species. Nevertheless, since the potential D2/D3 receptor related effects in rats and dogs on body weight and CNS effects are either not adverse or described in the proposed summary of products characteristics (SmPC), this is considered acceptable.

Overall, results on the mode of action suggest that pridopidine, by activating S1R, restores ER Ca2+ levels, reduces ER stress and oxidative stress, improves mitochondrial function and autophagy and reduced cell death in HD cell models. In addition, pridopidine enhanced axonal BDNF transport and increased dendritic spines in corticostriatal neurons, in line with the observed improvement in synaptic plasticity. Thus, pridopidine rescues cellular pathways downstream of S1R activation which are impaired in HD, leading to neuroprotection. It should be noted that the neuroprotective actions of S1R by targeting MAM disruption, excitotoxicity, ER stress, BDNF levels and mitochondrial dysfunction, are also implicated in other neurodegenerative diseases. Pridopidine also significantly reduces the size of mHTT aggregates in vitro and in vivo, establishing a link between the mode of action of pridopidine's effects on S1R within HD specifically.

Pridopidine in vivo PD studies included a PET imaging target engagement/RO study in Wister rats and the evaluation of molecular and behavioural outcomes in YAC128 HD and R6/2 mice. With PET imaging in rats, significant D2R occupancy was only observed at a dose 20-fold higher than was required for S1R occupancy. Based on this study this can be agreed, but the lowest dose at which pridopidine can occupy D2/D3 receptors was not demonstrated. At some of the pridopidine dose levels used in rat toxicology studies, D2/D3R (dopamine-3 receptor) occupancy can be expected. Notably, no in vitro affinity data of S1R affinity over D2/D3R affinity was provided for the long-term toxicology species. Of note, in HD patients, the blood-brain-barrier is altered, which may lead to different levels of pridopidine reaching the receptors in the CNS clinically.

In YAC128 HD mice in vivo, some beneficial effects of pridopidine was seen at both a molecular and behavioural level, but HD-related neuropathology was not rescued. Early treatment was mainly effective regarding motor function improvement, anxiety reduction and improvement of depression, while effects of late treatment were limited to the reduction of depressive-like phenotypes. In contrast, pridopidine exaggerated depression in HD clinical trials, suggesting a limited clinical translation. In addition, especially the motor function improvements were only observed at a high dose (30 mg/kg), therefore an adequate dose-response effect is lacking. Treatment with pridopidine in R6/2 HD mice improved motor performance, but given that only one dose level was used, no dose-response effect was established. Similar as in YAC128 HD mice, the effects on motor function in R6/2 HD mice were mainly indicative of a delay in motor deficits rather than a rescue. The beneficial in vitro effects appeared therefore not translatable to broad in vivo endpoints and the duration of effect in vivo is not documented in animals. Considering pridopidine is not suppressing the cause of the pathology, but the consequences, there is no non-clinical rationale to support daily dose in humans, and this relates to clinical effectiveness studies. Therefore, the non-clinical proof of concept of pridopidine in HD is limited and should be established clinically.

Regarding secondary pharmacodynamics, no major findings were observed for pridopidine binding in several screens of receptors, ion channels, and enzymes, except for low affinity for the human adrenergic α2C (Ki 1.58 μM), dopamine D3 (Ki 1.63 μM), serotonin (5-Hydroxytryptamine) 5-HT1A (Ki 3.63 μM) and dopamine D2L (Ki 29.5 μM). Considering that the clinical Cmax corresponds to 2.2 μM pridopidine, potential effects on adrenergic α2C (Ki 1.58 μM), dopamine D3 (Ki 1.63 μM), serotonin (5-Hydroxytryptamine) 5-HT1A (Ki 3.63 μM) and adrenergic α2 (non-selective) (Ki 3.74 μM) cannot be excluded. A discussion was provided if and how these adrenergic, dopamine D3, D2 and 5-HT1A receptors contribute to the mechanism of action of pridopidine, taking into account clinically reached pridopidine exposures and the affinity of pridopidine. It was repeated that the in vivo rat (PET) study has showed higher affinity of pridopidine over the D2/D3 receptors. It was further argued that since at a clinical dose, minimal or no D2/D3 receptor binding (~ 3%) was observed and considering the similar affinities for the α2C and 5-HT1A receptors as for the D3R, no relevant binding of pridopidine at these sites is expected in humans. Although it was acknowledged that there is a potential for D2 receptor mediated toxicological effects in animals, given the results on receptor occupancy in human PET studies, this is clinically unlikely. In addition, pridopidine's protective effect in in vitro HD models are mediated by S1R as demonstrated in pharmacological studies using the S1R antagonist NE100 or S1R knockout cells. These arguments can be supported. Thus, off-target binding to D2, α2C, D2/D3, and 5-HT1A receptors is minimal and unlikely to contribute to the primary mode of action. Section 5.1 of the proposed SmPC was amended accordingly.

Regarding safety pharmacology, in vitro studies suggest a risk for QT prolongation and in vivo studies indicate that pridopidine may cause adverse cardiovascular effects, including QT prolongation, at clinically relevant exposures. Based on findings in dogs and most likely pharmacology related, pridopidine-induced adverse CNS effects seem clinically relevant. CNS and cardiac findings were also found in animals upon repeated exposure at clinically relevant exposures. Respiratory safety studies

suggest a low risk for adverse respiratory effects, since no notable pridopidine-related effects were noted up to doses 5-fold the clinical Cmax at the MRHD and effects were transient.

Pharmacokinetics

PK studies included single dose studies in rats and dogs to determine the PK parameters of pridopidine and TV-45065 after oral and IV administration, as well as multiple dose studies in mice to support pharmacology models. In vitro PPB for pridopidine was determined in mouse, rat, rabbit, dog, monkey, and human and for the main metabolite, TV-45065, in human. In addition, in vitro binding to brain homogenate was studied in rodents. Studies using 14C-pridopidine in both rats and dogs examined the absorption, distribution, and excretion of 14C-pridopidine-related material and investigated the metabolite profiles in plasma and excreta.

After oral administration, pridopidine is quickly and widely distributed into tissues including the target organ, the brain. Oral absorption of pridopidine was found to be fast in all species (0.25-1h) but also declined rapidly after Cmax with t1/2 of 1-2 hrs in rodents and 2-3 hrs in dogs. Bioavailability was high in rat (>80%) and dog (>65%). The (PET) shape of the pridopidine concentration-time profile in brain is similar to the plasma PK profile, albeit brain concentrations are 2- to 4-fold higher than plasma levels, which correlates with the higher binding to brain matrix compared to plasma protein. PPB is low across species (≤32%), indicating a high free fraction (>70%), while binding to rodent brain homogenate (45%) was found to be 2-fold less than in plasma. In pigmented rats, pridopidine shows high affinity for skin and eyeball suggesting binding to melanin. However, pridopidine does not absorb light from 290 to 700 nm, therefore it is considered a low risk to be sufficiently reactive to cause phototoxicity (ICH S10).

Metabolite profiles were also determined in vitro across species (mouse, rat, rabbit, dog, monkey, and human) using 14C-pridopidine and the responsible enzymes were identified. Pridopidine undergoes N-dealkylation via cytochrome P450 (CYP) 2D6 to form the metabolite TV-45065, which is not pharmacologically active. In vitro, metabolism is slow and TV-45065 is the main metabolite in nonclinical species and humans. In vivo in plasma pridopidine and its metabolite TV-45065 are the main products present and are both predominantly excreted in urine. In rat, biliary excretion (37-49%) is an additional elimination pathway.

Toxicology

Pridopidine demonstrated low acute oral toxicity in rodents and moderate toxicity in dogs.

In the clinical data provided, weight loss was reported as a treatment-emergent adverse event (TEAE) in humans. This aligns with the significant weight reductions (>10%) seen in rats. However, the body weight loss observed in humans was primarily associated with gastrointestinal effects, while in animals no gastrointestinal effects were seen. The applicant has revised the proposed SmPC section 5.3 after the re-evaluation of all GLP studies in both rats and mice of both genders. In fact, body weight effects were observed in rats across repeat-dose toxicity studies, reproductive and developmental toxicity studies (both dams and pups), as well as in the juvenile toxicity study. In the repeat-dose toxicity studies, body weight decreases exceeded 10%, whereas such significant reductions were not observed in the other studies. However, in some development and reproductive toxicology studies, the decrease in body weight was dose-dependent, statistically significant, and associated with effects on the pups. Overall, the safety margins at the NOAEL were generally below 5. Since the clinical relevance of these effects cannot be excluded, this effect in all studies has been reflected in the proposed SmPC section 5.3 and proposed RMP non-clinical section.

The reproductive organ changes observed in rats after high-dose treatment with pridopidine are likely driven by elevated prolactin levels, a well-known consequence of D2 receptor antagonism. These effects are consistent with those seen in other D2 antagonists. In rats, in vivo PET imaging

demonstrated significant D2/D3 receptor occupancy (44-60%) at high doses (60 mg/kg), which likely explains the increased prolactin levels and subsequent reproductive changes.

However, reproductive organ changes are less likely to happen in humans. First of all, there is a minimal D2 RO in humans. At the therapeutic dose in humans (45 mg twice daily), pridopidine exhibits minimal D2/D3 receptor occupancy (~3%) after two weeks dosing. This is in contrast to the high D2/D3 occupancy (44-60%) seen in rats at toxic doses, indicating that humans are less likely to experience the same prolactin elevation. Secondly, unlike humans, rodents lack a spontaneous luteal phase, which means they are more prone to sustained prolactin elevation when D2 receptors are blocked. This prolonged increase in prolactin drives the observed reproductive organ changes in rats but is not expected in humans, who have a spontaneous luteal phase that regulates prolactin more effectively. At last, no similar reproductive toxicity findings were observed in dogs, suggesting that these prolactin-related changes are specific to rodents and not predictive of human risk. To conclude, given the physiological differences in prolactin regulation and the lack of significant D2 receptor antagonism at clinical doses, the reproductive organ changes observed in rats is less likely to occur in humans.

CNS-related clinical signs including tremor, shaking, salivation, passivity, subdued behaviour, hypoactivity and/or convulsions were observed across species in the repeat dose toxicity studies in a dose and Cmax dependent manner. Dogs were the most sensitive species. A low or no exposure multiple could be determined in dogs. Besides, in the safety pharmacology study, CNS effects in dogs including tremors, twitching, and convulsions, started at the lowest dose (4.4 mg/kg; Cmax 508 ng/ml), and no NOAEL could be established. Overall, the clinical relevance of these findings cannot be excluded and can most likely be explained by exaggerated pharmacology. Moreover, depression was identified as a side effect in clinical trials (see clinical AR). The applicant has addressed the CNS findings observed in animals in the proposed RMP Part II: Module SII - Non-clinical Part of the Safety Specification and in proposed SmPC section 5.3 .

The non-clinical findings suggest clinically relevant cardiovascular risks associated with pridopidine treatment. The applicant addressed the cardiovascular findings observed in animals in the proposed RMP Part II: Module SII - Non-clinical Part of the Safety Specification and adjusted the wording in proposed SmPC section 5.3.

Results from the provided in vitro Ames assay, in vitro mouse lymphoma Tk gene mutation assay, and in vivo micronucleus test did not indicate genotoxic potential of pridopidine.

The rationale for waiving the two-year rat carcinogenicity study, based on a WoE approach, is discussed in detail below.

In vitro studies demonstrated that pridopidine is selective for the S1R receptor, acting as an agonist, with significantly lower binding affinity (30- to 500-fold) for other CNS receptors. PET imaging in the brains of healthy volunteers further confirmed that pridopidine at a dose equivalent to 45 mg bid exhibits high (~90%) occupancy of S1R with minimal (~3%) occupancy of D2/3Rs. It should be noted that D2/D2R occupancy was not assessed in HD patients.

It can be agreed that pridopidine is neither mutagenic nor clastogenic in a standard battery of genotoxicity assays. In a 6-month transgenic mouse carcinogenicity study, aside from the finding of benign Harderian gland adenoma, which are considered irrelevant to humans since humans do not have Harderian glands, there was no evidence of carcinogenic potential. Existing data for S1R agonists, including other approved products, show no evidence of carcinogenicity.

Preclinical studies identified toxicities including significant body weight reduction, CNS toxicity, cardiac effects and changes in reproductive organs. Given the physiological differences in prolactin regulation

and the minimal D2 receptor antagonism at clinical doses, it is less likely that the reproductive organ toxicity observed in rodents will occur in humans.

The applicant provided an analysis addressing concerns regarding long-term carcinogenicity risk. Non-clinical studies in rats and dogs showed no time-dependent changes in toxicokinetics or emergence of new toxicities. Clinical data showed no PK or PD shifts and no increase in malignancies or endocrine-related adverse events (AEs). Pridopidine exhibits high selectivity for the S1R, with negligible D2/D3 receptor occupancy at therapeutic doses, reducing the likelihood of D2-mediated hormonal disruption. While PET imaging was limited to two weeks, chronic clinical and nonclinical safety data sufficiently support the conclusion. Overall, it can be agreed long term use of pridopidine is unlikely to produce a heightened risk for new side effects, cause hormonal disruption in humans or increase carcinogenic risk.

The applicant conducted a retrospective immunotoxicity assessment of pridopidine based on existing repeat-dose toxicity studies across rats, mice, and dogs. The analysis focused on key ICH S8 endpoints (e.g. haematology, immune organ weights, histopathology, protein fractions, infection incidence, and lymphocyte subsets). Immune-related findings were limited to three rat studies but lacked consistency and toxicological significance. Increased or decreased white blood cells and lymphocyte counts were observed, but were generally transient, reversible, or within historical control ranges. No correlating histopathological changes were found in immune system organs (thymus, spleen, lymph nodes, bone marrow), and no increased incidence of infections or tumours was reported. Other species (mice and dogs) showed no immune-related changes. A dedicated immunophenotyping study in rats found no impact on T-cell subsets, and a 6-month rasH2 carcinogenicity study in mice revealed adenomas in the Harderian gland at high doses, a tissue not present in humans. It can be agreed that pridopidine does not modulate the immune system and poses no increased carcinogenic risk via immunotoxic mechanisms.

In conclusion, the WoE is sufficient to omit the 2-year rat carcinogenicity study.

In the pivotal FEED study with female rats, there were no effects on fertility and copulation indices, the number of corpora lutea, number of implantations, pre-implantation loss, number of live embryos, number of resorptions, or post-implantation loss. The general toxicological NOAEL for the dams was 44.3 mg/kg/day, and the NOAELs for maternal reproductive ability and EED were considered to be 13.3 mg/kg/day and 132.8 mg/kg/day, respectively. At the maternal reproduction NOAEL (13.3 mg/kg/day), the GD 17 AUC0-24 values in pregnant female rats were 1.2-fold higher than human exposure at the MRHD. At the EED NOAEL (132.8 mg/kg/day), the GD 17 AUC0-24 values in pregnant female rats were 11.4-fold higher than the corresponding exposures in humans at the MRHD.

At higher dose (≥44.3mg/kg/day), disrupted oestrous cycle and decreased mean frequency of oestrus were seen in female rats. This effect is likely due to dopamine D2 receptor antagonism, which increases prolactin secretion, disrupting the cycle. Despite these disruptions, fertility indices and copulation timing were unaffected in rats that successfully mated, indicating that while prolactin-related changes influenced the oestrous cycle, reproductive function remained intact at these doses.

In the pivotal rat embryo-fetal development study, in pregnant rats dosed with 132.8 mg/kg, adverse pridopidine-related maternal effects included clinical signs (clonic convulsions, decreased spontaneous motility). At 44.3 and higher, there was a decrease in body weight and food consumption, leading to a significant decrease in body weight gain in the high dose group. Therefore, it can be agreed that the F0 NOAEL is 13.3 mg/kg. At 13.3 mg/kg, the AUC was 1.2-fold higher than the AUC at steady state in humans at the MRHD of 45 mg bid, suggesting that these findings are clinically relevant. In the high dose fetuses group, the incidence of fetuses with external abnormalities significantly increased as observed by cleft palates in 3.2% of all fetuses. Based on the incidences of cleft palate, indicating that pridopidine induces morphological abnormalities in rat fetuses, it can be agreed that the NOAEL for F1

is 44.3 mg/kg, corresponding to a safety margin of 4.3 fold compared to the humans at the MRHD of 45 mg bid based on AUC. Cleft palate in rats occurred at the highest dose (132.8 mg/kg/day). Malformations were not observed at the low and mid doses at which there is most likely no D2 receptor antagonism (based on the PET study in Sahlholm et al., 2015). Instead of involvement of the activity to the S1R as a pharmacological explanation, the malformation is, similar to other toxicity findings in repeated dose toxicity studies, possibly linked to a potential pharmacological effect via D2 receptor antagonism at high doses in animals which are not reached clinically and therefore clinically not relevant. Upon request, the applicant also explained that the D2-related side effects in the clinical study are mainly caused by concomitant medication use, further reassuring that pridopidine is mainly targeting S1R clinically. Overall, there is insufficient mechanism-based evidence for an absolute contraindication pregnancy. Adequate information has been added to Sections 4.6 and 5.3 of the proposed SmPC.

In the pivotal GLP embryo-foetal development rabbit study, abortions were observed in seven high dose animals at GD 18 – 21 related to a reduction in food consumption which was apparent from the mid dose and higher, since these dams ate little or no food during the treatment for 10 to 15 days before abortion. From the mid dose and higher, animals also had a decrease in body weight (gain). For the dams, it can be agreed that the NOAEL is 4.4 mg/kg, corresponding to an exposure margin of 0.47-fold the exposure in humans at the MRHD based on AUC, suggesting that the body weight findings are clinically relevant. There were no pridopidine-related teratogenic effects at doses up to 44.3 mg/kg/day. However, there was an insufficient number of live fetuses for a comprehensive assessment of potential teratogenic effects at the high dose, due to maternal death, total resorption, and high incidence of abortions. Therefore, it can be agreed that the NOAEL was 13.3 mg/kg/day for fetuses, corresponding to an AUC 1.5-fold higher than the AUC in humans at the MRHD. This has been adequately covered in proposed SmPC section 5.3.

In pre- and post-natal development studies, high doses of pridopidine administered during gestation and lactation were associated with less than 10% body weight reduction and effects on pup development, including reduced body weight gain and mild, transient delays in physical development. The NOAEL for the dams and growth and physical development of the offspring was 13.3 mg/kg/day and for behaviour and reproductive performance of the F1 generation 44.2 mg/kg/day. At the NOAEL for behaviour and reproductive performance of the F1 generation, the margin of exposure was 3.7 based on the AUC in humans at the MHRD. At the NOAEL for growth and development, the AUC values were 0.8-fold the AUC in humans at the MHRD, suggesting that these findings occurred at clinically relevant exposures. The effects in pups were only observed in the highest dosing group (44.2 mg/kg/day). A direct contribution of pridopidine cannot be completely excluded, as besides a decrease in body weight (<10%), no abnormalities in the nursing conditions of dams were observed in any dosage group and pridopidine is a small, permeable molecule likely to be excreted in breast milk. Women should therefore discontinue breast-feeding while being treated with Nurzigma, which is adequately reflected in the proposed SmPC section 4.6. Body weight effects in dams as well as effects on growth and development in pups has been reflected in detail in the proposed SmPC section 5.3 as well as in Part II: Module SII – Non-clinical section of the proposed RMP.

The applicant currently applies for the indication treatment in adults with HD. The applicant is yet to complete paediatric investigation plan but intends to develop the product for paediatric population. In main study females, organ weight observations included lower uterus/cervix weights, correlating to microscopic findings of atrophy of the vagina epithelium observed at ≥20 mg/kg and mucification of the vagina epithelium, follicular degeneration, decreased number of corpora lutea in the ovary and mammary gland hyperplasia at ≥10 mg/kg. These findings related to prolactinaemia are similar as observed in adult rats. Therefore, the NOAEL for pridopidine was considered by the applicant to be 50 mg/kg. However, as the observed effects are apparently reversible as they occurred only in the main

study phase, and are most likely rat-specific findings of prolactinaemia, does not mean that the observations are not adverse in rats. Therefore, there is no NOAEL in rats. The lowest dose of 10 mg/kg corresponds to 0.7-fold the exposure based on AUC at the MRHD. However, these effects are most likely not relevant for humans. Of note, low exposures (0.7, 1.9 and 5.7-fold the clinical AUC at the MRHD) were reached in juvenile rats, which should be taken into account for potential future paediatric indications. In the Morris water maze, there was a significant delay in learning in females dosed at 50 mg/kg during the first two sessions but no effect on memory during the third session (single probe trial). It is noted that learning and memory testing was conducted during the recovery period, at least 8 weeks after treatment cessation (between postnatal day 126 and 146, dosing stopped postnatal day70). The applicant indicates that the delay in acquisition time in high dosed vs. control females was slightly reduced from session 1 (11.6 s) to session 2 (8.6 s) suggesting an improvement in learning on 2 consecutive days. Actually, the decrease in latency time from sessions 1 to 2 is not unexpected for each group, but was not found to be higher in the high dose group compared to controls (-42.4% vs. -49.5%, respectively). However, it is agreed that the similar performance between control and treated groups during session 3 indicates an effect on learning with no permanent effect on memory. The effect on learning has been reported in proposed SmPC 5.3 and nonclinical part of the proposed RMP.

Overall, studies on the dependence potential of pridopidine demonstrated that pridopidine has a potential for psychological dependence, based on mild reinforcing properties for self-administration. No observations of physical dependence were noted based on the absence of physical withdrawal symptoms and the absence of sharing subjective interoceptive cues with known stimulants.

Environmental Risk Assessment

Pridopidine hydrochloride is not a PBT substance. Pridopidine hydrochloride is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

In general, the pharmacology studies demonstrated the mode of action of pridopidine. In vitro binding studies showed that pridopidine acts as an agonist at the human sigma 1 receptor. Pridopidine rescues cellular pathways downstream of S1R activation which are impaired in HD, leading to neuroprotection. In YAC128 and R6/2 HD mice in vivo, some beneficial effects of pridopidine was seen at both a molecular and behavioural level, with partial rescue of HD-related neuropathology in R6/2 mice only, but the beneficial in vitro effects appeared not translatable to broad in vivo endpoints. The non-clinical proof of concept in HD is limited and should be established clinically.

The absorption, distribution, metabolism, and excretion of pridopidine was adequately evaluated in in vitro systems (PPB, metabolism) and using in vivo PK studies (PO, IV) in the mouse, rat and dog. In addition, the in vivo multiple-dose TK of pridopidine was conducted via oral administration to Sprague-Dawley rats, New Zealand White rabbits and Beagle dogs, which were used as part of the non-clinical safety program.

The preclinical toxicology of pridopidine has been adequately evaluated. The principal adverse effects of pridopidine identified in non-clinical species were CNS-related clinical signs (all species), changes in reproductive organs (in rodents), significant body weight decrease (rats) and QT prolongation (in dogs). Furthermore, pridopidine-related embryo-fetal malformations (cleft palates) and temporal retardation of physical development were observed in reproductive and developmental toxicity studies but adequately reflected in the proposed SmPC.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- **Tabular overview of clinical studies**

Table 2: Tabular overview of clinical studies

study	description	dosing regimen
PK studies in healthy subjects		
TV7820-IMG-10082	PK and PD	single oral dose of 0.5 mg, 1 mg, 5 mg, 22.5 mg, 45 mg or 90 mg
ACR16C011	mass balance study	single oral dose of 45 mg [^{14}C]pridopidine
ACR16C016	food effect study	single oral dose of 90 mg pridopidine
ACR16C018	PK, PD, safety and tolerability	multiple oral dose twice daily of 45 mg, 67.5 mg, or 90 mg for 9 days
PK studies in patients with Huntington's disease		
TV7820-IMG-10082	PD and sparse PK sampling	single oral dose of 90 mg
ACR16C007	efficacy and sparse PK sampling	multiple oral dose of 50 mg once daily
ACR16C008	efficacy and sparse PK sampling	multiple oral dose of 45 mg once daily or 45 mg twice daily
ACR16C009	efficacy and sparse PK sampling	multiple oral dose of 10 mg, 22.5 mg or 45 mg once daily for 4 weeks followed by 10 mg, 22.5 mg or 45 mg twice daily for another 7 weeks
PL101-HD301	efficacy, safety and sparse PK sampling	multiple oral dose of 45 mg twice daily
TV-7820-CNS-20002	QT effect and sparse PK sampling	multiple oral dose of 45 mg, 67.5 mg, 90 mg or 112.5 mg twice daily for 52 weeks
PK studies in special populations		
ACR16C012	PK in CYP2D6 poor and normal metabolisers	multiple oral dose of 45 mg twice daily for 14 days
ACR16C013	renal impairment	multiple oral dose of 45 mg twice daily for 14 days
DDI studies		
ACR16C016	DDI study to assess the effect of pridopidine on metoprolol (CYP2D6 substrate)	single oral dose of 90 mg pridopidine
TV7820-DDI-10068	DDI study to assess the effect of pridopidine on metformin (substrate of OCT1, OCT2, MATE1 and MATE2-K)	multiple oral dose for 12 days Day 3: 45 mg twice daily Day 4 and 5: 67.5 mg twice daily Day 6 to 15: 90 mg twice daily

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

Pridopidine is proposed to be indicated for the treatment of early HD in adults who are not treated with ADMs. The proposed recommended initial dose is 45 mg once daily in the morning for 2 weeks. The proposed recommended final dose is 45 mg (one capsule) twice daily, one capsule in the morning and one capsule in the evening. Pridopidine can be taken with or without food. The clinical pharmacology of

pridopidine was assessed in healthy volunteers (8 studies) and patients with HD (6 studies). Dedicated healthy volunteer studies assessed the effect of food, relative bioavailability, intrinsic factors (renal impairment and CYP2D6 phenotype), and several DDI on the PK of pridopidine. Furthermore, a mass-balance study characterised absorption, metabolism and excretion of pridopidine. No clinical study in hepatic impairment subjects was conducted. Several *in vitro* studies were performed investigating the permeability, plasma protein binding, metabolic stability in human liver microsomes and human hepatocytes and if pridopidine was a substrate of CYP enzymes and transporters. Furthermore, *in vitro* studies were performed to investigate whether pridopidine was an inhibitor of CYP enzymes or transporters or an inducer via AhR, CAR and PXR.

Physical-chemical properties

The molecular formula of pridopidine is $C_{15}H_{23}NO_2$ HCl with a molecular weight of 317.87 g/mol. Pridopidine has no chiral centres.

Analytical methods

Several bioanalytical methods have been developed and validated to determine plasma (for pridopidine and TV-45065) and urine (for pridopidine and TV-45065) concentrations of pridopidine and TV-45065. LC-MS/MS with internal standards for both pridopidine and TV-45065 were used to measure plasma and urine concentrations. Analytical procedures differed in extraction method and liquid chromatography and mass spectrometry equipment and settings.

Liquid scintillation counting was carried out to determine the fraction of total radioactivity recovered in urine and faeces using a non-validated method.

Population PK (PopPK) modelling

A popPK model was developed aiming to quantify the PK of pridopidine at steady state in patients with HD and characterise influences of intrinsic and extrinsic factors on the PK profile. The final model was a 2-compartment model with first order absorption rate and clearance parameters. The pooled 9-study PopPK analysis dataset included 7349 PK observations determined at steady state from 1196 study participants, of whom 1037 (87%) were patients. Below limit of quantification observations accounted for <10% of all PK observations and deemed defendable to exclude from the analysis. Clearance and volume parameters were scaled by bodyweight using standard fixed allometric exponents of 0.75 and 1, respectively. Statistically significant covariates in the final model were patient status, CYP2D6 phenotype, body weight, age, sex, dose and renal function. Since no therapeutic window is available, it cannot be determined if the exposure due to the covariates renal impairment, hepatic impairment, gender, body weight, ethnic origin, and age will not lead to too high exposure in CYP2D6 poor and non-poor metaboliser patients.

Exposure-response modelling

No therapeutic window can be determined, since no efficacy was shown.

The applicant provided exposure-response curves and estimated the odds ratio at maximum minimum concentration for the most frequent reported AEs. The exposure-response curves showed no clear trends for nausea and anxiety. Somewhat of a trend is observed for insomnia, weight decrease and an inverted relationship for irritability. These findings are further supported by the odds ratio at maximum C_{min} which are 1.88 for insomnia, 2.45 for weight decrease and 0.16 for irritability. Furthermore, patients that are CYP2D6 poor metabolisers and have renal impairment are at higher risk of QTc prolongation. The applicant does not want to include mandatory CYP2D6 genotyping, but due to safety in all patient populations (not only Caucasians) mandatory genotyping could be considered. Instead a strong warning is included in section 4.4 of the proposed SmPC which is considered acceptable.

Pharmacokinetics in healthy volunteers

The PK of pridopidine in healthy volunteers CYP2D6 non-poor metabolisers were investigated following a single dose of 0.5 mg to 90 mg and following twice daily dosing over a dose range of 45 mg to 90 mg.

After a single dose of 45 mg pridopidine, the C_{max} is ~320 ng/mL and the $AUC0_{-\infty}$ is ~2500 ng × h/mL. Following twice daily dosing with 45 mg pridopidine, the $C_{max,ss}$ is ~500 ng/mL and the $AUC_{0-24,ss}$ is ~9000 ng × h/mL. The C_{max} and AUC of pridopidine are not significantly affected by food (high fat breakfast). The t_{max} increased from 1.5 hours to 3 hours when given with food. Based on the PK data from healthy CYP2D6 non-poor metaboliser volunteers following a single dose with pridopidine over a dose range of 0.5 mg to 90 mg, the C_{max} and AUC are more than dose proportional from 0.5 mg to 22.5 mg and dose-proportional from 22.5 mg to 90 mg. Following twice daily repeated dosing over a dose range of 45 mg to 90 mg, the C_{max} and AUC increase dose proportional. In CYP2D6 non-poor metabolisers, the C_{max} increased 1.6-fold and the AUC_{0-24} increased 2.4-fold following a dose of 45 mg twice daily. In the clinical studies, the intra-individual variability was between 11.2% and 14.2% for pridopidine and between 6.4% and 13.0% for TV-45065. The inter-individual variability for C_{max} ranged from 11% to 63% and for AUC ranged from 19% to 103% in subjects that were CYP2D6 non-poor metabolisers.

Absorption

Different capsule formulations produced by different manufacturers were used in the clinical PK studies. Furthermore, an oral dissolution was used in the mass balance study. Based on the results from the mass balance study, the oral absorption is almost complete. No absolute oral bioavailability study was conducted. The absolute oral bioavailability is unknown.

Distribution

The plasma protein binding of pridopidine and its main metabolite TV-45065 is low (26-32% and 3.8-6.7%, respectively). The ratio of total radioactivity in blood and plasma ranged from 0.98 to 1.1 in the mass balance study, indicating that pridopidine does not distributes significantly into blood cells. The estimated apparent central volume of distribution for pridopidine was 7.2 L in healthy volunteers. Pridopidine is able to pass the blood-brain barrier, but it is unknown to what extent since no cerebrospinal fluid sampling was performed.

Metabolism

In vitro, pridopidine is slowly metabolised by human liver microsomes and human hepatocytes with ~97% of the pridopidine remaining in human liver microsomes after 2 hours and 79.6-88.7% of the pridopidine remaining in human hepatocytes. No other metabolites than TV-45065 were observed at any concentrations of pridopidine examined. TV-45065 is a not a pharmacologically active metabolite. *In vivo*, the metabolism of pridopidine is to TV-45065 with parent compound the major component in plasma (~20% metabolite and ~80% parent over a 1 to 24 h period). The majority of the radioactivity is eliminated in urine with the majority as TV-45065 after a single dose in CYP2D6 normal metabolisers and as parent in the CYP2D6 poor metaboliser subject. A schematic of the biotransformation pathways of pridopidine in humans following a single dose is shown in the figure below.

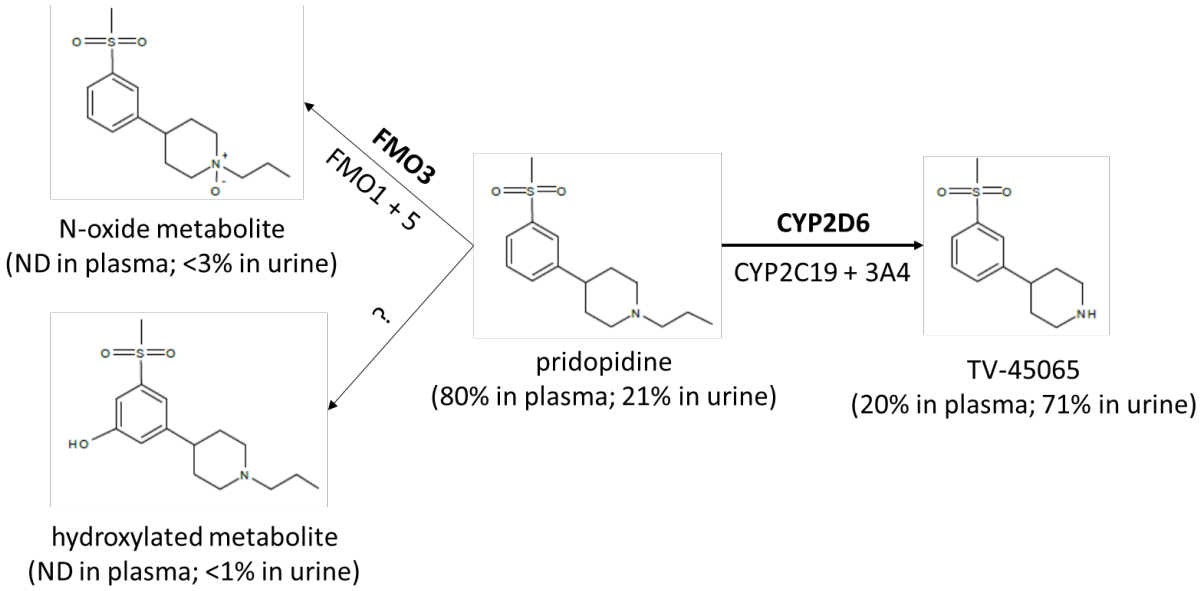


Figure 2: A schematic of the biotransformation pathways of pridopidine in humans following a single dose

Pridopidine is an auto-inhibitor of its own metabolism via CYP2D6. Therefore, the ratio between pridopidine and TV-45065 will change following multiple dosing; with a higher contribution of parent compound. Following repeated dosing, the Cmax decreased 1.9- to 2.7-fold and the AUC0-24,ss decreased 1.7- to 1.8-fold following twice daily dosing with 45 mg pridopidine.

CYP2D6 appears the major CYP enzyme responsible for the N-dealkylation of pridopidine to TV-45065, with a contribution of CYP3A4 and CYP2C19 to a lesser extent in CYP2D6 normal metabolisers. Flavin-containing monooxygenase 3 is the major enzyme responsible for the N-oxygenation of pridopidine to the N-oxide metabolite. CYP2C19 and 3A4 are most likely the major enzymes involved in the metabolism in CYP2D6 poor metabolisers. CYP3A5 is not involved in the metabolism.

Transporters

Pridopidine is not a substrate of P-glycoprotein, organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), multidrug and toxin extrusion protein 1 (MATE1), multidrug and toxin extrusion protein 2-K (MATE2-K), breast cancer resistance protein (BCRP), organic cation transporter 1 (OCT1), organic cation transporter 2 (OCT2), organic anion transporting polypeptide 1B1 (OATP1B1), organic anion transporting polypeptide 1B3 (OATP1B3), organic anion transporting polypeptide 1A2 (OATP1A2), or organic anion transporting polypeptide 2B1 (OATP2B1).

Elimination

The $t_{1/2}$ of pridopidine was ~9.5 h following a single dose of 45 mg pridopidine and 10.5 h following repeated twice daily dosing with 45 mg pridopidine. The renal clearance of pridopidine ranged from 75 mL/min to 122 mL/min and was not different after the first dose and steady-state. The renal clearance corresponds well to glomerular filtration rate in individuals with normal renal function.

The excretion of pridopidine related radioactivity is mainly via urine, only a small fraction (<2%) is eliminated via faeces. The elimination in urine is rapid and in-line with the observed $t_{1/2}$. The amount of pridopidine excreted in urine is ~25% after a single dose of 45 mg pridopidine and ~60% after twice daily repeated dosing with 45 mg pridopidine.

The metabolism and excretion indicate that pridopidine is an inhibitor of its own metabolism by CYP2D6, but that the renal elimination of pridopidine increases following repeated dosing and can

compensate the decreased metabolism. The $t_{1/2}$does not increases significantly following repeated dosing. However following repeated dosing the contribution of metabolism to the overall clearance decreases and the contribution of renal clearance increases.

Target population

The PK in HD was determined based on sparse blood sampling and popPK modelling. The exposure to pridopidine and its metabolite TV-45065 is higher in HD patients compared to healthy volunteers (~2-fold for pridopidine and ~1.5-fold for TV-45065), due to a lower clearance in patients versus healthy volunteers. No single factor was identified for the difference in clearance.

Special populations

The effect of renal impairment and CYP2D6 phenotype was investigated in clinical studies. The effect of hepatic impairment, gender, ethnic factors, body weight, and age on the PK of pridopidine was not investigated.

The effect of mild and moderate renal impairment on the PK of pridopidine and TV-45065 was investigated in a clinical study. The impact of severe renal impairment on pridopidine exposure has not been investigated. The C_{max} of pridopidine following single and repeated dosing with pridopidine is not affected by mild and moderate renal impairment. The AUC of pridopidine is also not affected by mild renal impairment. However, following single and repeated dosing with pridopidine, the AUC is increased ~1.7-fold in subjects with moderate renal impairment compared to normal renal function.

A clinical study was performed investigating the effect of CYP2D6 poor metaboliser versus CYP2D6 non-poor metaboliser on the PK of pridopidine and its major metabolite TV-45065. The C_{max} of pridopidine after the first dose was 1.8-fold higher and at steady state 1.2-fold higher in subjects that are CYP2D6 poor metabolisers compared to CYP2D6 normal metabolisers. The AUC of pridopidine after the first dose was 3.1-fold higher and at steady state 1.2-fold higher in subjects that are CYP2D6 poor metabolisers compared to CYP2D6 normal metabolisers. Furthermore, the exposure to pridopidine in ultra-rapid metabolisers is decreased ~2-fold compared to normal metabolisers. Pridopidine is an auto-inhibitor of CYP2D6 and therefore the decrease in difference following repeated dosing is most likely due to the CYP2D6 auto-inhibition by pridopidine. The C_{max} of TV-45065 after the first dose was 24-fold lower and at steady state 4.9-fold lower in subjects that are CYP2D6 poor metabolisers compared to CYP2D6 normal metabolisers. The AUC of pridopidine after the first dose was 5.8-fold lower and at steady state 6.7-fold lower in subjects that are CYP2D6 poor metabolisers compared to CYP2D6 normal metabolisers. The effect on exposure to TV-45065 by CYP2D6 phenotype was larger than the effect on the exposure to pridopidine, indicating that enzymes other than CYP2D6 are involved in the metabolism of pridopidine.

Most subjects in the clinical studies were <65 years of age. An overview of the age in the clinical studies in healthy volunteers and patients is provided in the Tables below.

Table 3: PK studies: number of subjects by age category

Study Number	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials, overall	9 / 210	1 / 210	0 / 210
ACR16C011	0 / 6	0 / 6	0 / 6
ACR16C012[a]	0 / 38	0 / 38	0 / 38
ACR16C013[b]	8 / 49	0 / 49	0 / 49
ACR16C016[c]	1 / 22	0 / 22	0 / 22
ACR16C018	0 / 36	0 / 36	0 / 36
TV7820-IMG-10082[d]	0 / 23	0 / 23	0 / 23
TV7820-DDI-10068[e]	0 / 28	0 / 28	0 / 28
ACR16IC010[f]	0 / 8	1 / 8	0 / 8

Source: Table SN0049.Q93.t.1.pk

[a] Study ACR16C012 enrolled 38 subjects, but only 36 subjects were included in the PK set.

[b] Study ACR16C013 enrolled 49 subjects, but only 48 subjects were included in the PK set.

[c] Study ACR16C016 enrolled 22 subjects, but only 21 subjects were included in the PK set.

[d] Study TV7820-IMG-10082 enrolled 23 subjects, but only 18 subjects were included in the PK set.

[e] Study TV7820-DDI-10068 enrolled 28 subjects, but only 22 subjects were included in the PK set.

[f] Study ACR16IC010 was a pharmacodynamic study (PET study to investigate regional cerebral glucose metabolism), which did not include pridopidine PK measurements. The study included 8 subjects.

PK=pharmacokinetic

Table 4: PK studies in patients: number of subjects by age category

	Age 65-74 (Older subjects number /total number)	Age 75-84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled trials Total n=1629	175/1629 (10.7%)	20/1629 (1.2%)	2/1629 (0.1%)
Non-controlled trials Total n=1368	142/1368 (10.4%)	14/1368 (1.0%)	1/1368 (0.1%)

Pharmacokinetic interaction studies

Pridopidine as victim

In vitro studies indicated that pridopidine is a substrate of CYP2C19, CYP2D6, and CYP3A4. Pridopidine is an auto-inhibitor of its own metabolism via CYP2D6. CYP2D6 is the major enzyme in CYP2D6 non-poor metabolisers and CYP2C19 and 3A4 most likely in CYP2D6 poor metabolisers. No clinical DDI studies with pridopidine as victim were conducted. The lack of a clinical study with pridopidine as victim of CYP2D6 inhibitors is agreed, since CYP2D6 inhibitors would lead to a similar exposure as in CYP2D6 poor metabolisers. The metabolism of pridopidine in CYP2D6 poor metabolisers is too limited to warrant clinical DDI studies with CYP2C19 and 3A4 studies (87% of the dose is eliminated unmetabolised in urine, the renal clearance is similar to the GFR, and pridopidine is not a substrate of renal transporters).

Pridopidine as perpetrator

In vitro studies were conducted to investigate the inhibition and induction potential of pridopidine towards CYPs and transporters. In vitro studies indicate that pridopidine is a direct inhibitor of CYP2D6 at maximal systemic and maximal intestinal concentrations. At clinically relevant concentrations, pridopidine also causes time-dependent inhibition of CYP2D6. Pridopidine is an inhibitor of OCT1 at maximal portal vein concentrations. At maximal systemic concentrations pridopidine is an inhibitor of MATE1. Pridopidine is not an inducer via AhR, CAR and PXR at clinically relevant concentrations.

Clinical DDI studies were conducted with pridopidine following repeated dosing (to take the accumulation of pridopidine following repeated dosing into account) to investigate the inhibition potential of pridopidine towards CYP2D6 (direct and time-dependent inhibitor) and the transporters OCT1 and MATE1. Metoprolol was used as reference substrate for CYP2D6 and metformin as reference substrate for (OCT1 and MATE1). The Cmax of metoprolol was increased 3.5-fold and the AUC by 6.6-fold when given concomitantly with pridopidine. The Cmax and AUC of metformin were similar in the absence and presence of pridopidine. The clinical studies indicate that pridopidine is a strong inhibitor of CYP2D6, but not of OCT1 and MATE1.

Exposure relevant for safety evaluation

For a pridopidine dose of 45 mg twice daily, Cmax was estimated at 618 ng/mL while AUC0-24 was estimated at 13100 ng × h/mL. For the main metabolite TV-45065, Cmax was 36.1 ng/mL and AUC0-24 was 674 ng × h/mL.

2.6.2.2. Pharmacodynamics

Mechanism of action

Pridopidine, a novel small molecule, is a highly selective and potent S1R agonist shown to exert neuroprotective effects in preclinical models of HD and other neurodegenerative diseases. At an exposure corresponding to that of the clinically recommended dose of 45 mg twice daily (bid), pridopidine shows selective and robust occupancy of the S1R in the human brain (>90% S1R occupancy) (Grachev et al 2021), demonstrating that its dominant pharmacological effect at this dosage is mediated via the S1R.

Through modulation of S1R activity, pridopidine exerts neuroprotective effects (see non-clinical section). Specifically, pridopidine improves key pathophysiological pathways implicated in HD including rescue of the mitochondrial associated membrane disruption (Naia et al 2021), enhancement of BDNF secretion and signalling (Geva et al 2016, Lenoir et al 2022), restoration of aberrant calcium signalling (Ryskamp et al 2017), rescue of synaptic plasticity and neuronal spine abnormalities (Smith-Dijak et al 2019), enhancement of autophagy (Wang et al 2023 and unpublished data), upregulation of mitochondrial function (Naia et al 2021), reduction of endoplasmic reticulum and oxidative stress (Shenkman et al 2021), and rescue of mHTT-induced cell death (Eddings et al 2019). These effects are mediated via the S1R, as either genetic deletion of the S1R gene or pharmacological S1R inhibition completely abolishes the effect of pridopidine.

Primary and Secondary pharmacology

Study ACR16IC010 (Regional Cerebral Metabolic Rate of Glucose Consumption)

Background

Regional Cerebral Metabolic Rate of Glucose Consumption (rCMRGlc) allows for quantitative determination of the cerebral metabolic rate of glucose utilisation. Cortical rCMRGlc is lower in patients with HD, and the severity of HD symptoms has been shown to correlate with relative reduction in glucose metabolism (Kuwert et al 1990).

Methods

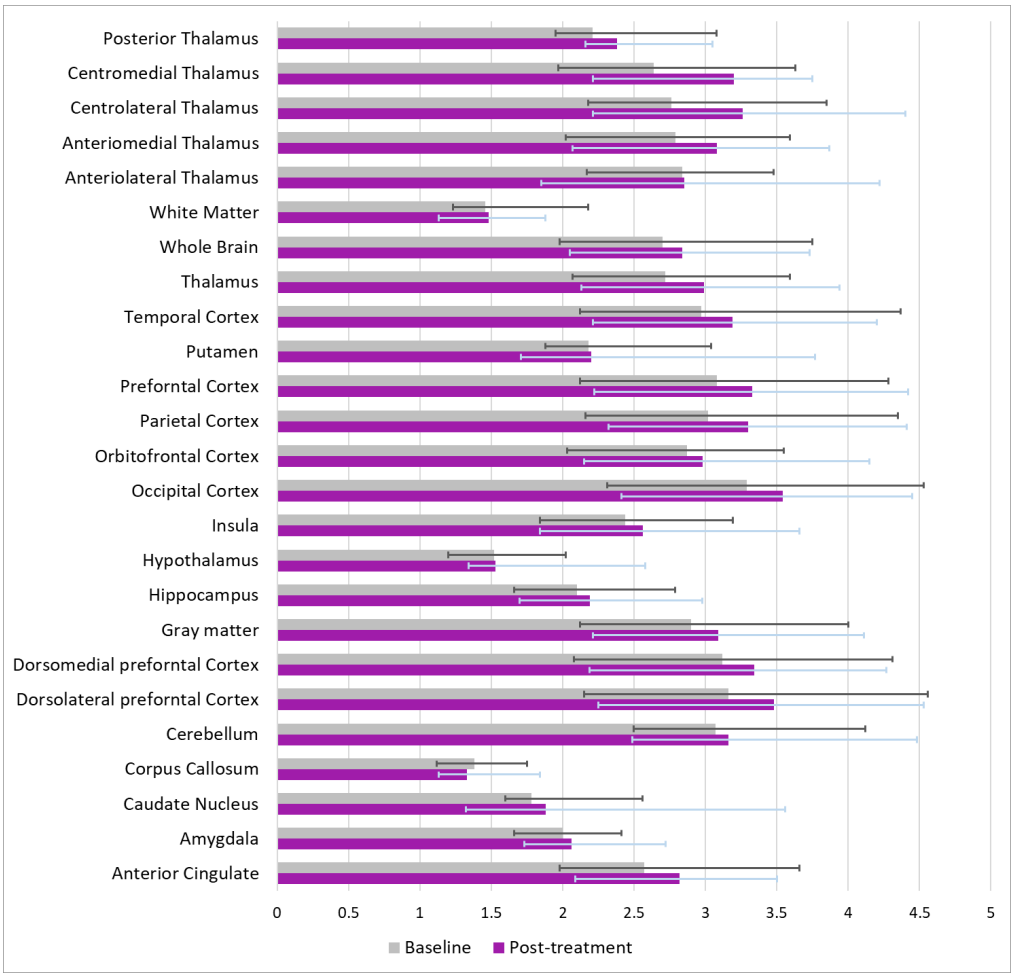
This was an open-label, single-sequence, Phase 1b study in adult male and female patients with HD. Participants underwent a magnetic resonance imaging (MRI) scan to confirm structural integrity of the brain and an FDG PET scan to assess the rCMRGlc at baseline. Thereafter, participants received 7 days of pridopidine 45 mg qd followed by 7 days of pridopidine 45 mg bid. A second FDG PET scan was carried out on Day 14. An MRI was co-registered to delineate anatomical brain regions and regions of interest (ROIs). RCMRGlc in each brain region was calculated using the measured tissue concentration of tracer at time T, multiplied by plasma glucose concentration, divided by lumped constant and the integral of glucose input function from time 0 to T.

Descriptive statistics were used for rCMRGIc of all ROIs at baseline and end of treatment. ANOVA was performed to analyse changes from baseline to end of treatment for each ROI. Exploratory voxel analyses, using statistical parametric mapping (SPM), were carried out to determine whether there were statistically significant local changes in metabolic activity. Pre- and post-treatment images were analysed by a paired t-test.

Results

Eight (8) patients with HD were enrolled (4 male; 4 female). Mean (SD) age was 52.8 (11.2) years.

There were no statistically significant changes in metabolic activity in the grey matter before and after pridopidine treatment. Exploratory SPM analysis revealed statistically significant increased metabolic activity after pridopidine treatment in several brain regions that the applicants finds relevant for HD, i.e., precuneus (Z-score = 5.78), left superior temporal gyrus (Z-score = 5.16), left middle frontal gyrus/premotor area (Z-score = 5.09) and left medial dorsal nucleus of the thalamus (Z-score = 4.36).



Min and max values are shown by grey (baseline) and blue (post-treatment) error bars. Data from 8 patients.

Figure 3. Median rCMRGIc (mg/100g/min) at baseline and after pridopidine treatment for examined regions of interest – study ACR16IC010.

Study TV7820-IMG-10082 (S1R and D2/D3rReceptor occupancy)

Methods

Receptor occupancy of S1R and D2/D3R in the living human brain was evaluated at the proposed dose of pridopidine (90 mg single dose, comparable to 45 mg bid at steady state).

This was a study in healthy male subjects and male HD patients. CYP2D6 PMs were excluded. Pridopidine doses of 0.5 mg, 1 mg, 5 mg, 22.5 mg, 45 mg and 90 mg were evaluated. PET scans were performed pre-dose and 2 hours after administration of a single dose pridopidine.

For S1R occupancy, PET scans in presence of [18F]fluspidine were carried in healthy volunteers (all doses) and in HD patients (90 mg dose). For D2/D3R occupancy, PET scans in presence of [18F]fallypride were carried out in healthy subjects (all doses).

Plasma samples were taken before and up to 24 hours after dosing, to determine the PK profile of pridopidine and TV-45065.

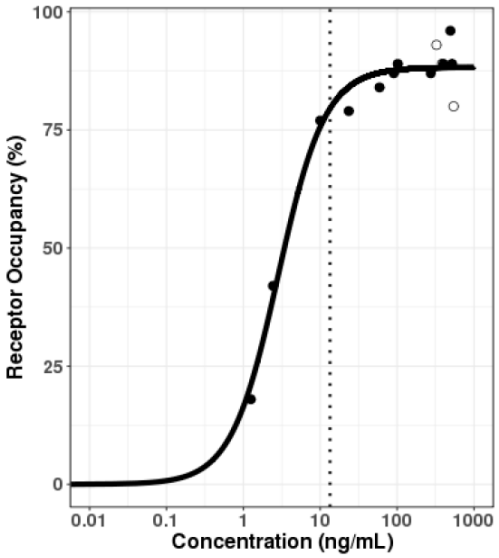
The RO of pridopidine to S1R was estimated from kinetic modelling parameters obtained before and after dosing with pridopidine using a 1 tissue compartment model. Since a suitable reference region was not yet determined for S1R in the brain, a metabolite corrected input function from arterial plasma was obtained. The occupancy data were combined with the administered pridopidine dose in mg to

graphically derive the in vivo affinity of pridopidine to S1R. The RO of pridopidine to D2/D3Rs was estimated from kinetic modelling parameters obtained before and after dosing with pridopidine using the cerebellum as a reference region and a simplified reference tissue model.

Spatial normalisation of the PET scan to a brain atlas template was performed using a corresponding MRI scan. All PET parameters were calculated globally, for the whole brain, and for specific predefined brain areas.

Results

The PK profile in healthy subjects and HD patients showed rapid absorption of pridopidine with median tmax varying between 1 and 2 hours. At single dose of pridopidine 90 mg (which results in comparable plasma exposure as the therapeutic pridopidine dosing of 45 mg bid at steady state), S1R occupancy was approximately 90% both in healthy subjects and HD patients (Figure 4).



Source: Study TV7820-IMG-10082 Imaging Report, Figure 2. Receptor occupancy was modelled with average pridopidine concentration as covariate, and with a Hill coefficient estimated at 1.42. Filled circles: healthy subjects; empty circles: HD patients; dotted line: EC_{90}.

Figure 4: TV7820-IMG-10082: S1R occupancy as a function of pridopidine exposure

After administration of pridopidine 90 mg, a small decrease in D2/D3R [18F]fallypride volume of distribution was observed (3.3%) indicating pridopidine has low occupancy of D2/D3R (Table 5).

Table 5: TV7820-IMG-10082 - S1R occupancy and D2/D3R 0ccupancy in healthy subjects

Population	Pridopidine (mg)	Number of Subjects	Mean RO, % (SD)	Min; Max, RO %
S1R Occupancy				
HD Patients	90	3	87.37 (6.51)	80.36; 93.23
Healthy	90	3	91.21 (3.87)	88.82; 95.67
Healthy	45	1	87.19 (NA)	87.19; 87.19
Healthy	22.5	3	86.67 (2.59)	84.06; 89.24
Healthy	5	2	77.96 (1.71)	76.75; 79.16
Healthy	1	1	41.77 (NA)	41.77; 41.77
Healthy	0.5	1	17.55 (NA)	17.55; 17.55
D2/D3R Occupancy				
Healthy	90	4	3.34 (2.05)	1.81; 6.14

Source: Study TV7820-IMG-10082, Table 16 D2R=dopamine-2 receptor; D3R=dopamine-3 receptor; HD=Huntington's disease; NA=not applicable; RO=receptor occupancy; S1R=sigma-1 receptor.

Study TV7820-CNS-20002 (PRIDE-HD) - effect of Pridopidine on QT Interval

An exposure-response analysis was carried on PK and ECGs data from PRIDE-HD in HD patients as results in healthy subjects suggested a dose-dependent QT interval corrected by Fridericia´s formula (QTcF) prolongation of potential clinical relevance. For 45 mg bid, ΔΔQTcF reached 18.4 msec and 18.0 msec 1 h after the morning and afternoon dose, respectively (study ACR16C018).

Methods

Concentration-QTc (C-QTc) analyses are an alternative way to evaluate QTc effects in the absence of thorough QT studies. The primary criterion is that the upper bound of the two-sided 90% confidence interval (CI) for the QTc effect is <10 msec at the highest clinically relevant exposure (EMA/CHMP/ICH/310133/2008).

For details on the study design of PRIDE-HD, refer to section 2.6.5.1.

Triplicate ECGs were carried out in 402 patients, before and 1 to 2 hours after the study drug administration (first morning dose). PK samples were collected at the same time pre-dose and 1 to 2 hours after study drug administration (after ECG; Table 6). All ECGs were centrally read by semi-automated measurement techniques.

Table 6: PRIDE-HD: schedule for ECG measurement and PK sample collection

Visit	Pre-dose	1-2 Hours Post-dose
Baseline/Day 1	√	√
Week 2	--	√
Week 4	√	√
Week 6	√	√
Week 12	--	√
Week 16	√	√
Week 20	--	√
Week 26	√	--
Week 52/LOV	√	--

Source: TV7820-CNS-20002 exposure response report, Table 1; ECG=electrocardiogram; LOV=last office visit.

For the primary analysis, data up to week 26 were used. A sensitivity analysis was performed including week 52/LOV data. ECGs were paired with PK samples (n=3071) and were used for the development of a cardiac C-QTc model. In total, there were 2753 ECGs from pridopidine-treated patients and 763 from placebo-treated patients. Linear mixed-effects modelling was used to describe the relationship between exposure (geometric mean Cmax, covariate) and ΔQTcF (dependent variable), with time and treatment (placebo, pridopidine) as fixed factors.

Results

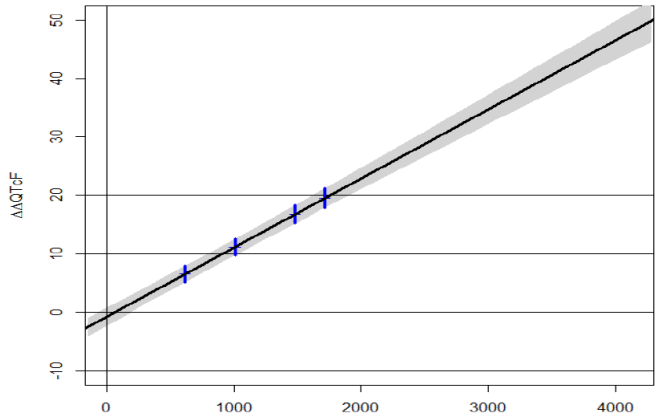
Overall, pridopidine causes a dose-dependent increase in QTcF. In the placebo group, mean change from baseline QTcF was very small across all post-dosing timepoints, with values varying between-–1.4 and 0.7 msec. Pridopidine's effect on QTcF prolongation corresponded to its plasma concentration with its effect increasing up to week 6 and plateauing thereafter. At 45 mg bid, the largest mean placebo-corrected ΔQTcF at any post-dosing timepoint was 8.3 msec (week 20 post-dose). The predicted placebo-corrected ΔΔQTcF, 90% CI at steady state plasma concentrations with 45 mg bid is 6.6 ms (geometric mean of 618 ng/mL), with an upper bound of 8 ms (ΔΔQTcF 90% CI). At 67.5 mg bid, the predicted mean effect is 11.2 ms (upper bound of 90% CI: 12.6 ms) (Table 7).

Table 7: Predicted ΔΔQTcF by observed pridopidine exposure

Pridopidine Dose	Geometric Mean C_{max} [ng/mL]	ΔΔQTcF [msec]	SE	90% CI [msec]
45 mg bid	618	6.6	0.85	5.2, 8.0
67.5 mg bid	1008	11.2	0.87	9.7, 12.6
90 mg bid	1480	16.7	0.96	15.2, 18.3
112.5 mg bid	1717	19.5	1.02	17.9, 21.2

Source: TV7820-CNS-20002 exposure-response report, Table 4 bid=twice daily; CI=confidence interval; C_{max}=observed maximum concentration; ΔΔQTcF=placebo-corrected change-from-baseline QT interval corrected by Fridericia formula; SE=standard error.

Pridopidine plasma concentrations around 900 ng/mL were predicted to result in a QT effect <10 msec and plasma concentrations around 1800 ng/mL predicted to result in QT effects <20 msec, as deemed by the upper bound of the 90% CI of the predicted effect (Figure 5). A sensitivity analysis including data from Week 52 showed similar results.



Source: TV7820-CNS-20002 exposure-response report, Figure 5; X-axis: pridopidine concentration (ng/mL); Y-axis: ΔΔQTcF in msec; Grey shading: 90% confidence interval.

Figure 5. PRIDE-HD predicted ΔΔQTcF at observed Geometric C_{max} of pridopidine

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

Analytical methods

Most analytical methods used appear to be sufficiently validated and suitable for the analysis of pridopidine and TV-45065. A cross-validation was performed of the analytical method used by the test facilities. Furthermore, the analytical method was added as covariate to the updated PopPK model. Analytical method was not identified as significant covariate. It seems therefore unlikely that the different analytical methods used for the measurement of pridopidine would affect the PK parameters.

PopPK modelling

An effect of patient status was identified on the rate of absorption of pridopidine into the central compartment. The applicant did not provide reasoning for the different absorption rate in patients versus healthy volunteers. HD patients are known to have gastrointestinal dysfunction (Ekwudo et al., 2025) which could impact the absorption. However, since only sparse sampling was performed in patients, the effect of difference in absorption cannot be identified. The incorporation of difference in absorption rate is a way to fit the data into the model. Furthermore, clearance was identified to be lower in patients compared to healthy volunteers. Also no reasoning for this observation was provided by the applicant, but is also solely based on sparse sampling. The issues raised for the popPK model could have been resolved when full sampling was performed in a subset of patients.

Exposure-response modelling

No therapeutic window could be determined, since no efficacy was observed.

Pharmacokinetics in healthy volunteers

Absorption

No absolute oral bioavailability study was conducted. Oral absorption is almost complete. Based on the amount pridopidine excreted in urine, the absolute oral bioavailability is at least 9% to 61% and is on average at least 28% following a single dose in CYP2D6 non-poor metabolisers and is highly variable. The absolute oral bioavailability may be increased following repeated dosing, since pridopidine is an auto-inhibitor of its own metabolism and the first pass metabolism could decrease following repeated dosing. Furthermore, the absolute oral bioavailability is most likely higher in CYP2D6 poor metabolisers compared to CYP2D6 non-poor metabolisers.

No overview was provided which capsule formulation was used in which study which is acceptable if formulation does not affect the exposure. Similar dissolution was shown using the quality control dissolution method. Differences in exposure in the different clinical studies were observed.

Metabolism

The applicant provided the metabolite profile in plasma from the mass balance study for all subjects and not per subject and per CYP2D6 phenotype.

Pharmacokinetics in target population

For a better understanding of the PK of pridopidine and TV-45065 in patients with HD and understanding possible differences in PK between patients and healthy volunteers, the applicant should have investigated the PK in a few patients using full sampling.

HD patients appear to have a higher exposure to pridopidine and TV-45065 compared to healthy volunteers.

Special populations

No therapeutic window can be determined and therefore it can also not be determined if the covariates patients status, CYP2D6 phenotype, renal impairment, hepatic impairment, gender, body weight, ethnic origin, and age are clinically relevant.

DDIs

Non-clinical data indicated that pridopidine is potentially teratogenic. Therefore, a clinical DDI study with oral contraceptives should be conducted, since the patient population partly consists of female patients of reproductive age. The applicant acknowledges the need for an additional clinical DDI study to assess the effect of pridopidine on oral contraceptives. The applicant committed to provide the study outcome in Q4 2026.

Pharmacodynamics

Mechanism of action

The putative mechanism of pridopidine in HD is through non disease-specific neuroprotection via agonism of the S1R, thereby influencing pathways affected in HD. There is evidence that S1R agonism can be therapeutically beneficial (e.g., S1R agonists fluvoxamine and fluoxetine in depression). However, clinical benefit of S1R agonism in neurodegenerative diseases and HD specifically has not been established.

A link specific to HD pathology was reduction of mHTT aggregates after overexpression of S1R in vitro. However, the in vivo proof-of-concept of pridopidine is limited. Consequently and especially in a therapeutic area of many failed effects studies as HD, to establish pridopidine as treatment in HD the clinical data need to be particularly compelling.

Primary pharmacology

TV7820-IMG-10082 was a PET study assessing affinity of pridopidine to S1R and D2/D3R in the brain.

At Cmax,ss levels of 45 mg bid, pridopidine was brain-penetrant and had high-affinity for S1R in healthy volunteers and HD patients (~90% occupancy in HD patients). These data support that pridopidine is brain-penetrant S1R ligand in the target population, and support dose selection of 45 mg bid.

In TV7820-IMG-10082, D2/D2R occupancy was relatively low in healthy volunteers (mean 3.3%), but was not measured in HD patients. It is uncertain if extrapolation from healthy subjects to HD patients can be readily made as a) blood-brain-barrier function may be altered in HD, and b) S1R- and D2/D3R receptor-interactions may differ in HD. Nonetheless, it is considered unlikely that these functions are changed to such an extent in HD to alter the conclusion that pridopidine mainly targets S1R. Hence, the lack of data on D2/D2R occupancy in HD patients will not be further pursued. This uncertainty does mean that potential effects on D2/D3R cannot be excluded and are taken into account at the efficacy and safety assessment.

ACR16IC010 was a PET-FDG study assessing changes in cerebral glucose consumption in HD patients. No significant changes were observed but exploratory statistical parametric mapping showed increased metabolic activity in several brain regions that the applicant considers relevant for HD.

ACR16IC010 is considered of limited use to support the action mechanism of pridopidine. ACR16IC010 was based on the hypothesis that pridopidine was primarily a D2/D3R ligand with rapid effects (i.e., within weeks). However, the currently proposed mechanism is long-term treatment via S1R agonism. The applicant discussed a link between cerebral glucose consumption and HD, but did not for pridopidine and glucose consumption other than indicating that S1R agonism, amongst others, may improve mitochondrial function. In addition, ACR16IC010 was not placebo-controlled. Hence, without a firm mechanistic basis, the effects seen on exploratory mapping cannot to be readily attributed to pridopidine, nor can it be considered proof that pridopidine has therapeutic benefit in HD. However, no questions apply that would impact the overall benefit-risk balance.

Secondary pharmacology

An exposure-response analysis was carried out using PRIDE-HD data from HD patients, as potentially clinically relevant and dose-dependent QTcF prolongation were observed in the healthy volunteer study ACR16C018 (ΔΔQTcF increase of 18-18.4 msec in the 45 mg bid group; 90% upper bound CI was a prolongation of 23.3-23.7 msec). According to guidance, the upper bound of the two-sided 90% CI for the QTc effect should be <10 msec at the highest clinically relevant exposure to state that there is no relevant QTc prolongation (EMA/CHMP/ICH/310133/2008).

In advice in 2017, CHMP considered this analysis in PRIDE-HD simplistic and unsuitable to assess the impact of inter-individual variability. A popPKPD model was proposed. However, as discussed above, the popPK model provided at this MAA is not adequate. No rationale could be provided why the QTc data are convincing without the popPK model.

ECGs were assessed baseline-adjusted and semi-automated, according to guidance (EMA/CHMP/ICH/310133/2008). The population studies in PRIDE-HD was representative for the target population in terms of gender and age, both factors known to increase risk of prolonging QTc.

The applicant argues that there was no evidence for increased risk for clinically meaningful QT prolongation as the 90% CI upper bound for 45mg bid (618ng/mL) was 8 msec (i.e., <10 msec). A dose-dependent increase was observed; QT prolongation of 10 msec is expected at an exposure of 900 ng/mL.

This is not agreed. The data are not reassuring as there are concerns on (inter-individual) variability. Relevant QTc prolongation is expected at a concentration of 900 ng/mL, not far above that of the proposed dose (618 ng/mL). Similarly the 90% CI upper bound was not far of the margin (8 msec vs 10 msec). The following concerns apply:

In PRIDE-HD only ECGs after the morning dose were conducted. ACR16C018 data indicate that QTC prolongation varied between morning and afternoon doses. Influence of pridopidine on circadian rhythm cannot be excluded; e.g., another S1R agonist donepezil restored rhythmicity of the clock gene expression in neurons. (Kenche et al., 2021) Inference of drug-induced QTc prolongation may be misleading if the drug effect on QTc circadian rhythm is unaddressed. (Huh et al., 2020). The applicant indicates that as the time of ECG assessments and PK sampling relative to pridopidine administration was recorded and is considered in the exposure response modelling, a potential impact of circadian rhythm has been taken into account implicitly. This further indicates that the effect on QTc interval prolongation cannot be reliably assessed without an appropriate popPK model.

Moreover, data are lacking for multiple factors which may influence exposure but (e.g., hepatic/renal impairment, poor CYP2D6 metabolisers, ethnic factors, body weight). In their response, the applicant only focused on hepatic/renal impairment and poor CYP2D6 metabolisers. The concerns regarding these groups remain.

Further, medications that are often concomitant used in HD (e.g., citalopram) prolong the QT interval, further increasing the risk for clinically meaningful QT prolongation. A warning has been added to section 4.5 of the proposed SmPC.

Although the popPK model is still inadequate, it indicated that patients with severe renal impairment are at risk for QT prolongation with the proposed dose. Hence, the contraindication for pridopidine use in patients with severe renal impairment is agreed. In the proposed SmPC also warnings and precautions are included for patients with mild renal impairment, which are also agreed.

Altogether, the exposure-response data currently do not convince that there is no risk that pridopidine 45mg bid prolongs QTc to a relevant extent. This risk for QT prolongation is supported by non-clinical observations. Therefore, it is agreed to include it in the Safety Specification as 'important potential risk' in the proposed RMP although then worded as 'arrhythmias including Torsades de points'

2.6.4. Conclusions on clinical pharmacology

Pharmacokinetics

The clinical pharmacology of pridopidine was assessed in healthy volunteers and patients with HD. No therapeutic window can be determined and therefore it can also not be determined if the covariates

patients status, CYP2D6 phenotype, renal impairment, hepatic impairment, gender, body weight, ethnic origin, and age are clinically relevant.

Pharmacodynamics

The provided data support that pridopidine is brain-penetrant S1R agonist with high occupancy at the proposed 45 mg bid dose in the target population. Pridopidine potentially has an indirect treatment effect in HD. The evidence to support that S1R engagement by pridopidine results in (potentially) therapeutic effects is weak. Hence, the basis on which efficacy of pridopidine is claimed is not robust from a pharmacological perspective and warrants strong evidence from (non-)clinical studies.

Moreover, the ECG analysis of PRIDE-HD currently does not reassure that there is no risk for QT prolongation at 45mg bid due to concerns on (inter-individual) variability. This risk for QT prolongation is supported by non-clinical observations. Therefore, it is agreed to include it in the Safety Specification as 'important identified risk' (although then worded as 'Arrhythmias including torsades de points')

The concern on QT prolongation is further supported by observations in patients with moderate renal impairment, which show an increase in the frequency of adverse events. Based on these clinical findings and the data from the popPK model, a warning and precaution for use was included for patients with moderate renal impairment and patients with severe renal impairment are contraindicated.

2.6.5. Clinical efficacy

Table 8: Clinical studies

Study ID	Enrolment status Start date Total enrolment/ enrolment goal	Design Control type	Study & control drugs Dose, route of administration and duration Regimen	Population Main inclusion/ exclusion criteria
PROOF-HD (Phase 3) PL101HD301 Incl. OLE	Start: Oct 2020 Completed: mar 2023 *Enrolment* Planned: 480 Actual: 499 Pr 45 mg bid = 250; Placebo = 249 OLE: results pending	R, DB, PC	Pridopidine 45 mg bid or placebo Duration: 65-78 weeks (common closing design)	- HD patients ≥25 years, with onset of signs and symptoms ≥18 years of age. - Baseline TFC 7-13
PRIDE-HD (Phase 2) TV7820-CNS-20002 Incl. OLE	Start: feb2014 End: jul2016 *Enrolment* Planned: 400 Actual: 408 Pr 45 mg bid: 81 Pr 67.5 mg bid: 82 Pr 90 mg bid: 81 Pr 112.5 mg bid: 82 Placebo: 82 OLE: Pr 45 mg bid: 248	R, DB, PC	Pridopidine 45, 67.5, 90, or 112.5 mg bid, or placebo Duration: 52 weeks OLE: pridopidine 45 mg bid for 104 weeks (+2 weeks FU)	- HD patients ≥21 years, with onset of signs and symptoms ≥18 years of age. - Baseline TFC 0-13
MermaiHD (Phase 3) ACR16C008 Incl. OLE	Start: Apr 2008 End: Nov 2009 *Enrolment* Planned: 420 Actual: 437 Pr 45 mg qd: 148 Pr 45 mg bid: 145	R, DB, PC	Pridopidine 45 mg qd or bid, or placebo Duration: 26 weeks OLE: pridopidine 45 mg bid for 26 weeks	- HD patients ≥30 years - Baseline TFC 0-13

	Placebo: 144 OLE: Pr 45 mg bid: 353			
HART (Phase 2b) ACR16C009 Incl. OLE	Start: Oct 2008 End: Jul 2010 *Enrolment* Planned: 220 Actual: 227 Pr 10 mg bid: 56 Pr 22.5 mg bid: 55 Pr 45 mg bid: 58 Placebo: 58 OLE: Pr 45 mg bid: 134	R, DB, PC	Pridopidine 10, 22.5 or 45 mg bid, or placebo Duration: 12 weeks OLE: pridopidine 45mg bid for 72 months*	- HD patients ≥30 years - Baseline TFC 0-13

*bid = twice daily; BL = baseline; DB = double-blind; HD = Huntington's disease; IEA = integrated efficacy analysis; OLE = open-label extension; Pr = pridopidine; PC = placebo-controlled; qd = once daily; R = randomised; TFC = Total Functional Capacity; US = United States. *: open-HART was planned to continue until pridopidine was authorised in Canada or USA or discontinued due to risk-benefit or commercial reasons*

2.6.5.1. Dose-response studies

Study Design

- **Overall design**

The PRIDE-HD study (PRIdopidine Dose Evaluation in Huntington's Disease, Study TV7820-CNS-20002, EudraCT Number: 2013-001888-23) was conducted at 53 sites (Europe, Australia, North America).

A total of 400 patients were planned to be randomised (1:1:1:1:1) to receive one of four pridopidine doses (45 mg bid, 67.5 mg bid, 90 mg bid or 112.5 mg bid) or placebo bid for 52 weeks, with the first patient randomised in February 2014 and the last patient last visit in July 2016. The study was followed by an OLE.

Patients were stratified at randomisation according to neuroleptic use (yes/no). The study consisted of a screening period, a 52-week double-blind treatment period (including a 4-week titration period), and a safety follow-up period (1 week after last dose).

The statistical model used was a repeated measures model with visit by treatment interaction, country, neuroleptic use or no use, baseline value, and visit by baseline interaction as fixed effects. The analysis population was the full analysis set (FAS), which are patients with baseline and at least 1 post-baseline assessment of the respective endpoint.

- **Study population**

Main inclusion criteria:

- Adult patients ≥21 years old weighing ≥50 kg, with a diagnosis of HD based on clinical features (diagnosed after 18 years old) and presence of ≥36 CAG repeats in the Huntingtin gene.
- A sum of ≥25 points on the total motor score (TMS) assessment at the screening visit.
- An Independence Scale (IS) score ≤90% at the screening visit.

Main exclusion criteria were creatinine clearance <60 mL/min at screening and otherwise were mainly safety related (e.g., abnormal QT interval or known history of long QT syndrome; clinically significant heart disease; active suicidal ideation or presenting a serious risk for suicide, or other serious medical illnesses).

- **Prohibited medication**

Following were not allowed from 6 weeks of baseline:

- Antipsychotics: ziprasidone, clozapine, haloperidol, mesoridazine, thioridazine, pimozide, zuclopenthixol, chlorpromazine, paliperidone, iloperidone, fluphenazine, prochlorperazine, trifluoperazine/trifluroperazine, flupentixol, benperidol, amisulpride, and sulpiride
- Antidepressants: lithium, trazodone, amitriptyline, nortriptyline, imipramine, desipramine, maprotiline, doxepin, clomipramine, protriptyline, amoxapine, citalopram, escitalopram, and fluoxetine
- Antiarrhythmics: disopyramide, procainamide, quinidine, flecainide, propafenone, amiodarone, dofetilide, ibutilide, and sotalol
- Medications Lowering Seizure Thresholds: maprotiline, dipipanone, dihydrocodeine, methadone, oxycodone, papaveretum, pentazocine, and tramadol
- Others due to QT effects or CYP interaction: astemizole, terfenadine, azithromycin, erythromycin, moxifloxacin, pentamidine, sparfloxacin, clarithromycin, chloroquine, halofantrine, bepridil, cisapride, domperidone, droperidol, levomethadyl, methadone, codeine, tramadol, sevoflurane, and tamoxifene.

- **Objectives and endpoints**

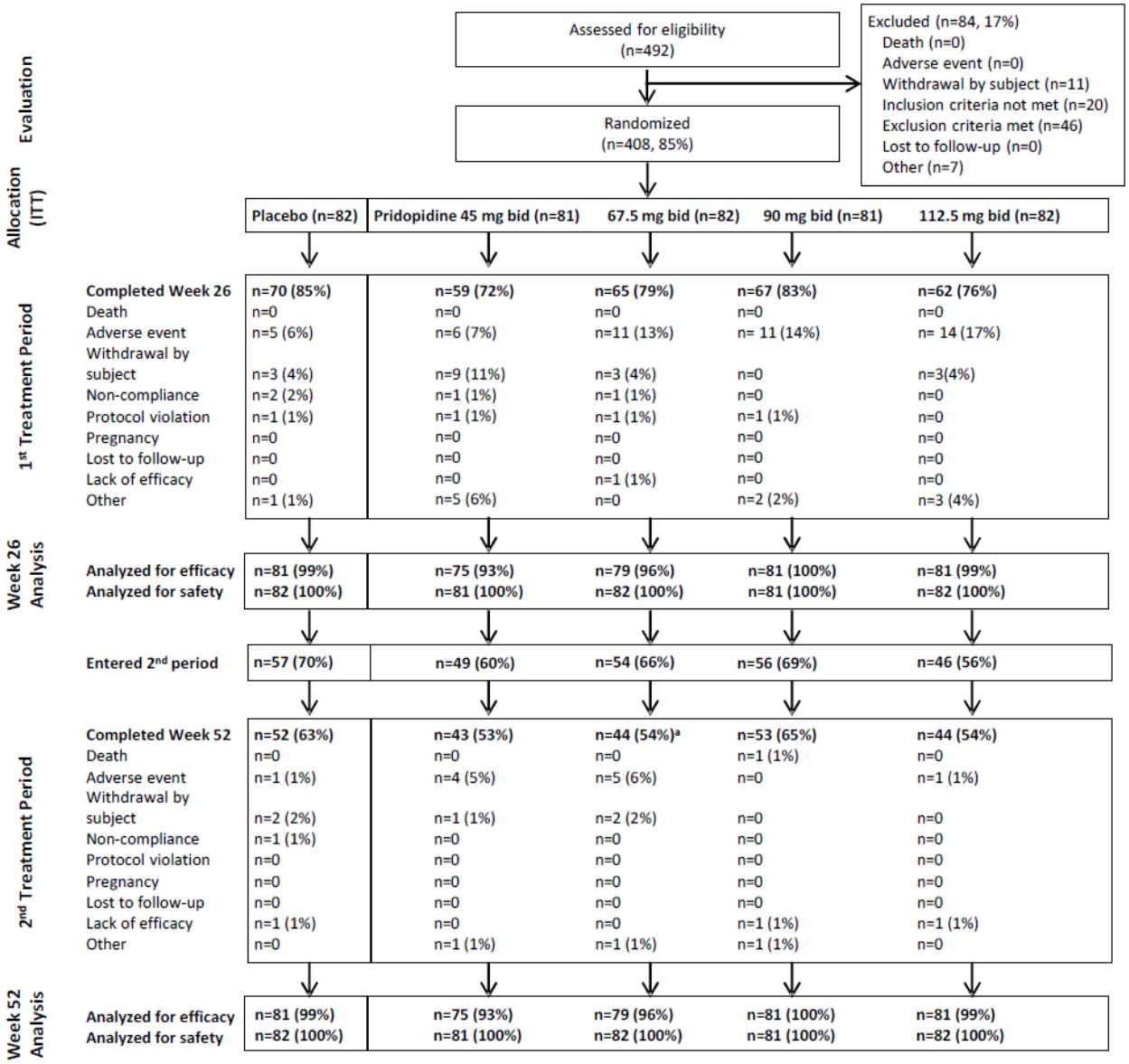
The primary endpoint was change from baseline to week 26 in total motor score (TMS). Other secondary and exploratory endpoints included TFC, Quantitative motor (Q-Motor), and Huntington's Disease health-related Quality of Life questionnaire (HD-QoL).

Results

When PRIDE-HD was designed, pridopidine was thought to act primarily as a dopamine D2/D3 receptor antagonist, but during the conduct evidence emerged that showed that pridopidine was mainly an S1R agonist. The study was amended during conduct to extend the double-blind period to 52 weeks. This allowed for the assessment of the impact of pridopidine on functional decline using TFC. The applicant indicated that a minimum of 52 weeks is needed for the placebo group to decline in TFC thereby allowing a window to detect a therapeutic effect of a drug (Marder et al., 2000).

- **Patient Disposition and Baseline Characteristics**

Overall, 408 patients received at least one dose of study drug. A total of 323 (79%) patients completed the first 26 weeks of the study. Among these, 262 (64%) continued to the extended double-blind period and 236 (58%) completed 52 weeks of treatment. Approximately 19% of patients had completed the double-blind study period of 26 weeks prior to Institutional Review Board approval for the study extension. These patients were unable to enter the double-blinded extension period up to Week 52, but could directly enrol in the OLE study.



a An additional 2 patients entered the second study period, but did not receive study drug and are therefore not included. bid = twice daily; ITT = intent-to-treat; n = number of subjects. Note: Numbers in parentheses are numbers of patients followed by percentage of patient population.

Figure 6: Pride-HD patient flow (all subjects)

Baseline demographics and disease characteristics were balanced between groups. The mean (SD) age was 50.4 (11.85) years; CAG repeat length was 44.7 (4.18). The majority were white (378 [93%]), and proportion of male and females was equal (50%:50%). Overall, 157 (38%) used a neuroleptic at baseline. Vesicular monoamine transporter 2 (VMAT2) inhibitors were not allowed in PRIDE-HD. The median TFC score at baseline was 8.0 in all groups (range between 0-13; Table 9).

Table 9: Baseline TFC scores in PRIDE-HD (FAS)

Variable	Time point Statistic	Placebo (N=81)	Pridopidine 45 mg bid (N=75)	Pridopidine 67.5 mg bid (N=79)	Pridopidine 90 mg bid (N=81)	Pridopidine 112.5 mg bid (N=81)
Total Functional Capacity	Baseline					
	n	81	75	79	81	81
	Mean	7.9	8.1	7.8	7.8	8.0
	SD	2.49	2.70	2.83	2.47	2.75
	SE	0.28	0.31	0.32	0.27	0.31
	Median	8.0	8.0	8.0	8.0	8.0
	Min, max	2.0, 13.0	2.0, 13.0	0.0, 13.0	3.0, 13.0	2.0, 13.0

Source: PRIDE-HD CSR, summary 15.1.12.1

- **TMS (primary endpoint)**

PRIDE-HD did not meet its primary endpoint. Negative change from baseline in TMS to Week 26 indicated an improvement in TMS in all treatment groups, which was sustained for placebo and in pridopidine 45 mg bid up to Week 52 (Table 10).

Table 10: PRIDE-HD - Change from baseline in TMS at week 26 and week 52 (FAS)

TMS Statistic	Placebo bid (N=82)	Pridopidine 45 mg bid (N=81)	Pridopidine 67.5 mg bid (N=82)	Pridopidine 90 mg bid (N=81)	Pridopidine 112.5 mg bid (N=82)
Change from baseline to Week 26/endpoint					
n	81	75	79	81	81
Mean (SD)	-4.5 (8.68)	-3.2 (7.97)	-3.1 (9.09)	-4.0 (9.22)	-3.0 (7.72)
SE	0.96	0.92	1.02	1.02	0.86
Median	-4.0	-3.0	-2.0	-4.0	-3.0
Min, max	-30.0, 13.0	-20.0, 17.0	-33.0, 15.0	-22.0, 25.0	-20.0, 19.0
LS mean (SE of LS mean)	-4.79 (0.99)	-3.37 (1.05)	-3.09 (1.02)	-4.13 (1.00)	-2.74 (1.01)
LS mean difference		1.42	1.70	0.66	2.04
95% CI		-1.39, 4.23	-1.06, 4.46	-2.07, 3.39	-0.71, 4.80
p-value		0.3202	0.2266	0.6348	0.1447
Change from baseline to Week 52/endpoint					
n	81	75	79	81	81
Mean (SD)	-2.5 (9.62)	-2.0 (7.95)	-1.0 (9.58)	-1.6 (11.71)	-1.0 (9.21)
SE	1.07	0.92	1.08	1.30	1.02
Median	-2.0	-2.0	-1.0	-2.0	-2.0
Min, max	-29.0, 24.0	-20.0, 18.0	-26.0, 24.0	-24.0, 36.0	-19.0, 23.0
LS mean (SE of LS mean)	-2.03 (1.25)	-1.43 (1.36)	0.54 (1.32)	-0.29 (1.27)	0.71 (1.34)
LS mean difference		0.60	2.57	1.74	2.73
95% CI		-3.02, 4.22	-0.98, 6.13	-1.74, 5.22	-0.86, 6.32
p-value		0.7447	0.1558	0.3258	0.1350

bid=twice daily; CI=confidence interval; LS=least squares; max=maximum; min=minimum; n=sample size; N=population size; SD=standard deviation; SE=standard error of the mean; TMS=Total Motor Score. The LS mean difference, 95% CI, and p-value under each treatment group column are for the comparison of that treatment group to the placebo group.

- **TFC (exploratory endpoint)**

The largest LS mean difference in change from baseline at Week 52 between pridopidine and placebo was observed in the 45 mg bid group (difference: 0.87 points; 95% CI 0.29, 1.45; nominal p=0.0032) (Table 11). A post hoc analysis indicated that the effect of pridopidine 45 mg bid on TFC was most evident in HD1/HD2 patients (TFC 7-13) (Δ vs placebo 1.16; nominal p=0.0003).

Table 11: PRIDE-HD - TFC at week 26 and 52 (FAS)

TFC Statistic	Placebo bid (N=82)	Pridopidine 45 mg bid (N=81)	Pridopidine 67.5 mg bid (N=82)	Pridopidine 90 mg bid (N=81)	Pridopidine 112.5 mg bid (N=82)
Change from baseline to Week 26/endpoint					
n	81	75	78	81	81
Mean (SD)	-0.3 (1.55)	-0.1 (1.23)	-0.2 (1.41)	-0.1 (1.41)	-0.1 (1.36)
SE	0.17	0.14	0.16	0.16	0.15
Median	0.0	0.0	0.0	0.0	0.0
Min, max	-5.0, 2.0	-4.0, 3.0	-5.0, 3.0	-4.0, 4.0	-3.0, 4.0
LS mean (SE of LS mean)	-0.49 (0.16)	-0.15 (0.17)	-0.28 (0.17)	-0.16 (0.16)	-0.07 (0.16)
LS mean difference		0.33	0.21	0.32	0.42
95% CI		-0.12, 0.79	-0.24, 0.65	-0.12, 0.77	-0.03, 0.86
p-value		0.1490	0.3680	0.1521	0.0676
Change from baseline to Week 52/endpoint					
n	81	75	78	81	81
Mean (SD)	-0.6 (1.67)	0.0 (1.35)	-0.5 (1.63)	-0.4 (1.48)	-0.4 (1.60)
SE	0.19	0.16	0.18	0.16	0.18
Median	0.0	0.0	-0.5	0.0	0.0
Min, max	-5.0, 3.0	-4.0, 3.0	-5.0, 4.0	-5.0, 4.0	-4.0, 4.0
LS mean (SE of LS mean)	-0.83 (0.20)	0.04 (0.22)	-0.72 (0.21)	-0.65 (0.20)	-0.59 (0.22)
LS mean difference		0.87	0.11	0.19	0.24
95% CI		0.29, 1.45	-0.46, 0.68	-0.37, 0.75	-0.33, 0.82
p-value		0.0032	0.7042	0.5099	0.4061

bid=twice daily; CI=confidence interval; LS=least squares; max=maximum; min=minimum; n=sample size; N=population size; SD=standard deviation; SE=standard error of the mean; TFC= Total Functional Capacity; TMS=Total Motor Score. The LS mean difference, 95% CI, and p-value under each treatment group column is for the comparison of that treatment group to placebo. Note: Full Analysis Set includes patients that have baseline and at least 1 post-baseline TMS (primary endpoint) assessment. Full Analysis Set per each endpoint, includes patients that have baseline and at least 1 post-baseline assessment of the endpoint.

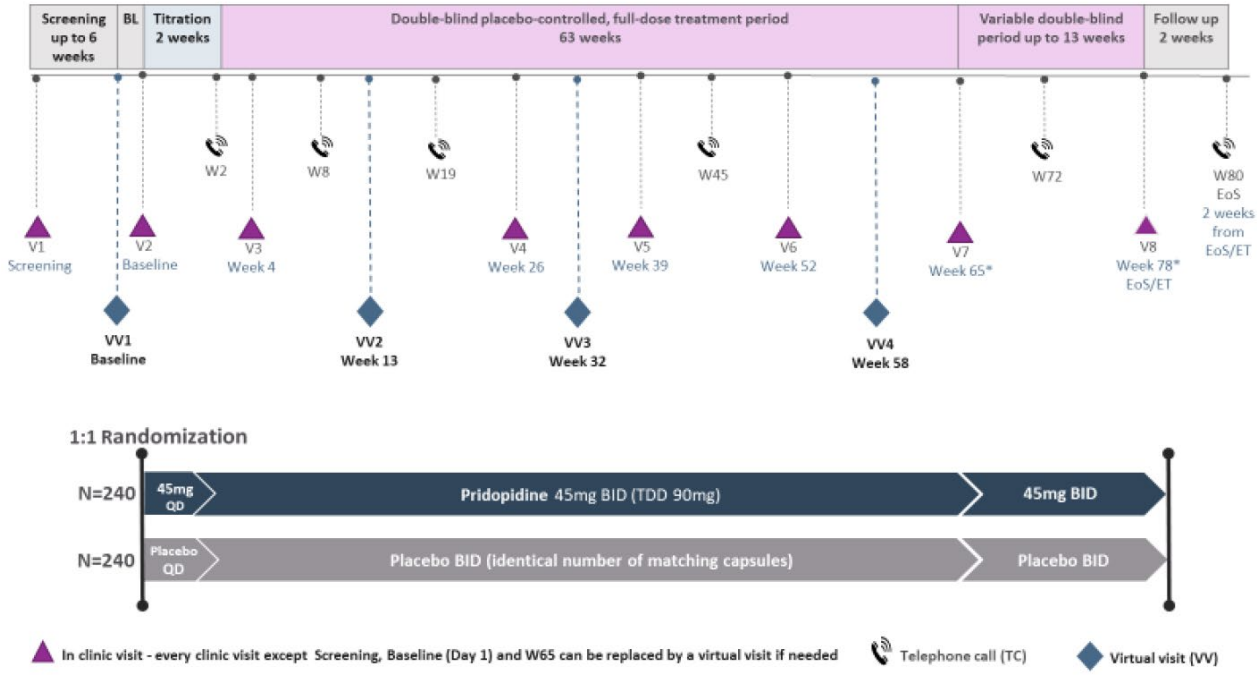
2.6.5.2. Main study – PROOF-HD

PROOF-HD - PRidopidine Outcome On Function in Huntington Disease

Methods

- **Study design**

PROOF-HD included a 65- to 78-week double-blind treatment period. This was composed of a 2-week titration period, a 63-week treatment period and followed by a "common closing" end (i.e., variable extension of 13 weeks). Eligible patients who completed the double-blind phase could enrol in the OLE.



BID = twice daily; BL = baseline; EoS = end of study; ET = early termination; QD = once daily; TDD = total daily dose; V = visit; VV = virtual visit; W = week
** For each participant, the last treatment visit was the EoS at either Week 65 or Week 78 if the participant completed all study visits; or ET visit if the participant withdrew from the study before Week 65.*

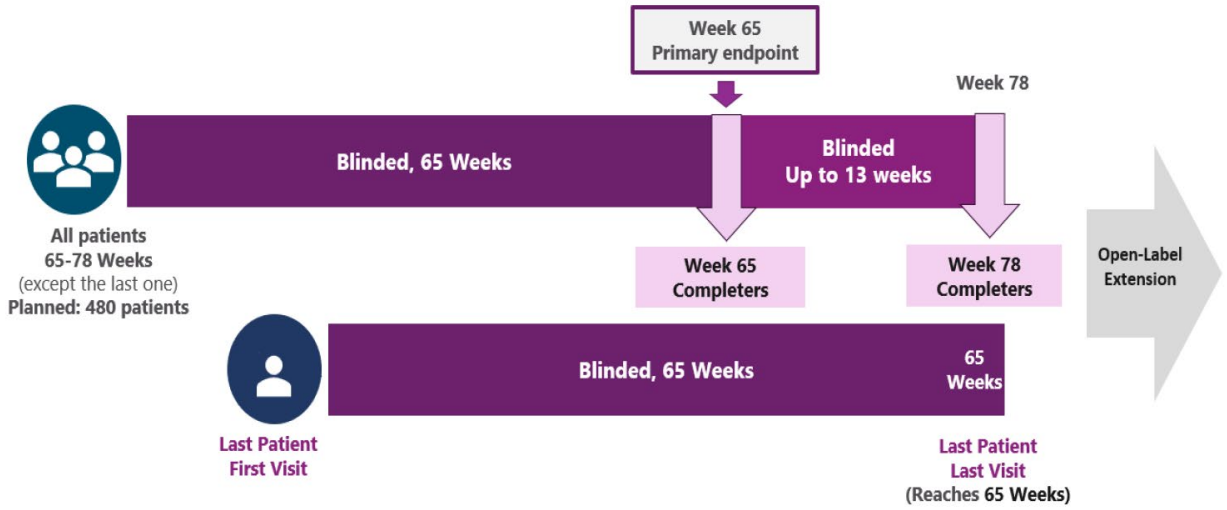


Figure 7: PROOF-HD Study schema excluding open label extension phase

- **Study Participants**

Main inclusion criteria:

1. Twenty-five years of age (inclusive) and older, at the time of signing the informed consent.
2. Diagnosis of HD based on clinical features and the presence of ≥36 CAG repeats in the Huntingtin confirmed by historical laboratory quantified results or by a diagnostic test at Screening.

3. Diagnostic confidence level of 4 (unequivocal motor signs, ≥99% confidence) on the standardized motor exam Unified Huntington Disease Rating Scale total motor score (UHDRS-TMS). UHDRS-TMS ≥20 at Screening.
4. Adult-onset HD with onset of signs and symptoms ≥18 years of age.
5. Stage 1 or Stage 2 HD, defined as a UHDRS-TFC score of ≥7, at Screening.
6. UHDRS IS score ≤90% at Screening.

Main exclusion criteria:

1. Use of pridopidine within 12 months before the baseline visit.
2. [enrolment criteria based on safety reasons; further discussed in the safety section (3.3.7.)].

Note: for the definition of the off-ADM subgroup, the reader is referred to the first paragraph in the subsection 'Ancillary efficacy analyses in patients off ADMs', below.

- **Treatments**

Oral administration of pridopidine 45 mg bid or placebo. First two weeks titration phase qd (morning dose); thereafter bid dosing (morning dose and second dose 7 to 10 hours after the morning dose).

The following medications were prohibited within four weeks of baseline visit:

- Antipsychotics: haloperidol, mesoridazine, thioridazine, pimozide, chlorpromazine, sulpiride and levomepromazine
- Antidepressants: citalopram >20 mg/day, escitalopram >10 mg/day and fluoxetine
- Antiarrhythmics: disopyramide, procainamide, flecainide, propafenone, amiodarone (prohibited within 6 weeks of baseline visit), dofetilide, ibutilide and sotalol
- Others: astemizole, terfenadine, azithromycin, erythromycin, moxifloxacin, pentamidine, sparfloxacin, clarithromycin, chloroquine, hydroxychloroquine, halofantrine, bepridil, cisapride, domperidone, droperidol, levomethadyl, sevoflurane, anagrelide, budipine, fluconazole, levofloxacin, lidoflazine, ondansetron, probucol, terodiline and vandetanib.

- **Objectives**

Primary objective

- To assess the effect of pridopidine on functional capacity in participants with Stage 1-2 HD.

Key secondary objective

- To assess the effect of pridopidine on a composite measure of disease progression in participants with HD

Secondary objective

- To evaluate the effect of pridopidine on functional capacity, motor function, and other measures of efficacy over time in participants with HD

- **Outcomes/endpoints**

Primary endpoint

- Change from baseline to Week 65 in the UHDRS-TFC score.

Key secondary endpoint

- 1. Change from baseline to Week 65 in composite UHDRS (cUHDRS) total score

Secondary endpoints (multiplicity-adjusted)

- 2. Proportion of participants with improvement or no worsening (change from baseline ≥ 0 points) at Week 65 in UHDRS-TFC
- 3. Change from baseline to Week 52 in UHDRS TFC score
- 4. Change from baseline to Week 78 in UHDRS TFC score
- 5. Change from baseline to Week 65 in Q-Motor finger tapping inter-onset interval (IOI) mean (Digitomotography)
- 6. Change from baseline to Week 65 in UHDRS TMS score
- 7. Change from baseline to Week 65 in Symbol Digit Modalities Test (SDMT)
- 8. Change from baseline to Week 52 in UHDRS TMS score
- 9. Proportion of participants with improvement or no worsening in Clinical Global Impression of Change (CGI-C) at Week 65

Note: all (key) secondary endpoints listed are included in a hierarchical testing strategy and ordered according to this testing hierarchy.

Study assessments

The cUHDRS is a global composite measure of clinical progression in HD, combining key measures of the disease: function (TFC), motor (TMS), and cognition (Stroop Word Reading (SWR) and SDMT). The total cUHDRS score represents an equally weighted average of each of these components and is therefore able to address disease heterogeneity in HD (Schobel et al 2017). Increases on cUHDRS indicate improvement. Based on an analysis in early HD patients, a change in the annual decline of 0.2-0.3 points was considered clinically meaningful (Schobel et al 2017).

The TFC scale is a clinical scale for staging and tracking the progression of HD with respect to functional capacity (Shoulson and Fahn 1979; Marder et al 2000). The TFC consists of five domains which assess the functional capacity of the patient, i.e., to maintain their occupation, take care of finances, perform domestic chores, activities of daily living, and care level. Scores range from 0 to 13, with 13 being unaffected and 0 as complete incapacity. Score for TFC stage 1: 11–13, stage 2: 7–10, stage 3: 3–6, stage 4: 1–2, and stage 5: 0. In HD1 and HD2 (TFC 7-13), TFC has been observed to progress with a rate of ~1 point per year (Marder et al 2000; Waters et al 2018) (Marder et al 2000; Waters et al 2018).

The TMS is a categorical clinical rating scale and the standard clinical tool for tracking the progression of motor symptoms in patients with HD. Multiple domains of motor disability in HD are assessed including oculomotor function, dystonia, gait and balance, bradykinesia, chorea, and postural stability. TMS scores are between 0 and 124; higher scores indicate worsening of motor symptoms

The SDMT is another accepted measure of cognitive function in HD that measures visual attention and processing speed. The subjects match symbols and digits based on a key located at the top of the page, and the total score indicates the number of correct responses in a 90 s period (higher scores are better). A meta-analysis of data from 4 HD studies (TRACK-HD, COHORT, CARE-HD, and 2CARE) demonstrated a decline in SDMT of ~1.83 points/year in patients with early HD (TFC 7-13) (Schobel et al 2017).

The SWR is a widely used, validated clinical measure to assess cognitive function in HD patients. It is a measure of attention and psychomotor speed and relies on verbal motor output and ability to articulate words. The words in the Stroop Word Reading are in Black print. The participants read the name of the colours ("red" "green" "blue") that appear in black ink/print. Scores reflect the number of correct responses in 45 seconds. Higher scores indicate better performance. A meta-analysis of data from 4 HD studies (TRACK-HD, COHORT, CARE-HD, and 2CARE) demonstrated a decline in SWR of ~4.19 points/year in patients with early HD (TFC 7-13) (Schobel et al 2017). Changes from baseline to different timepoints in SWR scale are only measured as non-multiplicity-adjusted secondary endpoints.

Q-Motor is a computerized and rater-independent test battery. Pre-calibrated and temperature-controlled force transducers and 3D position sensors are used for quantitative measurements. In PROOF-HD, digitomotography (speeded index finger tapping (FT)) and dysdiadochomotography (pronation/supination hand tapping) were used. Q-Motor tasks are useful for detection and quantification of motor function, such as fine motor skills.

The Clinical Global Impression of Severity (CGI-S) (modified) scale was only collected at baseline and served as the baseline value for CGI-C assessments. The assessment is based on qualified site personnel judgment, supported by a comprehensive, semi-structured, participant/caregiver interview. The CGI-C (CGI-change) scale measures the change in the patient's clinical status from a specific point in time, using a 7-point scale, ranging from 1 (very much improved) to 7 (very much worse), with a score of 4 indicating no change. Patients were classified into following categories based on CGI-C: (a) who had no change or improved (Scores of 1, 2, 3, or 4) (b) who Minimally or more improved (Scores of 1, 2, or 3) (c) who were Much or Very Much improved (Scores of 1 or 2) (d) who were Very Much improved (Score of 1).

The HD-QoL is a standardized instrument for measuring health-related QoL in HD patients. The total score ranges from 0 to 240, with higher scores indicating worse QoL. 40 items are tested over four domains ('Physical-Functional', 'Cognitive', 'Mood Self', and 'Worries'). Changes from baseline to different timepoints in HD-QoL scale are only measured as exploratory endpoints.

- **Sample size**

Based on PRIDE-HD data in early HD patients, the difference in mean change from Baseline to Week 65 between the 45 mg bid treated and placebo groups was expected to be 0.7 points on the UHDRS-TFC with a standard deviation (SD) of 1.9 points. A total sample size of 372 participants would provide 94% power using a two-tailed t-test at a significance level of 0.05. Assuming a dropout rate of 22.5%, a total of 480 participants were needed to be randomized.

For analysis of UHDRS-TFC under assumption of Missing Not at Random (MNAR) with imputed values for all discontinued participants estimated based on the trajectory of placebo participants with available data, a treatment difference in change from Baseline for imputed values at Week 65 is anticipated to be 0.1 points for the 22.5% expected drop-outs. The overall difference would then be 0.565 (0.7*0.775+0.1*0.225), with a SD of 1.9 a 480 participants would provide 90% power.

- **Randomisation and blinding (masking)**

All participants were centrally randomized on a 1:1 basis to receive either pridopidine or placebo. Randomisation was stratified by baseline HD stage (HD1 [TFC 11-13] vs. HD2 [TFC 7-10]) and baseline neuroleptic use (yes/no).

All participants, site staff, sponsor, contract research organisation and vendors involved with the study remained blinded to treatment assignments until the database was locked and the study unblinded. No interim analyses were planned for this study.

- **Statistical methods**

The primary efficacy variable change from baseline to Week 65 in the UHDRS-TFC will be analysed – upon EMA request - in the intent to treat (ITT) population including all randomized participants using a MMRM. The model includes: treatment, baseline UHDRS-TFC, region (Europe, North America), neuroleptic use (yes, no), baseline HD stage (HD1 and HD2), categorical week, and treatment by categorical week interaction. Use of unstructured covariance matrix was planned, with an ordered set of simpler covariance structures in case convergence issues occurred. The model-based least square mean (LSM) with its 95% CI and p-value for the comparison of treatment arms at Week 65 will be presented. Values collected after treatment discontinuation were included in the analysis (reflecting a treatment-policy strategy), whereas a pattern-mixture model (PMM) with control-based imputation will be used for missing values after a last observation without any available follow-up assessments. Imputed values below 0.5 and above 12.5 were rounded to 0 (minimum possible score on UHDRS-TFC) and 13 (maximum possible score on UHDRS-TFC) and imputed values between 0.5 and 12.5 were rounded to the nearest integer. Although, statistical analysis plan (SAP) mentioned that only data up to week 65 will be included in the analysis, also outcomes at 78 weeks seem to have been included in all analyses. The endpoints other than the primary endpoint were analysed in modified ITT (mITT) defined as all participants in the ITT population who received at least one dose of study drug and had valid in-clinic TFC score both at baseline and at least one post-baseline timepoint.

Primary efficacy variable, key secondary efficacy variable and secondary efficacy variables will be sequentially tested using a significance level of 5%. No interim analyses are planned for the study.

Table 12: Estimands for primary objective

Population	Early HD Participants (HD1 & HD2) defined through the study inclusion/exclusion criteria
Treatment condition	Pridopidine 45 mg bid or placebo (on background of standard of care) that participants are randomized to
Endpoint (variable)	Change from Baseline to Week 65 in UHDRS-TFC
Population-level summary	LS-Mean difference between pridopidine 45 mg bid and placebo from MMRM model in change of UHDRS-TFC from Baseline to Week 65
Intercurrent events and strategy to handle them	
Treatment discontinuation Death	Treatment policy strategy as these values reflect the remaining off drug treatment effect in reality. All observed values including collected after treatment discontinuation will be included in the analysis. Hypothetical strategy will apply to missing values after the last observed values. The method of multiple imputation (MI) will be applied to impute the missing data using PMM with control-based pattern imputation under MNAR assumptions

Assessor's note: missing data on itself is not considered an ICE. Treatment discontinuation does not necessarily result in missing data and missing data should not be listed here as ICE. Ideally ICEs would have been better defined. Also refer to related discussion in section 2.6.6.

Data quality assurance

All participant data was recorded on electronic eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). Data handling, including data quality assurance, was conducted according to the regulatory guidelines (e.g., ICH and GCP).

Database unlock

The database was unlocked following observation of anomalous values for the cUHDRS components SWR and SDMT during the statistical analysis. There were calculation errors in the source data, and discrepancies between the source data and eCRF were transcription errors which were not identified during monitoring. A error rate <1.5% was detected in data for the various cUHDRS components. Following correction and reverification of the data quality, the database was locked again, and the statistical analysis was repeated, which did not impact the efficacy conclusions. A Corrective and Preventive Action was generated for this deviation with details related to the root cause investigation and the corrective/preventive actions implemented.

Results

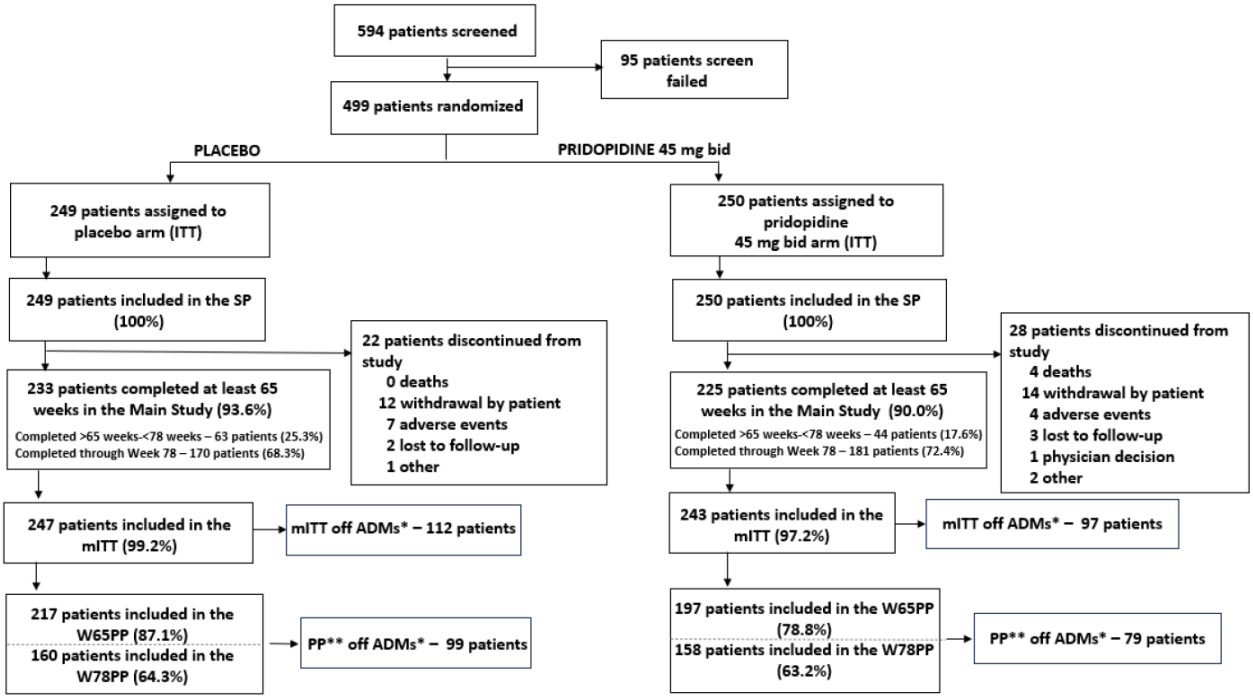
- **Participant flow**

The study enrolled 499 patients; all received at least one dose of study drug and were all included in ITT. The mITT included 490 patients (see detailed description in Table 13 and Figure 8).

Note: for the definition of the off-ADM subgroup, the reader is referred to the first paragraph in the subsection 'Ancillary efficacy analyses in patients off ADMs', below.

Table 13: Summary of patient disposition PROOF-HD

Analysis group	Statistics	Placebo	Pridopidine 45 mg bid	Total
Participants randomized (Intent to Treat [ITT] analysis set)	N	249	250	499
Safety Population (SP) - Participants randomized and who received at least one dose of study drug)	n (%)	249 (100)	250 (100)	499 (100)
Modified Intent to Treat (mITT) analysis set - All participants in the ITT who received at least one dose of study drug and have valid in-clinic TFC scores both at baseline and at least one post-baseline timepoint)	n (%)	247 (99.2)	243 (97.2)	490 (98.2)
Per Protocol Week 65 population (W65PP)	n (%)	217 (87.1)	197 (78.8)	414 (83.0)



ADMs = antidopaminergic medications; bid = twice daily; ITT = intent to treat; mITT = modified intent to treat; PP = per protocol; SP = safety population; W65PP = per protocol Week 65 population; W78PP = per protocol Week 78 population
** "Off ADMs" refers to patients who did not receive ADM treatment at any point during the study.*
*** PP represents the analysis set consisting of patients from both W65PP and W78PP.*
Note: the ITT analysis set – all randomized patients; mITT analysis set - all patients in the ITT who received at least one dose of study drug and had valid in-clinic TFC scores both at baseline and at least one post-baseline timepoint; SP analysis set - patients randomized and who received at least one dose of study drug; W65PP analysis set - subset of the mITT that includes all patients who had a valid UHDRS-TFC at Week 65, were on study drug with compliance >80% during the study, and did not have any important protocol deviations; W78PP analysis set - subset of the mITT that includes all patients who had a valid UHDRS-TFC at Week 78, were on study drug with compliance >80% during the study, and did not have any important protocol deviations.
Note: A total of four treatment-emergent deaths occurred in the study: one death in the placebo arm and three deaths in the pridopidine arm. The recorded reason for study discontinuation for the placebo patient was the TEAE of road traffic accident that eventually led to death, and therefore there are 0 patients with study discontinuation due to death in the placebo arm. In addition, there was one patient in the pridopidine arm who died of a cardiac arrest one year after being off study treatment. The death led to study discontinuation, but the event was not deemed as treatment-emergent and not counted in the total count of deaths.

Figure 8: PROOF-HD patients numbers in different study populations

- **Recruitment**

The PROOF-HD study was conducted in North America (US and Canada) and Europe (Austria, Czech Republic, Germany, France, Italy, the Netherlands, Poland, Spain, and the United Kingdom). The double-blind phase was conducted between Oct 2020 – Mar 2023.

- **Conduct of the study**

Protocol amendments

The protocol was amended seven times; protocol V1 and V2 were finalized prior to first randomisation. Their impact on study outcomes are considered negligible and are consequently not discussed. Key changes in other amendment were. Changes considered of importance are:

Amendment 3 (25 October 2020)
- Added text for handling intercurrent events
- Added statement on separate analyses for the primary endpoint for EMA and non-EMA regions

Amendments 4 (15 February 2021) and 5 (15 March 2021) were amendments on request of the France competent authority (ANSM). Those changes were incorporated globally within Amendment 6 (13 May 2021).

Amendment 6 (13 May 2021)
- Added objective and endpoints for the OLE
- Updated enrolment criteria:
    - 14 (participants should be on stable dosages of concomitant medications at the start of the baseline visit; changed wording to 'substance use disorder' and adjusted timeframe for suicidal ideation)
    - 2c (to allow inclusion of those with HR <50 bpm if not clinically significant)
    - 11 (exclude participation in studies with tominersen)
    - 13e (clarification for exclusion associated with total bilirubin)
- COVID-19 related changes (drug accountability, expansion in-clinic visit window)
- addition of NfL plasma biomarker analysis in double-blind period.
- Changes to concomitant medication:
    - Added fluphenazine, medications for management of chorea, and COVID-19 vaccines to list of permitted medications.

Amendment 7 (27 January 2022)
- Added Q-motor to efficacy endpoints of the OLE
- Reduced number of phone visits
- Added C-SSRS (since last visit) in accordance with clarification letter 30 September 2021
- Changed post-discontinuation visits to phone visits except for the early termination visit, Week 65 and Week 78/end of study

Amendment 8 (10 November 2022)
- Hierarchy of secondary endpoints changed (cUHDRS moved up to #1, proportion of participants with improvement or no worsening in UHDRS-TFC moved to #2, TFC at Week 52 and 78 moved up to #3 and #4, Q-Motor lowered to #5, TMS lowered to #6) and change from Baseline to Week 65 in SDMT added to #7 in the hierarchy
-OLE-related changes: extended to 12 months. Added NfL plasma biomarker analysis
-primary estimand further defined
-Sensitivity analyses for multiplicity-adjusted secondary endpoints; changes to handling missing data, and addition of and OLE analyses
-Only in-clinic UHDRS-TFC assessments will be used in the primary analysis and secondary analyses

Protocol deviations

The incidence of protocol deviations was comparable between study arms (Table 14). A total of 419 (84.0%) patients had protocol deviations, of which 187 (37.5%) had major protocol deviations. The most common consisted of study procedures not performed (n=104; 20.8%).

Table 14: Summary of protocol deviations (ITT)

Parameters	Placebo (N = 249) n (%)	Pridopidine 45 mg bid (N = 250) n (%)	Overall (N = 499) n (%)
Participants with any protocol deviations	**205 (82.3)**	**214 (85.6)**	**419 (84.0)**
Participants with any important (major) protocol deviations	91 (36.5)	96 (38.4)	187 (37.5)
Study procedure not performed[a]	50 (20.1)	54 (21.6)	104 (20.8)
Other	18 (7.2)	19 (7.6)	37 (7.4)
Visit not performed	19 (7.6)	16 (6.4)	35 (7.0)
Incorrect treatment or dose	14 (5.6)	14 (5.6)	28 (5.6)
Prohibited concomitant treatment	9 (3.6)	14 (5.6)	23 (4.6)
Study procedure out of window	5 (2.0)	5 (2.0)	10 (2.0)
Breaches of GCP[b]	2 (0.8)	3 (1.2)	5 (1.0)
SAE reporting	3 (1.2)	1 (0.4)	4 (0.8)
Eligibility criteria not met	2 (0.8)	0	2 (0.4)
IP storage and handling	1 (0.4)	1 (0.4)	2 (0.4)
Lab documents, supplies or samples	0	1 (0.4)	1 (0.2)
Study procedure deviation	0	1 (0.4)	1 (0.2)
Withdrawal criteria not implemented	1 (0.4)	0	1 (0.2)
Participants with any important (major) protocol deviations due to COVID-19	0	0	0

a Under this category, there was a serious breach relevant to EoS (Week 78) ECGs not performed for four patients at one site. This was reported to the relevant competent authority.
b None of the five cases of "Breaches of GCP" were considered as a serious breach, and therefore were not required to be reported to local competent authorities.
** One patient in the placebo arm had a medical history which was only disclosed after the double-blind study database lock and during the OLE of PROOF-HD. This major protocol deviation is therefore not included in this table. This incident will be fully documented in the Clinical Study Report of the OLE, from which the patient was immediately withdrawn in this context. This patient is included in all tables and listings but was not included in the mITT Off ADMs population as this patient was on ADMs.*
Note: "Participant/s" is used to denote patient/s.
Note: Patients could have protocol deviations in multiple categories, and hence could be counted in more than one row.
bid = twice daily; COVID-19 = coronavirus disease 2019; GCP = Good Clinical Practice; IP = investigational product; SAE = serious adverse event

- **Baseline data**

Patient demographics were consistent amongst ITT and mITT. In addition, baseline demographics and disease characteristics were comparable between the two study arms. Overall, in the ITT population, mean (SD) age was 52.5 (11.7) years, 51.9% of patients were female, and the majority of patients (>90%) were non-Hispanic and White (Table 15).

Table 15: Baseline demographic characteristics, ITT population

Parameter	Statistics	Placebo	Pridopidine 45 mg bid	Total
Age (years)	n (missing)	249 (0)	250 (0)	499 (0)
	Mean (SD)	52.7 (11.39)	52.2 (11.93)	52.5 (11.66)
	Median	54.0	53.0	53.0
	Q1, Q3	45.0, 61.0	44.0, 61.0	44.0, 61.0
	min, max	27, 79	25, 86	25, 86
BMI (kg/m^2)	n (missing)	247 (2)	249 (1)	496 (3)
	Mean (SD)	25.24 (4.774)	25.00 (4.952)	25.12 (4.861)
	Median	24.64	23.99	24.37
	Q1, Q3	21.64, 27.82	21.72, 27.85	21.71, 27.84
	min, max	17.2, 45.6	17.1, 44.3	17.1, 45.6
Age group (years)				
<55	n (%)	130 (52.2)	136 (54.4)	266 (53.3)
≥55	n (%)	119 (47.8)	114 (45.6)	233 (46.7)
<65	n (%)	213 (85.5)	207 (82.8)	420 (84.2)
≥65	n (%)	36 (14.5)	43 (17.2)	79 (15.8)
≥55 to <65	n (%)	83 (33.3)	71 (28.4)	154 (30.9)
Sex				
Female	n (%)	127 (51.0)	132 (52.8)	259 (51.9)
Male	n (%)	122 (49.0)	118 (47.2)	240 (48.1)
Race				
Not permitted to collect*	n (%)	7 (2.8)	4 (1.6)	11 (2.2)
Asian	n (%)	0	2 (0.8)	2 (0.4)
Black or African American	n (%)	2 (0.8)	0	2 (0.4)
Native Hawaiian or other Pacific Islander	n (%)	1 (0.4)	0	1 (0.2)
White	n (%)	235 (94.4)	242 (96.8)	477 (95.6)
Multiple	n (%)	2 (0.8)	1 (0.4)	3 (0.6)
Other	n (%)	2 (0.8)	1 (0.4)	3 (0.6)
Ethnicity				
Not permitted to collect*	n (%)	7 (2.8)	4 (1.6)	11 (2.2)
Hispanic or Latino	n (%)	8 (3.2)	10 (4.0)	18 (3.6)
Not Hispanic or Latino	n (%)	234 (94.0)	236 (94.4)	470 (94.2)

bid = twice daily; BMI = body mass index; max = maximum; min = minimum; Q1, Q3 = quartile 1, 3; SD = standard deviation
** As France did not allow for collection of race and ethnicity data, patients recruited in France appear under the category Not permitted to collect.*

Mean (SD) CAG repeat length was 43.9 (3.54). Overall, 41.1% of patients had HD1 (TFC 11-13) and 58.9% had HD2 (TFC 7-10) at baseline (Table 16).

Table 16: Baseline disease characteristics, ITT population

Parameter	Statistics	Placebo	Pridopidine 45 mg bid	Total
Duration since onset of symptoms (years)	n (missing)	248 (1)	249 (1)	497 (2)
	Mean (SD)	4.61 (4.572)	4.28 (3.158)	4.45 (3.927)
	Median	3.05	3.70	3.20
	Q1, Q3	1.80, 6.25	2.00, 5.90	1.90, 6.10
	min, max	0.0, 26.2	0.0, 17.9	0.0, 26.2
HD stage (at randomization for stratification)				
HD1 (UHDRS-TFC 11-13)	n (%)	103 (41.4)	102 (40.8)	205 (41.1)
HD2 (UHDRS-TFC 7-10)	n (%)	146 (58.6)	148 (59.2)	294 (58.9)
CAG repeat length	n (missing)	248 (1)	250 (0)	498 (1)
	Mean (SD)	43.6 (3.28)	44.2 (3.78)	43.9 (3.54)
CAP[1]	n (missing)	248 (1)	250 (0)	498 (1)
	Mean (SD)	494.6 (92.39)	513.4 (83.60)	504.0 (88.50)
Neuroleptic use (at randomization for stratification)[2]				
Yes	n (%)	73 (29.3)	74 (29.6)	147 (29.5)
No	n (%)	176 (70.7)	176 (70.4)	352 (70.5)
UHDRS-IS score (collected at screening)[3]	n (missing)	249 (0)	250 (0)	499 (0)
	Mean (SD)	81.4 (6.65)	81.8 (6.55)	81.6 (6.60)
UHDRS-TFC score	n (missing)	249 (0)	250 (0)	499 (0)
	Mean (SD)	9.9 (1.70)	9.8 (1.70)	9.9 (1.70)
UHDRS-TMS score	n (missing)	249 (0)	250 (0)	499 (0)
	Mean (SD)	32.8 (10.93)	33.8 (11.10)	33.3 (11.02)
SDMT score	n (missing)	249 (0)	249 (1)	498 (1)
	Mean (SD)	23.2 (9.29)	22.7 (9.10)	23.0 (9.19)
SWR score	n (missing)	249 (0)	249 (1)	498 (1)
	Mean (SD)	61.9 (18.11)	60.7 (17.78)	61.3 (17.94)
cUHDRS score[4]	n (missing)	249 (0)	249 (1)	498 (1)
	Mean (SD)	8.9 (2.65)	8.6 (2.54)	8.8 (2.60)
HD-QoL score	n (missing)	244 (5)	250 (0)	494 (5)
	Mean (SD)	60.8 (37.55)	62.4 (40.83)	61.6 (39.21)
CGI-S score	n (missing)	249 (0)	250 (0)	499 (0)
	Mean (SD)	3.2 (0.79)	3.3 (0.81)	3.2 (0.80)
UHDRS-TMS gait and balance score[5]	n (missing)	249 (0)	250 (0)	499 (0)
	Mean (SD)	3.1 (1.77)	3.1 (1.65)	3.1 (1.71)
Finger tap speed IOI - average of both hands (msec)	n (missing)	249 (0)	250 (0)	499 (0)
	Mean (SD)	353.2 (137.78)	352.1 (128.35)	352.6 (133.01)
Finger tap speed IOI - SD of both hands (msec)	n (missing)	249 (0)	250 (0)	499 (0)
	Mean (SD)	121.8 (77.67)	128.7 (78.65)	125.3 (78.16)

bid = twice daily; CAG = Cytosine-adenosine-guanine; CAP = Cytosine-adenosine-guanine-age-product; CGI-S = Clinical Global Impression of Severity; cUHDRS = composite Unified Huntington's Disease Rating Scale; HD = Huntington Disease; HD-QoL =

Huntington Disease Quality of Life questionnaire; IOI = inter-onset interval; IS = Independence Scale; msec = milliseconds; NfL = neurofilament; SD = standard deviation; SDMT = Symbol Digit Modalities Test; SWR = Stroop Word Reading; TFC = total functional capacity; TMS = total motor score; UHDRS = Unified Huntington's Disease Rating Scale
1 CAP = Age × (CAG – 33.66).
2 Percentages for this section are based on total number of patients with an answer 'Yes' to the question 'Is the patient on a neuroleptic'?
3 Independence Scale.
4 cUHDRS = [((TFC – 10.4) / 1.9) – ((TMS – 29.7) / 14.9) + ((SDMT – 28.4) / 11.3)) + ((SWR – 66.1) / 20.1)] + 10.
5 Gait and balance score, defined as the sum of UHDRS-TMS items 13, 14 and 15 (gait, tandem walking, and retropulsion pull test).

Table 17: PROOF-HD demographics, baseline disease characteristics (mITT population, off-, and on ADMs groups)

PROOF-HD	**mITT**		**mITT on ADMs** any time during the study**		**mITT off ADMs* All the time during the study**	
	Placebo (N = 247)	**Pridopidine 45 mg bid (N = 243)**	**Placebo (N =135)**	**Pridopidine 45 mg bid (N =146)**	**Placebo (N = 112)**	**Pridopidine 45 mg bid (N = 97)**
Age (years), mean (SD)	52.6 (11.37)	52.4 (11.90)	53.0 (11.48)	53.3 (12.42)	52.3 (11.28)	50.9 (10.97)
Age group, n (%)						
<65 years	212 (85.8)	202 (83.1)	116 (85.9)	115 (78.8)	96 (85.7)	87 (89.7)
≥65 years	35 (14.2)	41 (16.9)	19 (14.1)	31 (21.2)	16 (14.3)	10 (10.3)
BMI (kg/m), mean (SD)	25.21 (4.778)	24.98 (5.010)	25.7 (5.04)	25.0 (5.12)	24.6 (4.39)	25 (4.87)
Gender, n (%)						
Female	126 (51.0)	130 (53.5)	64 (47.4)	75 (51.4)	62 (55.4)	55 (56.7)
Male	121 (49.0)	113 (46.5)	71 (52.6)	71 (48.6)	50 (44.6)	42 (43.3)
Duration since onset of symptoms (years), mean(SD)	4.63 (4.586)	4.32 (3.183)	5.1 (4.97)	4.7 (3.30)	4.1 (4.02)	3.8 (2.93)
HD stage (at randomisation for stratification)						
HD1 (TFC 11-13)	102 (41.3)	100 (41.2)	45 (33.3)	54 (37.0)	57 (50.9)	46 (47.4)
HD2 (TFC 7-10)	145 (58.7)	143 (58.8)	90 (66.7)	92 (63.0)	55 (49.1)	51 (52.6)
CAP[1], mean (SD)	494.4 (92.76)	513.2 (83.30)	516.8 (92.06)	523.3 (83.42)	467.6 (86.63)	498 (81.20)
IS score[2] (collected at screening), mean (SD)	81.4 (6.64)	81.9 (6.52)	79.8 (6.67)	81.2 (6.72)	83.3 (6.10)	82.9 (6.07)
TFC score, mean (SD)	9.9 (1.71)	9.8 (1.69)	9.5 (1.71)	9.6 (1.69)	10.3 (1.60)	10.2 (1.59)
TMS score, mean (SD)	32.9 (10.95)	33.8 (11.15)	35.0 (11.54)	35.4 (10.96)	30.3 (9.64)	31.4 (11.04)
SDMT score, mean (SD)	23.3 (9.31)	22.8 (9.01)	20.4 (8.21)	20.9 (8.56)	26.7 (9.42)	25.6 (8.96)

PROOF-HD	mITT		mITT on ADMs** any time during the study		mITT off ADMs* All the time during the study	
	Placebo (N = 247)	Pridopidine 45 mg bid (N = 243)	Placebo (N =135)	Pridopidine 45 mg bid (N =146)	Placebo (N = 112)	Pridopidine 45 mg bid (N = 97)
SWR score, mean (SD)	62.0 (18.15)	61.0 (17.67)	56.2 (17.56)	58.5 (17.44)	68.9 (16.40)	64.6 (17.48)
cUHDRS score[3], mean (SD)	8.9 (2.65)	8.7 (2.52)	8.0 (2.53)	8.2 (2.42)	9.9 (2.42)	9.4 (2.51)
HD-QoL score, mean (SD)	60.8 (37.68)	61.8 (40.57)	66.8 (39.30)	66.6 (40.30)	53.5 (34.44)	54.6 (40.10)
CGI-S score, mean (SD)	3.2 (0.79)	3.3 (0.81)	3.3 (0.73)	3.4 (0.77)	3.1 (0.85)	3.1 (0.85)
TMS gait and balance score[4], mean (SD)	3.2 (1.77)	3.1 (1.66)	3.5 (1.86)	3.3 (1.58)	2.8 (1.57)	2.9 (1.75)
PBA-s apathy score[5], mean (SD)	1.5 (2.59)	1.5 (2.54)	1.8 (2.91)	1.6 (2.66)	1.2 (2.11)	1.2 (2.34)
Finger tap speed IOI - average - both hands (msec), mean (SD)	353.3 (137.78)	353.2 (129.72)	373.0 (162.67)	353.2 (140.72)	329.5 (95.29)	353.1 (111.84)
Finger tap speed IOI - SD - both hands (msec), mean (SD)	121.6 (77.85)	129.5 (79.34)	132.1 (83.30)	130.6 (77.69)	109 (69.00)	127.9 (82.14)

Source: From PROOF-HD CSR Table 13 and Table SN0005.Q70d.t.4.onany
Note: One patient off ADMs at all the time in pridopidine group had all post-baseline TFC assessments done virtually and should be excluded from the mITT population. Due to the minimal impact, this table was not updated to exclude this patient.
** "Off ADMs" refers to patients who did not receive ADM treatment at any point during the study.*
*** "On ADMs" refers to patients who received ADM treatment at any point during the study*
1 CAP = Age × (CAG – 33.66).
3 cUHDRS = [((TFC – 10.4) / 1.9) – ((TMS – 29.7) / 14.9) + ((SDMT – 28.4) / 11.3)) + ((SWR – 66.1) / 20.1)] + 10.
4 Gait and balance score, defined as the sum of UHDRS-TMS items 13, 14 and 15 (gait, tandem walking, and retropulsion pull test).
5 Apathy score is calculated as the product of Severity and Frequency for the item Lack of Initiative.
ADM = antidopaminergic medications; BMI = body mass index; CAP = Cytosine-adenosine-guanine-age-product; CGI-S = Clinical Global Impression of Severity; cUHDRS = composite Unified Huntington's Disease Rating Scale; HD = Huntington Disease; HD-QoL = Huntington Disease Quality of Life questionnaire; IOI = inter-onset interval; IS = Independence Scale; mITT = modified intent to treat; msec = milliseconds; PBA-s = Problem Behaviours Assessment short form; SD = standard deviation; SDMT = Symbol Digit Modalities
Test; SWR = Stroop Word Reading; TFC = total functional capacity; TMS = total motor score;

Table 18: Treatment compliance in PROOF-HD Safety population

	Placebo (n=249)	Pridopidine 45mg bid (n=250)	Total (n=499)
N (missing)	249 (0)	250 (0)	499 (0)
Mean (SD)	98.89 (9.053)	94.11 (10.743)	94.50 (9.933)
Median	97.90	97.80	97.90
Q1, Q3	91.9, 99.8	90.2, 99.6	90.9, 99.7
Min, Max	40.8, 120.5	40.8, 128.2	40.8, 128.2

At baseline, in the ITT population, 83 (33.3%) patients in the placebo group and 79 (31.6%) patients in the pridopidine group used neuroleptics. VMAT2 inhibitors were used by 38 (15.3%) of patients in

the placebo group and by 57 (22.8%) patients in the pridopidine group at baseline. Together, 138 (55.4%) and 126 (50.4%) patients were off ADMs at baseline (neuroleptics and VMAT2 inhibitors) in the placebo and pridopidine groups, respectively. Patients could initiate treatment with ADMs post-baseline. Considering ADM use at any time during the study, 112 (45.0%) patients in the placebo group and 100 (40%) patients in the pridopidine group were off ADMs all the time (Table 17, Table 18 and Table 19).

Table 19: The most common concomitant medications (in ≥20% of patients overall by drug ATC chemical level 2 term and ≥10% patients overall) (Safety population)

ATC level 2 term Standardized Drug Names	Placebo (N = 249) n (%)	Pridopidine 45 mg bid (N = 250) n (%)	Overall (N = 499) n (%)
Number of participants with at least one concomitant medication	244 (98.0)	246 (98.4)	490 (98.2)
Psycholeptics	162 (65.1)	165 (66.0)	327 (65.5)
Olanzapine	31 (12.4)	38 (15.2)	69 (13.8)
Melatonin	24 (9.6)	36 (14.4)	60 (12.0)
Risperidone	27 (10.8)	33 (13.2)	60 (12.0)
Psychoanaleptics	146 (58.6)	173 (69.2)	319 (63.9)
Sertraline	55 (22.1)	66 (26.4)	121 (24.2)
Trazodone	27 (10.8)	25 (10.0)	52 (10.4)
Vaccines	137 (55.0)	117 (46.8)	254 (50.9)
COVID-19 vaccine	131 (52.6)	114 (45.6)	245 (49.1)
Influenza vaccine	37 (14.9)	23 (9.2)	60 (12.0)
Analgesics	88 (35.3)	81 (32.4)	169 (33.9)
Paracetamol	55 (22.1)	50 (20.0)	105 (21.0)
Vitamins	80 (32.1)	87 (34.8)	167 (33.5)
Vitamins NOS	37 (14.9)	37 (14.8)	74 (14.8)
Cholecalciferol	25 (10.0)	27 (10.8)	52 (10.4)
Anti-inflammatory and antirheumatic products	79 (31.7)	76 (30.4)	155 (31.1)
Ibuprofen	58 (23.3)	50 (20.0)	108 (21.6)
Other nervous system drugs	54 (21.7)	82 (32.8)	136 (27.3)
Deutetrabenazine	22 (8.8)	41 (16.4)	63 (12.6)
Tetrabenazine	25 (10.0)	33 (13.2)	58 (11.6)
Antibacterials for systemic use	52 (20.9)	52 (20.8)	104 (20.8)

,

ATC = anatomical therapeutic chemical; bid = twice daily; WHO = World Health Organization
Note: "Participant/s" is used to denote patient/s.
Note: Therapeutic sub-groups (level 2) was used for ATC classification. Medications were coded using WHO Drug Dictionary version March 2020 B3.
Note: Concomitant medications are those medications taken on or after the first day of study drug treatment.
Note: ATC drug classifications (and Standardized Drug Names within ATC Class) are listed by descending frequency of number of patients in the total column. Patients are counted only once in each therapeutic class category, and only once in each Standardized Drug Name category.

ADM use in PROOF-HD was higher than expected. In PRIDE-HD and MermaiHD, between 38% and 43% of patients used ADMs at any time during the study compared with 55% to 60% of patients in PROOF-HD. This could at least in part be attributed to COVID 19 pandemic and lockdowns (October 2020 and February 2022). Increased use of neuroleptics has been reported for other neuropsychiatric diseases during the COVID-19 pandemic, including Alzheimer's disease and dementia (Howard et al 2020; Macdonald et al 2023) and depression (Armitage 2021; Bliddal et al 2023).

Table 20: Summary of Concomitant Neuroleptic Medications by Standardized Drug Name Classification (Safety population)

Standardized Drug Names	Placebo (N = 249) n (%)	Pridopidine 45 mg bid (N = 250) n (%)	Overall (N = 499) n (%)
Participants with at least one neuroleptic concomitant medication	**107 (43.0)**	**109 (43.6)**	**216 (43.3)**
Olanzapine	31 (12.4)	38 (15.2)	69 (13.8)
Risperidone	27 (10.8)	33 (13.2)	60 (12.0)
Tiapride	23 (9.2)	20 (8.0)	43 (8.6)
Aripiprazole	16 (6.4)	17 (6.8)	33 (6.6)
Quetiapine	17 (6.8)	14 (5.6)	31 (6.2)
Fluphenazine	3 (1.2)	6 (2.4)	9 (1.8)
Haloperidol	2 (0.8)	4 (1.6)	6 (1.2)
Lithium	1 (0.4)	1 (0.4)	2 (0.4)
Ziprasidone	2 (0.8)	0	2 (0.4)
Amisulpride	1 (0.4)	0	1 (0.2)
Asenapine	0	1 (0.4)	1 (0.2)
Cariprazine	1 (0.4)	0	1 (0.2)
Chlorpromazine	0	1 (0.4)	1 (0.2)
Clotiapine	1 (0.4)	0	1 (0.2)
Cyamemazine	1 (0.4)	0	1 (0.2)
Flupentixol	0	1 (0.4)	1 (0.2)
Prochlorperazine	1 (0.4)	0	1 (0.2)
Promazine	1 (0.4)	0	1 (0.2)
Prothipendyl	1 (0.4)	0	1 (0.2)

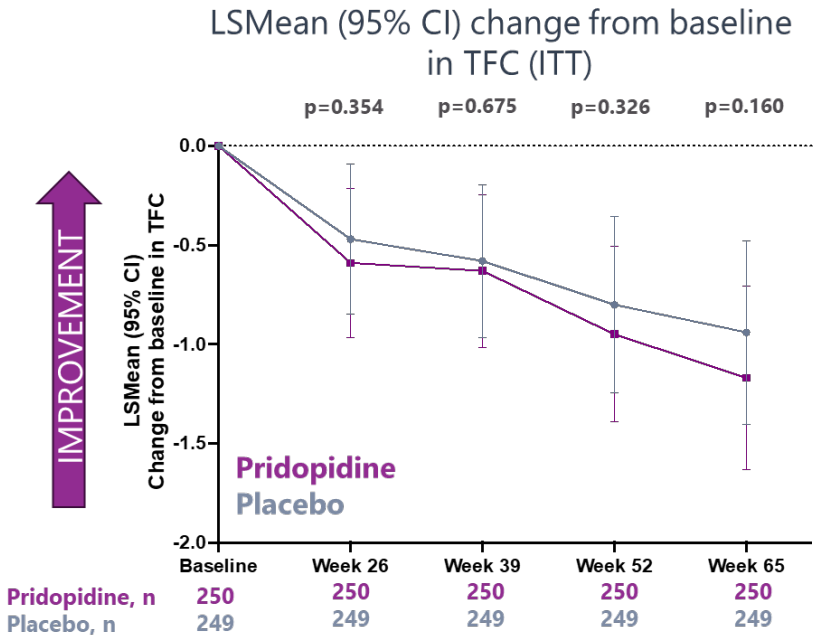
bid = twice daily; WHO = World Health Organization.
Note: "Participant/s" is used to denote patient/s.
Note: Medications were coded using WHO Drug Dictionary version March 2020 B3.
Note: Concomitant medications are those medications taken on or after the first day of study drug treatment.
Note: Standardized Drug Names are listed by descending frequency of number of patients in the total column. Patients are counted only once in each Standardized Drug Name category.

According to the applicant, in the subgroup of patients off ADMs (all the time, mITT population), baseline characteristics were similar to those in the overall population, with no notable differences between treatment arms.

- **Outcomes and estimation**

Primary Endpoint – UHDRS-TFC (ITT population)

In ITT, the change-from-baseline least square (LS) mean difference at Week 65 was -0.23 in favour of placebo (95% CI: -0.55, 0.09; p=0.160) (Table 21 and Figure 9). Results in the mITT were comparable. PROOF-HD did not meet its primary endpoint.



Source: PROOF-HD CSR, Missing data were imputed using a pattern-mixture model with control-based MI under assumption of MNAR. Symbols show LS Mean change from baseline and 95% CI.

Figure 9: PROOF-HD: Summary and MMRM Analysis of TFC Through Week 65 (ITT population)

Table 21: Change from Baseline to Week 65 in UHDRS-TFC (ITT population)

Week (visit)	Placebo		Pridopidine 45 mg bid	
	Actual	Change from baseline	Actual	Change from baseline
ITT*				
Day 1 (Visit 2) (baseline)				
n (missing)	249 (0)		250 (0)	
Mean (SD)	9.9 (1.70)		9.8 (1.70)	
Median	10.0		10.0	
Q1, Q3	8.0, 11.0		9.0, 11.0	
Min, max	7, 13		5**, 13	
Week 65 (Visit 7)				
n		249		250
LS mean (SE)		-0.94 (0.120)		-1.17 (0.120)
95% CI		-1.18, -0.71		-1.41, -0.94
LS mean difference (SE) versus placebo				-0.23 (0.162)
95% CI versus placebo				-0.55, 0.09
p-value versus placebo				0.1598

bid = twice daily; CI = confidence interval; LS = least square; max = maximum; min = minimum; Q1, Q3 = quartile 1, 3; SD = standard deviation; SE = standard error

** For the ITT analysis, missing data were imputed using MI under assumption of MNAR. Analysis and p-value for comparison of pridopidine versus placebo were generated by combining the results from MMRM on each imputed dataset. Summary statistics are not applicable due to multiple imputation. In the MMRM, change from baseline in TFC score is the dependent variable, and independent variables include treatment arm, baseline TFC, region, neuroleptic use or no use, baseline HD stage (HD1 and HD2), categorical week,*

and treatment by categorical week interaction, with Kenward-Roger approximation for degrees of freedom. The unstructured covariance matrix is used for repeated measurements at patient level.
*** One patient was screened with TFC ≥ 7 but the patient's score had declined to below 7 by the baseline visit.*

Key Secondary Endpoint – cUHDRS (mITT population)

As the primary endpoint was not met, p-values are nominal in all subsequent analyses. In mITT population, LS mean difference between pridopidine and placebo at Week 65 was -0.11 in favour of placebo (95% CI: -0.40, 0.18; nominal p=0.454) (Figure 10 and Table 22).

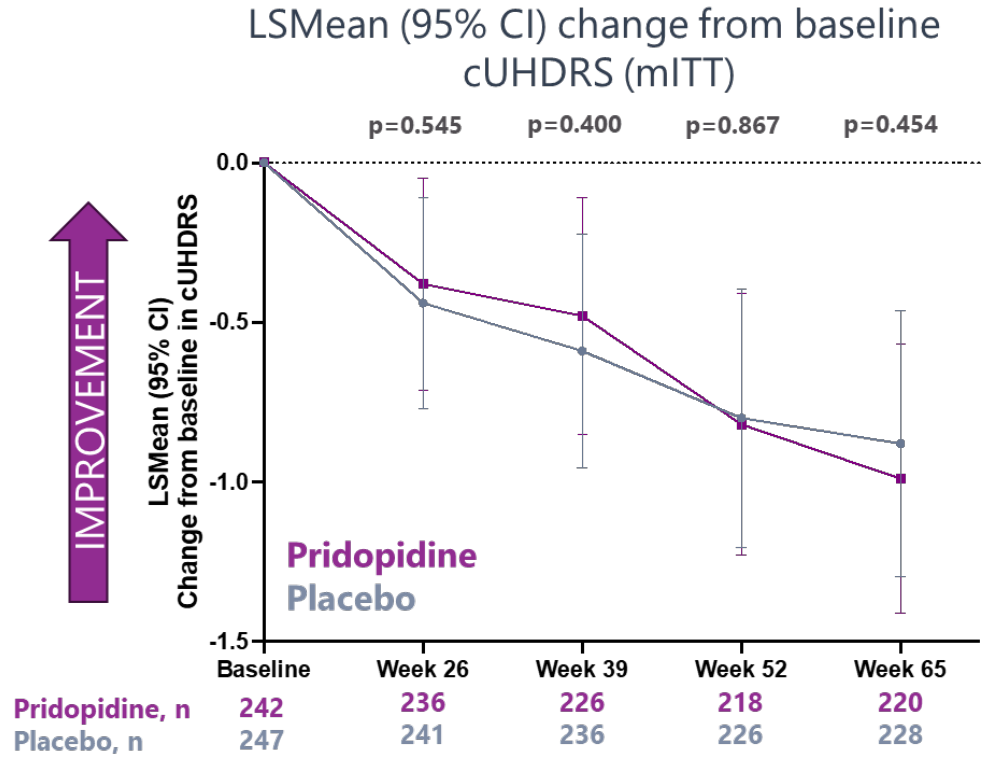


Figure 10: PROOF-HD: summary and MMRM analysis of cUHDRS through week 65 (mITT population)

Table 22: Change from baseline to week 65 in cUHDRS (mITT population)

Week (visit)	Placebo (N = 247)		Pridopidine 45 mg bid (N = 243)	
	Actual	Change from baseline	Actual	Change from baseline
Day 1 (Visit 2) (baseline)				
n (missing)	247 (0)		242 (1)	
Mean (SD)	8.86 (2.655)		8.68 (2.525)	
Median	8.90		8.80	
Q1, Q3	7.20, 10.70		7.30, 10.50	
Min, max	0.9, 15.4		1.9, 16.9	
Week 65 (Visit 7)				
n (missing)	228 (19)	228 (19)	221 (22)	220 (23)
Mean (SD)	8.18 (3.272)	-0.80 (1.576)	7.95 (3.167)	-0.87 (1.682)
Median	8.10	-0.70	7.90	-0.65
Q1, Q3	6.20, 10.55	-1.80, 0.30	5.80, 10.10	-2.00, 0.30
Min, max	-1.2, 17.3	-4.6, 4.8	-1.8, 16.0	-6.3, 3.7
LS mean (SE)		-0.88 (0.108)		-0.99 (0.109)
95% CI		-1.09, -0.66		-1.20, -0.77
LS mean difference (SE) versus placebo				-0.11 (0.148)
95% CI versus placebo				-0.40, 0.18
p-value versus placebo*				0.4544

bid = twice daily; CI = confidence interval; cUHDRS = composite Unified Huntington's Disease Rating Scale; LS = least square; max = maximum; min = minimum; Q1, Q3 = quartile 1, 3; SD = standard deviation; SE = standard error
** The p-values presented are nominal.*
Note: Analysis and p-value were generated on observed data from MMRM for comparison of pridopidine versus placebo. In the MMRM, change in cUHDRS score from baseline was the dependent variable, while independent variables included treatment arm, baseline cUHDRS, region, neuroleptic use or no use, baseline HD stage (HD1 and HD2), categorical week, and treatment by categorical week interaction, with Kenward-Roger approximation for degrees of freedom. The unstructured covariance matrix was used for repeated measurements at patient level. No imputation was performed on missing data.

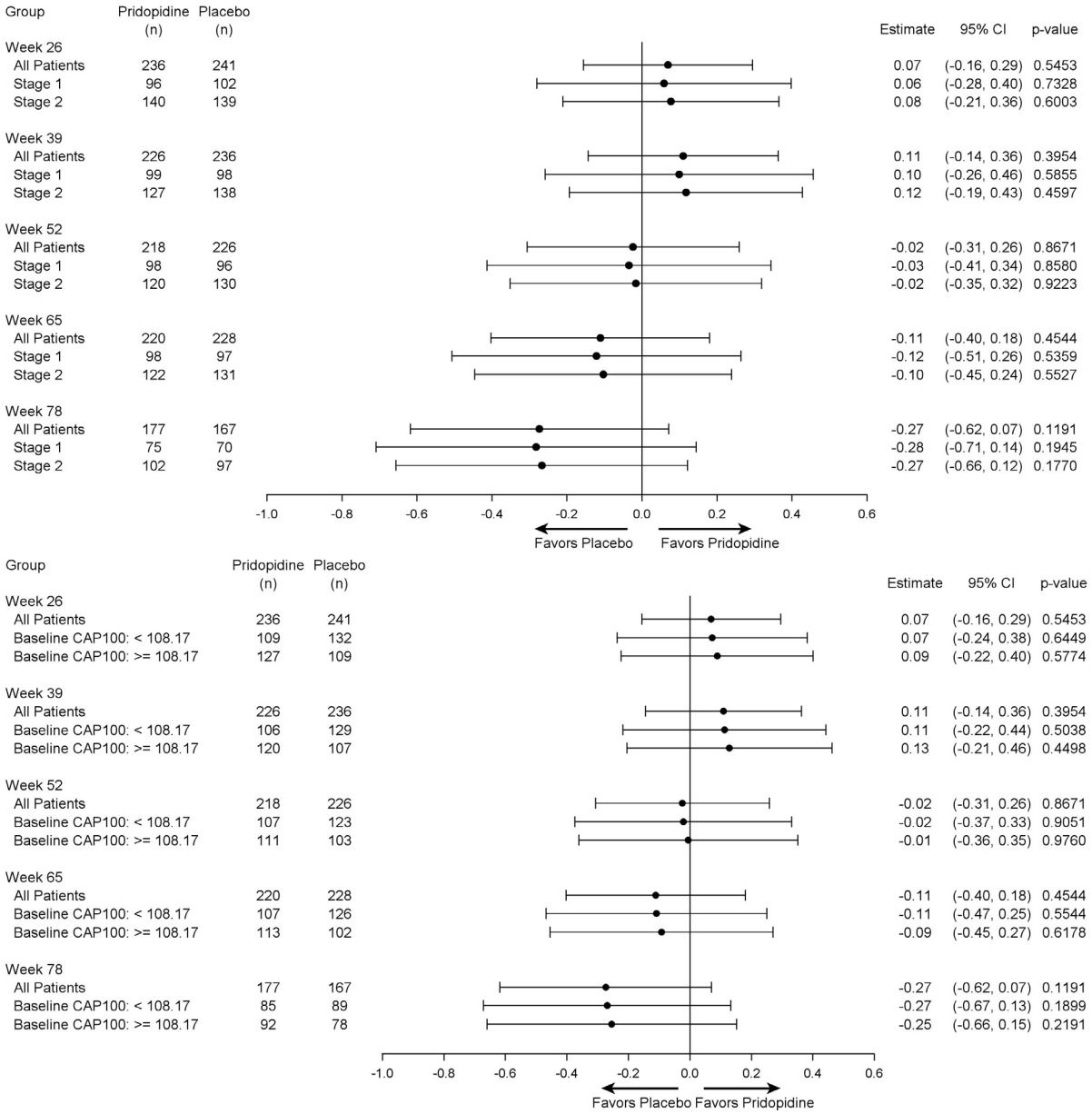
Other secondary endpoints – SWR, SDMT, TMS, CGI-C, Q-motor FT IOI, and exploratory endpoint HD-QoL (mITT population)

There was no benefit of pridopidine observed on any of the other secondary endpoints or HD-QoL.

- **Ancillary analyses**

Predefined subgroup analyses (mITT population)

In the CHMP AR, only analyses on cUHDRS are shown and only for subgroups that are related to disease progression for HD (i.e., disease stage and CAG-Age product (CAP)100 score).



Note: the CAP100 score has been calculated based on Warner et al 2022; Long et al 2023.

Figure 11: Change-from-baseline cUHDRS score per visit and by HD-stage (top) or CAP100 score (down) Ancillary efficacy analyses in patients off ADMs

Subgroup analysis based on ADM use

In the PROOF-HD SAP v3 (28 Mar 2023; database lock was 04apr2023) the subgroup by concomitant chorea medication (VMAT2 inhibitors) any time was specified. In addition, in SAP v3 a sensitivity analysis was defined wherein patients who received neuroleptics at any time during the study were excluded. Applying the sensitivity analysis of excluded patients on neuroleptics (at any time) to the subgroup of VMAT2 inhibitors (at any time), allowed to evaluate patients who did not take a neuroleptic and also did not take a VMAT2 inhibitor at any time. This represents the subgroup off ADMs all the time/at any time.

TFC (primary endpoint)

In patients off ADMs all the time in mITT, the treatment difference for TFC numerically favoured pridopidine on TFC at all timepoints through Week 78.

Table 23: PROOF-HD: statistical analysis results; TFC in patients off ADMs (mITT population)

	Placebo	Pridopidine 45 mg bid
Day 1 (visit 2; baseline) actual value		
n (missing)	112 (0)	97 (0)
Mean (SD)	10.3 (1.6)	10.2 (1,65)
Median	11	10
Q1, Q3	10, 11.5	9, 11
Min, Max	7, 13	5, 13
Week 65 (visit 7) - change from baseline		
n (missing)	106 (6)	93 (4)
Mean (SD)	-0.6 (1.52)	-0.5 (1.56)
Median	0	0
Q1, Q3	-1, 0	-1, 0
Min, Max	-5, 4	-7, 3
LS Mean (SE)	-0.54 (0.15)	-0.49 (0.156)
95% CI	-0.83, -0,24	-0.8, -0,18
LS Mean Difference (SE) vs Placebo		0.05 (0.215)
95% CI vs Placebo		-0.38, 0.47
Nominal p-value vs Placebo		0.8242
Week 78 (visit 8) - change from baseline		
n (missing)	74 (40)	71 (26)
Mean (SD)	-0.5 (1.63)	-0.2 (1.46)
Median	0	0
Q1, Q3	-1, 0	-1, 1
Min, Max	-5, 3	-4, 3
LS Mean (SE)	-0.54 (0.163)	-0.42 (0.166)
95% CI	-0.86, -0,22	-0.74, -0,09
LS Mean Difference (SE) vs Placebo		0.12 (0.231)
95% CI vs Placebo		-0.33, 0.58
Nominal p-value vs Placebo		0.5918

Table made by assessor; source: PROOF-HD CSR, Table 14.2.01.5.21.3; Table 14.2.01.5.22.3.

cUHDRS (key secondary endpoint)

In patients off ADMs all the time in mITT, the treatment difference for cUHDRS numerically favoured pridopidine on TFC at all timepoints through Week 78.

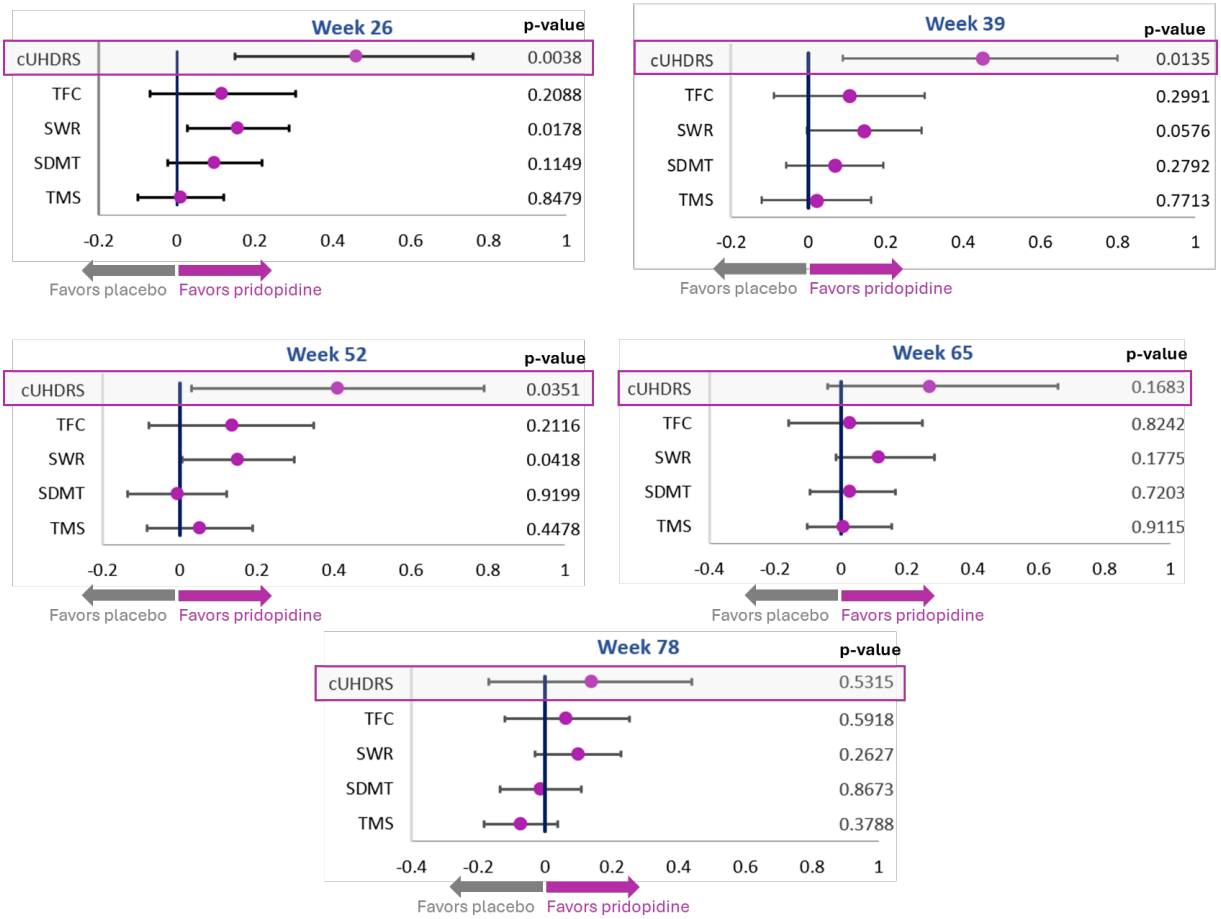
Table 24: PROOF-HD: statistical analysis results; cUHDRS in patients off ADMs (mITT)

	Placebo	Pridopidine 45 mg bid
Day 1 (visit 2; baseline) actual value		
n (missing)	112 (0)	97 (0)
Mean (SD)	9.92 (2.422)	9.43 (2.507)
Median	9.85	9.5
Q1, Q3	8.7, 11.8	8.1, 11.3
Min, Max	3.4, 15.4	2.2, 16.9
Week 65 (visit 7) - change from baseline		
n (missing)	106 (6)	91 (6)
Mean (SD)	-0.45 (1.48)	-0.2 (1,502)
Median	-0.25	-0.1
Q1, Q3	-1.3, 0.4	-1,2, 0,7
Min, Max	-4.3, 4.8	-3,5, 3,7
LS Mean (SE)	-0.53 (0.137)	-0.26 (0.143)
95% CI	-0.8, -0,26	-0.54, 0.02
LS Mean Difference (SE) vs Placebo		0.27 (0.197)
95% CI vs Placebo		-0.12, 0.66
Nominal p-value vs Placebo		0.1683
Week 78 (visit 8) - change from baseline		
n (missing)	71 (41)	70 (27)
Mean (SD)	-0.64 (1.722)	-0.22 (1.554)
Median	-0.6	-0.1
Q1, Q3	-1.5, 0.4	-1, 0.8
Min, Max	-4.7, 4.1	-4.4, 2.9
LS Mean (SE)	-0.54 (0.158)	-0.4 (0.159)
95% CI	-0.85, -0,23	-0.71, -0,08
LS Mean Difference (SE) vs Placebo		0.14 (0.223)
95% CI vs Placebo		-0.3, 0.58
Nominal p-value vs Placebo		0.5315

Table made by assessor; source: PROOF-HD CSR, Table 14.2.02.1.10.3; Table 14.2.02.1.11.3.

cUHDRS components

A critical assumption underlying the use of the multicomponent cUHDRS in clinical studies is that if a putative neuroprotective therapy successfully targets the disease mechanisms underlying clinical progression, then each individual measure making up the cUHDRS should show concordant improvement in response to this treatment (Schobel et al, 2017). Figure 12 shows a forest plot with the contribution of each individual component of the cUHDRS at each visit in patients off ADMs (mITT population).



Source: PROOF-HD CSR, Tables 14.2.02.1.10.3, 14.2.02.1.11.3, 14.2.01.5.21.3, 14.2.01.5.22.3, 14.2.07.6.3, 14.2.07.7.3, 14.2.05.8.3, 14.2.05.9.3, 14.2.04.1.11.3, and 14.2.04.1.12.3. Note: MMRM analysis for each of the four components of the cUHDRS excluding patients on ADMs. The treatment difference and 95% CIs estimated from each model, along with the nominal p-value are shown in the forest plots. The four components of cUHDRS were re-scaled by respective standardisation factors used in Schobel's formula for cUHDRS to visualize their relative contribution in forest plots (Schobel et al 2017).

Figure 12: PROOF-HD: change from baseline through week 78 in cUHDRS and its individual components (Function, Cognition, and Motor) in patients off ADMs (mITT)

Q motor FT IOI (secondary endpoint)

In the patients off ADMs (mITT population), the effect favoured pridopidine at all timepoints through 78 weeks.

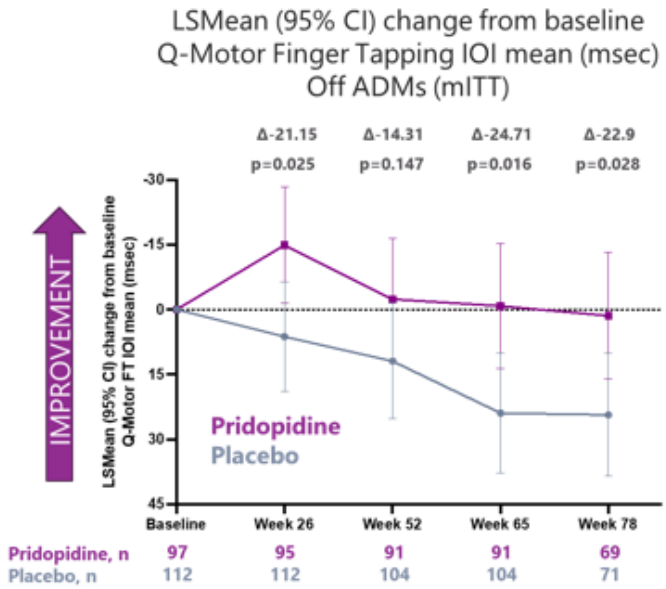


Figure adjusted by the assessor to show treatment difference values and nominal p-values in the same figure. Source: PROOF-HD CSR, Tables 14.2.03.1.9.11.3 and 14.2.03.1.9.12.3. For consistency with other measures presented, the applicant inverted the y-axis so improvement is reflected upwards.

Figure 13: PROOF-HD: Q motor FT IOI mean in patients off ADMs (mITT)

Secondary endpoint CGI-C and exploratory endpoint HD-QoL

No benefit for pridopidine was observed in CGI-C or HD-QoL total score in the off-ADM group in mITT population.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 25: Summary of efficacy for pivotal trial PROOF-HD

Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Parallel Arm, Multicenter Study Evaluating the Efficacy and Safety of Pridopidine in Patients With Early Stage of Huntington Disease			
Study identifier	PL101-HD301		
Design	Randomized, double-blind, placebo-controlled, parallel arm, multicentre study conducted in Austria, Canada, Czech Republic, France, Germany, Italy, Netherlands, Poland, Spain, United Kingdom, and United States.		
	Duration of main phase: Duration of Run-in phase:		65 to 78 weeks not applicable
Hypothesis	Superiority		
Treatments groups	Pridopidine		45 mg pridopidine twice daily (bid), main phase and extension phase
	placebo		Matching placebo, main phase
Endpoints and definitions	Primary endpoint: Change from Baseline (CFB) in TFC Score to Week 65	CFB in TFC to Week 65	The primary efficacy endpoint for this study was the change from baseline to Week 65 in the TFC (defined as the sum of all TFC 5-items ratings [domestic chores, activities of daily living, finances, care level, and occupation]). The TFC is the standard and well-accepted clinical scale for staging and tracking the progression of HD using functional capacity. Scores range from 0 to 13, with 13 as the least affected and 0 as complete incapacity.

Key subgroup	Patients who were not on VMAT2 inhibitors and neuroleptics (i.e., ADMs), abbreviated as 'Off ADMs'.		
Database lock	04 Apr 2023		
Results and Analysis			
Analysis description	Primary Analysis		
Analysis population and time point description	ITT population, including all randomized participants Time point: Baseline and Week 65		
Descriptive statistics and estimate variability	**Treatment group**	**Pridopidine**	**Placebo**
	Number of participants at Baseline	250	249
	TFC at Baseline Mean Standard deviation	 9.8 1.70	 9.9 1.70
	Number of participants at Week 65	233	228
	TFC at Week 65 Mean Standard deviation	 8.8 2.30	 9.0 2.33
	CFB in TFC to Week 65 Mean Standard deviation	 -1.1 1.82	 -0.9 1.72
Effect estimate per comparison	Primary endpoint: CFB in TFC to Week 65	Comparison groups	Pridopidine vs Placebo
		LS Mean Difference	-0.23
		95% confidence interval	-0.55, 0.09
		P-value based on Wald test combining inferences from multiply imputed datasets	0.1598
Notes	Missing data were imputed using control-based pattern imputation under assumption of MNAR. Analysis and p-value for comparison of Pridopidine vs Placebo were generated by combining the results from MMRM on each imputed dataset. In MMRM model, change in TFC score from baseline is the dependent variable and independent variables include treatment group, Baseline TFC, region, neuroleptic use or no use, Baseline HD stage (HD1 and HD2), categorical week, and treatment by categorical week interaction, with Kenward-Roger approximation for degrees of freedom. The unstructured covariance matrix is used for repeated measurements at participant level. Note: no tabulated result for the key secondary endpoint was provided. Data for the off-ADM group were provided but as that was not part of the primary analysis, it is not included here.		

2.6.5.3. Clinical studies in special populations

No dedicated clinical studies were conducted in older adult HD patients, but no upper age limit was imposed in controlled clinical studies, except in Study ACR16C007 (upper age limit of 75 years). The applicant indicates that the age distribution approximates the general HD population (Evans et al., 2013; Langbehn et al., 2023; Ohlmeier et al., 2019).

Table 26: Age distribution

	Age 65-74 (Older subjects number /total number)	**Age 75-84 (Older subjects number /total number)**	**Age 85+ (Older subjects number /total number)**
Controlled trials Total n=1629	175/1629 (10.7%)	20/1629 (1.2%)	2/1629 (0.1%)
Non-controlled trials Total n=1368	142/1368 (10.4%)	14/1368 (1.0%)	1/1368 (0.1%)

2.6.5.4. In vitro biomarker test for patient selection for efficacy

Not applicable

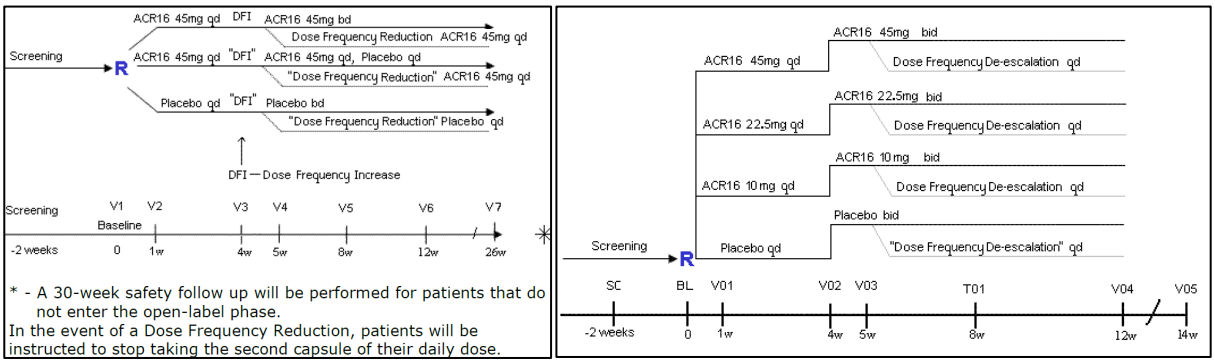
2.6.5.5. Analysis performed across trials (Integrated Efficacy Analysis; IEA)

The objectives of the IEA were to assess whether a pooled analysis of prior studies with pridopidine was consistent with PROOF-HD study. PROOF-HD, PRIDE-HD, MermaiHD and HART studies were included based on the criteria that they were double-blind, randomized, placebo-controlled studies in HD patients with baseline TFC 7-13 that evaluated pridopidine 45 mg bid and had a treatment duration of ≥12 weeks.

Design of the studies MermaiHD and HART

MermaiHD study was conducted across Europe; HART study was conducted in the US and Canada. Dose administration in all arms was titrated: first 4 weeks qd administration, all weeks thereafter bid administration. Refer to Table 8 for a tabulated overview of key design features of both studies.

Figure 14: Study schema MermaiHD (left) and HART (right)



Study population

Both studies: Male or female patients aged ≥30 years with confirmed HD (CAG≥36) were included. Patients at all disease stages (HD1-HD4, TFC 0-13) were enrolled though they had to be ambulatory, being able to travel to the assessment centre for the duration of the study. Patients had to have a mMS score of ≥10 at the screening visit. The mMS consists of a subset of the TMS scale that assesses voluntary motor function, but excludes chorea, dystonia, and eye movements (i.e. sum score of items 4-10 and 13-15 of the UHDRS motor assessment).

MermaiHD study: Patients were stratified on antipsychotic medication use at randomisation; >50% were planned to be off antipsychotic medication.

Prohibited medications

Both studies: dose should have been kept constant for at least 6 weeks before randomisation.

MermaiHD study: Neuroleptics were allowed with restrictions; allowed neuroleptics were amisulpride, haloperidol, olanzapine, risperidone, sulpiride, or tiapride.
HART study: All antidepressants and psychotropics were allowed except tetrabenazine, antipsychotic medication (neuroleptics) and tricyclic antidepressants

Objectives and endpoints

Primary objective: assessment of effects of pridopidine on voluntary motor function in HD patients, using as primary endpoint the change in mMS from baseline to Week 26 (MermaiHD study) or Week 12 (HART study).

Components of cUHDRS were separately evaluated as secondary or tertiary endpoint.

Analysis plan of IEA

The SAP for the integrated efficacy analysis was finalized on 5 March 2024 which was eleven months after database lock for PROOF-HD (4 April 2023) and only one week before release of CSR for PROOF-HD study (12 March 2024).

The analysis used the treatment policy estimand and the composite estimand corresponding with those of PROOF-HD study. The statistical model included as fixed effects: treatment, baseline (for the actual endpoint), baseline TFC (replaced by HD stage for analysis of TFC), region (Europe, North America), ADMs use at baseline (yes, no) (not included as covariate in the analysis of ADMs-subgroups), categorical week, and treatment by categorical week interaction. Study was included as a fixed effect. Outcomes after a last observation will be imputed using a control-based imputation (composite/hypothetical strategy) and all recorded outcomes after other intercurrent event will be used (treatment-policy strategy).

The null hypothesis was no difference between treatments. All tests were 2-sided and performed at the 5% significance level. No adjustment for multiple testing was done to account for testing at multiple endpoints at different timepoints. Nominal p-values were reported together with the corresponding 95% CI.

In the IEA, the analyses were carried out on the ITT population which was similarly defined as in PROOF-HD study.

Table 27: IEA: schedule of assessments of cUHDRS, cUHDRS(-SWR), TFC, and Q-Motor

Study	**Week**						
	4	**12**	**26**	**39**	**52**	**65**	**78**
PROOF-HD	Not assessed		cUHDRS cUHDRS (-SWR) TFC Q-Motor	cUHDRS cUHDRS (-SWR) TFC	cUHDRS cUHDRS (-SWR) TFC Q-Motor	cUHDRS cUHDRS (-SWR) TFC Q-Motor	cUHDRS cUHDRS (-SWR) TFC Q-Motor
PRIDE-HD[a]	cUHDRS (-SWR) TFC Q-Motor	cUHDRS (-SWR) TFC Q-Motor	cUHDRS (-SWR) TFC Q-Motor	Not assessed	cUHDRS (-SWR) TFC Q-Motor	-	
MermaiHD	Not assessed		cUHDRS cUHDRS (-SWR) TFC	-			
HART	Not assessed	cUHDRS* cUHDRS (-SWR) TFC	-				

*Source: IEA SAP, Table 2. cUHDRS(-SWR) was calculated based on TFC, TMS, and SDMT. a: SWR was not evaluated in PRIDE-HD. *: assessor note: not analysed in IEA, though protocol indicates that HART included SWR.*

Explanation of cUHDRS(-SWR)

The cUHDRS(-SWR) is derived from three components of the composite scale: TFC, TMS, and SDMT, retaining a measure in the domains of function, motor, and cognition. All four studies assessed TFC, TMS, and SDMT, but PRIDE-HD study did not measure SWR.

Demographics and Baseline Characteristics of patients in the IEA

The IEA included patients from MermaiHD, HART, PRIDE-HD and PROOF-HD studies. Patients with HD1 or HD2 (TFC 7-13) at baseline and receiving pridopidine 45 mg bid were included.

There were several differences between enrolment criteria among the four clinical studies, including TFC-score (TFC7-13 in PROOF-HD study; TFC0-6 in PRIDE-HD study, MermaiHD and HART studies) age (≥25 years in PROOF-HD study; ≥21 years in PRIDE-HD study; ≥30 years in MermaiHD and HART studies), independency score (UHDRS-IS of ≤90% in PROOF-HD and PRIDE-HD studies; no criterion in MermaiHD and HART studies) and motor function (TMS score of ≥20 in PROOF-HD study; TMS ≥25 in PRIDE-HD study; and sum of ≥10 points on the mMS (subscore of TMS) in MermaiHD and HART studies). Refer to Table 35 for number of patients based on ADM use.

Table 28: IEA: Patients with Baseline TFC 7-13 per ADM Usage Subgroups (ITT population)

Population/ subgroup	PROOF-HD[a]		PRIDE-HD		MermaiHD		HART		Total	
	Placebo	**Prido 45 mg bid**	**Placebo**	**Prido 45 mg bid**	**Placebo**	**Prido 45 mg bid**	**Placebo**	**Prido 45 mg bid**	**Placebo**	**Prido 45 mg bid**
ITT population, n (%)										
All patients	249 (100)	249 (100)	62 (100)	64 (100)	89 (100)	90 (100)	48 (100)	46 (100)	448 (100)	449 (100)
On ADMs at baseline	111 (44.6)	124 (49.8)	25 (40.3)	17 (26.6)	32 (36.0)	31 (34.4)	1 (2.1)	1 (2.2)	169 (37.7)	173 (38.5)
Off ADMs at baseline	138 (55.4)	125 (50.2)	37 (59.7)	47 (73.4)	57 (64.0)	59 (65.6)	47 (97.9)	45 (97.8)	279 (62.3)	276 (61.5)
On ADMs at any time	137 (55.0)	150 (60.2)	26 (41.9)	18 (28.1)	34 (38.2)	32 (35.6)	1 (2.1)	1 (2.2)	198 (44.2)	201 (44.8)
Off ADMs all the time	112 (45.0)	99 (39.8)	36 (58.1)	46 (71.9)	55 (61.8)	58 (64.4)	47 (97.9)	45 (97.8)	250 (55.8)	248 (55.2)

Source: IEA, Table 8. [a] One patient in PROOF-HD was screened with TFC ≥7 but had a TFC decline to below 7 at baseline. Therefore, this patient was not included in the integrated analysis of efficacy (499 patients enrolled in the PROOF-HD study, data for 498 patients included in the IEA). Note: Percentage is based on all patients in the corresponding study population. Note: For PROOF-HD, PRIDE-HD, and MermaiHD, neuroleptics use at baseline was a stratification factor. The ADM use is based on the actual ADM recorded as concomitant medications. There is a difference of 11% between the actual use and randomisation stratification factor. Also, the randomisation is not stratified by baseline TFC. When subsetting the patients with TFC 7-13, it makes the treatment further off-balance, resulting in the apparent discrepancy for PRIDE-HD where neuroleptic use at baseline for the placebo arm (40.3%) appears higher compared to that of the treated arm (26.6%).

Results of the IEA

TFC (assessed in all four studies)

Overall population (ITT population; irrespective of ADM use)

There were no meaningful differences between placebo and pridopidine Table 29).

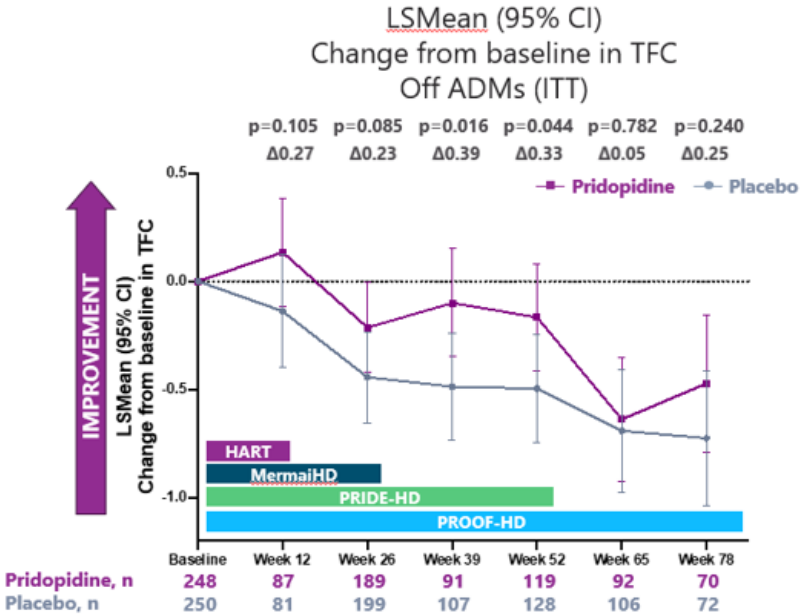
Table 29: Change from baseline through week 78 in TFC (ITT population, treatment policy estimand)

			LS MEANS		LS MEANS (Pridopidine-Placebo)-difference		
Treatment group	Visit	N	Estimate	95% CI	Estimate	95% CI	P-value
45mg bid	Week 4	59	-0.265	(-0.515, -0.016)	-0.085	(-0.396, 0.225)	0.588
	Week 12	101	-0.238	(-0.483, 0.007)	0.053	(-0.262, 0.369)	0.740
	Week 26	376	-0.479	(-0.663, -0.295)	0.007	(-0.196, 0.210)	0.948
	Week 39	230	-0.475	(-0.684, -0.266)	0.107	(-0.126, 0.339)	0.368
	Week 52	266	-0.758	(-0.979, -0.538)	0.066	(-0.194, 0.327)	0.617
	Week 65	227	-1.011	(-1.249, -0.772)	-0.048	(-0.335, 0.239)	0.745
	Week 78	179	-1.072	(-1.332, -0.811)	-0.071	(-0.400, 0.257)	0.670
Placebo	Week 4	62	-0.180	(-0.420, 0.060)			.
	Week 12	108	-0.291	(-0.527, -0.055)			.
	Week 26	387	-0.486	(-0.668, -0.304)			.
	Week 39	237	-0.582	(-0.789, -0.374)			.
	Week 52	276	-0.825	(-1.044, -0.606)			.
	Week 65	233	-0.963	(-1.199, -0.727)			.
	Week 78	170	-1.000	(-1.261, -0.739)			.

CI=Confidence interval ; LS Means= Least Square Means; N = Number of subjects with observed data.
Source: IEA v1 2024-07-15, Table 29

Subgroup off ADMs

The treatment difference favoured pridopidine group through week 78 (Figure 15).



Figures adjusted by the assessor to show treatment difference values and nominal p-values in the same figure.
Source: IEA, Table 1.1.1.2.2.

Figure 15: IEA: TFC through week 78 (off ADMs all the time, ITT, treatment policy estimand)

cUHDRS(-SWR) (assessed in all four studies)

Overall population (ITT population; irrespective of ADM use)

The treatment difference favoured pridopidine until Week 65 and placebo at Week 78 (Table 30).

Table 30: Change from baseline through week 78 in cUHDRS(-SWR) (ITT, treatment policy estimand)

			LS MEANS		LS MEANS (Pridopidine-Placebo)-difference		
Treatment group	Visit	N	Estimate	95% CI	Estimate	95% CI	P-value
45mg bid	Week 12	94	0.013	(-0.193, 0.220)	0.076	(-0.188, 0.341)	0.569
	Week 26	367	-0.148	(-0.293, -0.004)	0.098	(-0.057, 0.253)	0.214
	Week 39	226	-0.248	(-0.423, -0.074)	0.151	(-0.046, 0.347)	0.133
	Week 52	250	-0.527	(-0.705, -0.348)	0.089	(-0.120, 0.299)	0.403
	Week 65	219	-0.635	(-0.824, -0.446)	0.016	(-0.209, 0.241)	0.889
	Week 78	177	-0.867	(-1.080, -0.653)	-0.121	(-0.389, 0.146)	0.373
Placebo	Week 12	105	-0.063	(-0.258, 0.132)			.
	Week 26	378	-0.246	(-0.389, -0.103)			.
	Week 39	236	-0.399	(-0.572, -0.226)			.
	Week 52	264	-0.616	(-0.792, -0.440)			.
	Week 65	229	-0.651	(-0.838, -0.464)			.
	Week 78	167	-0.745	(-0.959, -0.531)			.

CI=Confidence interval ; LS Means= Least Square Means; N = Number of subjects with observed data.
Source: IEA v1 2024-07-15, Table 27

Subgroup off ADMs

The treatment difference favoured pridopidine group through Week 78 (Figure 16).

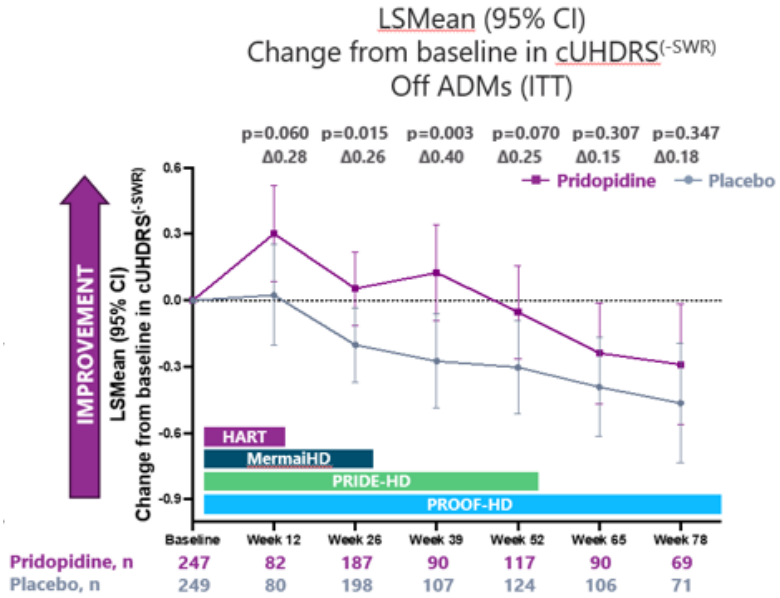


Figure adjusted by the assessor to show treatment difference values and nominal p-values in the same figure.
Source: IEA, Table 3.1.1.2.2.

Figure 16: IEA: cUHDRS(-SWR) in patients off ADMs all the time in ITT, treatment policy estimand

2.6.5.6. Supportive study(ies)

Open HART study

- **Overall design**

This was an OLE of pridopidine 45 mg bid in patients who completed HART or PRIDE-HD studies, and ran from Mar 2011- Jan 2018. The study was planned to continue until pridopidine was authorized in Canada or USA or discontinued due to risk-benefit or commercial reasons.

Collection of long-term information on UHDRS development was the primary objective, which was collected at virtual visits every 52 weeks and at EOS/ET. No formal inferential statistics were applied.

Prohibited medications were mostly comparable to HART study. Also deutetrabenazine was prohibited in open-HART study; it was not yet approved by Food Drug Administration at time of HART study.

- **Results**

Patient disposition and baseline results

Efficacy was evaluated in 123 patients, of which 30 completed Month 72; 94 patients (70%) discontinued from the study. The most frequent reasons for study discontinuation were withdrawal by subject (23 patients [17%]) and AEs (21 patients [16%]).

Mean age was 52.4 years; mean weight 74.7 kg. The majority was white (n=129 [96%]). Proportion male and female patients was equal (50%/50%). The majority (n=120 [90%]) was extensive CYP2D6 metabolizer; most (n=133 [>99%]) did not use neuroleptics at baseline. Mean CAG repeats was 43.5.

Therapeutic medication classes used most frequently during the study included psychoanaleptics (102 [76%]), vitamins (68 [51%]), and analgesics (59 [44%]).

Efficacy results

UHDRS-TFC

Based on natural history studies in HD (Shoulson and Fahn 1979, van der Burg et al 2017), there is a reason to expect a 0.5- to 1.0-unit annual decline in UHDRS-TFC (i.e., 3 to 6 units over the duration of this study). Overall, a mean 3-unit decline in UHDRS-TFC was observed from baseline to month 72.

UHDRS-TMS

Based on natural history studies in HD there is a reason to expect a 3-4 unit annual decline in UHDRS-TMS (i.e., 18-24 units over the course of this study) (van der Burg et al 2017). A change of 18 units was observed from baseline over the course of the study.

Open PRIDE-HD

- **Overall design**

This was an OLE with pridopidine 45 mg bid in adults with HD who participated in PRIDE-HD and Open-HART studies. The study was conducted globally in 11 countries and ran Sept 2015-Jan 2018.

The open-label treatment period was up to 104 weeks. Long-term effects on UHDRS-TMS, UHDRS-TFC and Q-Motor assessments were evaluated as secondary objective. Prohibited medications were comparable to PRIDE-HD. No formal inferential statistics were applied to efficacy results.

- **Results**

Patient disposition and baseline results

The study was terminated early by the sponsor (Teva) as it served its purpose. A total of 248 patients were dosed; 221 (89%) patients withdrew from the study. The most frequent reason for withdrawal was Other, which occurred for 173 (70%) patients. Specifically, 167 (67%) patients were withdrawn due to study termination by the sponsor, site closure, or sponsor decision.

Mean age was 50.6 years, weight 71.4 kg. The majority of patients were white (n=227 [92%]); proportion males and females was similar (48% vs 52%). The majority (n=214 [86%]) were extensive CYP2D6 metabolisers; mean CAG repeats was 44.8. In total, 94 patients used neuroleptics. Most frequently used medications before and during the study included olanzapine (n=31 [13%] before, and n=41 [17%] during the study), paracetamol (n=13 [5%] before, and n=31 [13%] during the study), and ibuprofen (n=11 [4%] before, and n=24 [10%] during the study).

Efficacy results

UHDRS-TFC: overall, a mean 1-unit decline in UHDRS-TFC was observed from baseline to End of Study.

UHDRS-TMS: Potential improvement was observed up to week 26, however, a subsequent increase was observed from week 52 (2.5 units) through End of Study (7.2 units), indicating worsening in the motor performance).

Q motor: No improvement was observed in any of the Q-Motor assessments. The mean change from baseline in the digitomotography assessments of pronation-supination-frequency decreased (indicating a trend toward decline) at week 52 or End of Study.

2.6.6. Discussion on clinical efficacy

Clinical development plan

Pridopidine has been in clinical development for over 20 years, by several owners. In total, 8 clinical studies in HD were performed of which three included >400 HD patients (MermaiHD, PRIDE-HD and PROOF-HD) and of which two were labelled as phase III studies (MermaiHD and PROOF-HD). The applicant proposes that PROOF-HD is the single source of pivotal evidence to substantiate the proposed indication.

This is agreed. MermaiHD and HART are of limited support for this MAA as they focused on evaluating rapid effects on motor symptoms, and had a duration of up to 26 weeks. PRIDE-HD is considered supportive as being the dose-finding study for PROOF-HD. PRIDE-HD tested several treatment regimens and collected 52-week data on the TFC score, which was used as primary variable in PROOF-HD. In extension of this reasoning it is also agreed that ACR16C007 is not discussed as it had a duration of 4 weeks and tested a different pridopidine dose (50mg qd) than the posology under evaluation (45mg bid).

It should be noted that a therapeutic area with a history of failed studies or failures to confirm seemingly convincing results is listed as a scenario why it is usually prudent to plan for more than one study in the phase III program (CPMP/EWP/2330/99). Furthermore, pridopidine as a S1R agonist has a novel action mechanism in the treatment of HD. Additionally, from non-clinical data the link between pridopidine's effects on S1R and in HD specifically appears limited. Despite these uncertainties, a single source of pivotal evidence (PROOF-HD) is presented to support this MAA. In line with the points to consider on application with 1. Meta-analysis; 2. One pivotal study, in cases where the confirmatory

evidence is provided by one pivotal study only, this study was expected to be exceptionally compelling (CPMP/EWP/2330/99). This was not the case (see below).

Dose finding study: PRIDE-HD

Design

Efficacy assessments, including UHDRS-TMS (primary endpoint) and UHDRS-TFC (TFC; exploratory endpoint) were mostly comparable to the pivotal study. Refer to the respective discussion section of the pivotal study, below, for details.

PRIDE-HD was a 26-week randomized (1:1:1:1), double-blind, placebo-controlled study performed to evaluate effects of higher pridopidine doses on motor function (doses: 45mg bid; 67.5mg bid; 112.5mg bid). While its design was sound for this purpose, during conduct the study was extended from 26 to 52 weeks. The applicant indicates this change was based on emergent data that pridopidine was primarily a S1R agonist rather than dopamine stabilizer. The extension allowed assessing functional decline using TFC, as the applicant argued that at least 52 weeks are needed to measure TFC-decline in the placebo group. However, protocol amendment 4 (12jan2015) states that reason for study extension was to collect long-term safety data (PRIDE-HD CSR). Moreover, the clinical PET study assessing S1R occupancy (refer to section 2.6.2.2.), was performed only after PRIDE-HD. I.e., information on S1R was limited to preclinical data. No concrete evidence was provided to prove that the non-clinical insights on S1R led to altered expectations for the TFC endpoint specifically. It thus remains uncertain if the TFC result was observed by chance (see next).

Moreover, the study extension while PRIDE-HD was ongoing raises concerns on the quality of the data. 113 patients were enrolled at time of extension, which may have influenced their expectations on long-term benefit; i.e., positively biased their efficacy results at Week 52. This may (partly) explain the considerable placebo response, and/or have created bias if patients were unbalanced across treatment arms at that time. However, as there are serious concerns on the pivotal study results (PROOF-HD; see below), and PRIDE-HD data are supportive, uncertainties on PRIDE-HD are not further pursued.

Results

PRIDE-HD did not meet its primary endpoint (TMS at Week 26). The applicant argues that this is partly because TMS was not the most appropriate endpoint for the effect of pridopidine, and because there was a large placebo response. Nonetheless, it is considered that further results are exploratory.

Across treatment arms, a comparable HD population seemed to be enrolled - except that it could not fully be confirmed if patients were balanced according to TFC disease-stage. In light of serious concerns on the pivotal study results (see below), this uncertainty is not further pursued.

The applicant attributes the bell-shaped-like dose-response curve in PRIDE-HD to S1R agonism. This reasoning can be followed: bell-shaped effects have been described for other S1R ligands as well (e.g., Cobos, 2008; Brimson 2020).

It is agreed that the 45mg bid dose appears most promising, but concerns apply. On TFC, the largest negative change-from-baseline was observed with 67.5 mg bid, although results for 90 and 112.5mg bid were roughly similar. Still these results are not exactly as expected for a bell-shaped effect (i.e., least effect at the highest doses). While a floor effect may play a role, it does not fully address why the smaller dose increase from 45 to 67.5 mg shows the largest effect difference. This leads to question if not instead the 45 mg bid result on TFC may be a chance finding. Even more so as many of the other endpoints did not show the same clear trend as the applicant described for TFC and Q-motor finger tapping IOI mean. Also recall that there are uncertainties regarding the study extension.

Thus, while the data are not overly convincing, the choice for 45mg bid and TFC as primary endpoint in PROOF-HD is sensible based on a) a known bell-shaped curve effect of S1R, b) the most favourable effect of 45mg bid on TFC in PRIDE-HD, and c) near-optimal occupancy in the PET study (>90%).

Pivotal study: PROOF-HD

Design

PROOF-HD had an overall sound design. It was a randomized (1:1), double-blind placebo-controlled study to collect pivotal efficacy data of pridopidine 45mg bid up to 78 weeks in an early HD patient population. The study was followed by a 2-year OLE to evaluate maintenance of effects. Together this dataset is considered acceptable to determine efficacy of pridopidine for the intended chronic use.

The applicant indicates that a common closing design was used to collect more longitudinal double-blind placebo-controlled efficacy data after the primary timepoint (i.e., up to 78 weeks; primary timepoint 65 weeks) until the last patient completed its Week 65 visit. In Scientific Advice in 2017 (EMA/CHMP/SAWP/645332/2017), a primary timepoint at Week 78 was proposed, which since then has been trimmed back to this design. This current design is also acceptable, however, as data till Week 78 are double-blind and placebo-controlled both Week 65 and Week 78 results are of key importance for efficacy assessment.

The study population is not in line with the proposed broad indication (i.e., 18+ years, all HD severity stages). PROOF-HD enrolled patients with adult-onset early HD (i.e., aged 25+ years and UHDRS-TFC score of ≥7 at Screening (HD1, HD2)). HD patients TFC0-6 were excluded based on an expected floor effect on the primary endpoint (TFC). While sensible, extrapolation of efficacy results from patients TFC7-13 to TFC0-6 is not clear-cut. This issue was resolved as the applicant restricted the indication to early HD during the procedure.

A comprehensive list of prohibited medicines was enforced which includes certain antipsychotics that are commonly used in HD patients (e.g., haloperidol). During the procedure, the applicant proposed updates to section 4.4. of the proposed SmPC, to discuss concomitant use of such medicines with pridopidine, which are not agreed. This is pursued as part of the wider issues on the 'off-ADM group' (see below).

Endpoints

Most primary and secondary efficacy assessments are part of the validated UHDRS (i.e., TFC, SWR, SDMT, TMS) and conventional in HD clinical trials.

In Scientific Advice 2023 (EMA/SA/0000105622), CHMP considered TFC acceptable but its use as sole primary endpoint was questioned. A validation report including justification of a minimally important treatment difference was requested to be included at the time of MAA. It was included upon request during this procedure (see results section below for details). Moreover, as TFC is limited to measuring functional impairment, to support a claim of broad treatment effects (i.e., on multiple HD domains) it needs support from other endpoints that assess other domains, e.g., motor and cognition.

To this end, use of cUHDRS as key secondary endpoint next to TFC is supported. cUHDRS is strongly correlated to its separate four components (e.g., Smith et al., 2021) and sensitive to disease progression in early HD patients. (Schobel et al., 2017). Its use as key endpoint and as substitute for the full UDHRS in early HD clinical trials is increasingly recognized. Without an approved treatment for HD, a minimally clinical important change has yet to be established. For HD patients TFC7-13, a broad panel of (clinical) scientists involved in HD reached consensus that slowing decline of cUHDRS with 0.2-0.3 pt./year is clinically meaningful in trial context. (Schobel et al., 2017). It is agreed that this reduction is appropriate as margin for clinical meaningfulness of cUHDRS results.

According to the PROOF-HD protocol the paper-and-pencil SDMT version was used. SDMT results may be influenced by e.g., writing competence or motor impairment. It is unclear how this was accounted for. Nonetheless, SDMT and TMS scores were comparable between treatment arms at baseline in mITT. Hence, there does not appear to be such a disbalance in writing competence between arms that could have affected SDMT outcomes to a notable degree. The uncertainty is therefore not pursued.

Other endpoints of interest were Q-motor FT IOI mean (a computerized test assessing fine hand motor function); global impression of change (GCI-C) and HD-QoL (quality of life questionnaire).

Analysis plan

Hierarchical strategy was used to control inflation of the alpha risk across primary and multiplicity-adjusted secondary endpoints. This is acceptable.

The primary analysis plan was discussed in detail in Scientific advice (EMA/CHMP/SAWP/645332/2017; EMA/SA/0000105622). The CHMP concluded that the primary analysis should be conducted in the ITT population and using a control-pattern based imputation. Ideally, a separate strategy should have been defined to handle different intercurrent events, such as use of rescue/concomitant medication for HD symptoms, stopping treatment due to lack of efficacy, stopping treatment because of an adverse effect and lack of treatment compliance. The treatment policy strategy was recommended in scientific advice and is considered acceptable to handle the intercurrent event of treatment discontinuation (regardless of the reported reason).

The sample size was based on results of PRIDE-HD, using an expected treatment difference of 0.7 on TFC. This is not understood as it is lower than the actual differences observed in PRIDE-HD (0.87pt. at Week 52 in ITT; 1.16pt. at Week 52 in a subgroup of patients with TFC 7-13). As the assumption made in the sample size calculation is not key for the overall benefit-risk balance, the uncertainty is not further pursued.

The applicant amended the SAP to v3 (28mar2023) days before database lock (04apr2023). It was far after the last protocol amendment (Amendment 7, 27 January 2022). This raised concerns as SAP v3 included a new subgroup analysis on chorea treatment (yes/no), which plays a key role in the applicant's benefit claim (see further sections). During the procedure, the applicant showed that interest in the use of chorea medicines was also mentioned in earlier SAP versions (i.e., since v1) in 'the 'other efficacy analysis section' ('*to explore potential impact on efficacy based on co-medication […] some will be participants taking tetrabenazine/deutetrabenazine/valbenazine vs. not those not taking these medications*"). While this resolves the concern, how interest in VMAT2i was exploratively defined is perpendicular to the importance now given to this analysis by the applicant.

The protocol was amended often and included changes to enrolment criteria, (key) secondary endpoints and the analysis approach. The primary endpoint remained unchanged. Changes to the enrolment criteria and other endpoints are not considered to impact efficacy determination.

The update to the concomitant use section in protocol amendment 6 (13may2021) raised concerns as it suggested that chorea medicines use was not allowed before that amendment. During the procedure, the applicant clarified that chorea medicines were always allowed as they were never 'prohibited medication'. In amendment 6 it was clarified that tetrabenazine and deutetrabenazine were allowed as response to a Health Canada query. This resolves the concern on whether allowing use of chorea medicines was changed during conduct of PROOF-HD. However, the importance the applicant now gives to use of these medicines (see below), does not align with the reasoning that they were initially not mentioned at all under 'permitted medication'.

The database was unlocked to correct efficacy data, which raised concerns on data integrity. During the procedure, the applicant indicated that data anomalies were discovered post-database lock on SWR

and SDMT which sparked the need for re-checking data (i.e., apparent switch of SWR and SDMT results; clear outliers such as '0', and illogical identical values). It was clarified that not only SWR (0.7% error rate) and SDMT (2%), but also TFC (0.2%) and TMS data (0.1%) were re-checked and corrected. Forest plots of these endpoints pre- and post-data corrections showed a considerable impact on SWR in mITT population, and on SDMT in off-ADM group in mITT population. However, the impact on TFC, TMS and overall impact on these endpoints' their composite score, i.e., cUHDRS, was acceptable. The anomalies that were highlighted were reasonable to correct and it is agreed that there is no impact on overall study conclusions.

Baseline characteristics of study population

Overall, occurrence of protocol deviations was comparable between treatment groups for all categories in ITT population. The occurrence of deviations in the 'study procedure not performed' category is notably higher than in the 'visit not performed' category (20.8% vs 7% respectively). This implies that a proportion of visits were only partly completed, implying there may be a disbalance in the type of assessment that was not performed. Moreover, no breakdown of these data was provided on the deviations in patients off-ADM, increasing the uncertainty of results in this subgroup. However, as investigations in the off-ADM subgroup are not considered suitable to support a claim, this was not pursued.

The ITT (i.e., all randomized patients) population was used only as pre-specified population for the primary analysis; for the other endpoints this was mITT population (i.e., those that received at least one dose and had baseline and at least one post-baseline TFC value). The number of patients in mITT population was comparable between groups (placebo vs pridopidine: n=247 vs n=243). This was also the case for the number of patients that withdrew on own initiative (n=12 vs. n=14). It is not likely that the limited between-group differences have notably influenced study conclusions. Use of mITT population is in general not preferred but in this case accepted.

In the ITT population, a comparable number of subjects completed Week 65 (placebo vs pridopidine: 93.6% vs 90%), and through Week78 (68.3% vs 72.4%, respectively).

Treatment compliance details were provided in the safety population (i.e., all that received at least one dose) and was overall high and comparable between groups). No data were found on compliance in the mITT population or mITT off ADM group specifically, but this issue is not pursued as it was observed that the vast majority of patients had a high compliance.

Treatment compliance in the ITT population was high and comparable between groups. The ITT and mITT populations were found to only differ to a limited extent, hence absence of treatment compliance data in mITT population is not further pursued. Treatment compliance data in the off ADM group in mITT population were not found. However, as investigations in the off-ADM subgroup are not considered suitable to support a claim, this was not pursued.

A comparable group of adults with early HD (TFC7-13) patients was enrolled in the pridopidine and placebo arms (ITT population) in terms of demographics and disease characteristics). Most patients were above 44 years (i.e., first quartile boundary) and median age was 53 years. These data emphasize that extrapolation to the lower age limit (18+) requires support from other sources than PROOF-HD study.

Prohibited concomitant use was higher in the pridopidine group with 5.6 % (n=14), compared to placebo with 3.6% (n=9). Moreover, use of VMAT2 inhibitors (VMAT2i) was considerably higher in the pridopidine group (placebo vs pridopidine, for deutetrabenazine: 8.8% vs 16.4%; for tetrabenazine 10% vs 13.2%). This disbalance is further discussed as part of the 'off-ADM subgroup' analysis, below.

Information on concomitant treatment use throughout the study, specifically VMAT2i and ADMs, were initially not comprehensive, but adequate details were provided upon request (see below).

Primary efficacy analysis

PROOF-HD did not meet its primary endpoint.

In the ITT population, pridopidine performed worse than placebo on the primary endpoint TFC and on the key secondary endpoint cUHDRS. Patients worsened over-time in both treatment arms. No benefit was shown for pridopidine on any of the remaining secondary endpoints.

It does not seem that a large placebo response was causative for PROOF-HD study not meeting its primary endpoint in ITT population. For TFC, an annual decline of approx. -0.9 has previously been reported for HD patients that received placebo and had a baseline TFC of ~7-10 (Waters et al., 2018,). The decline reported in PROOF-HD was comparable, albeit the placebo group performed slightly better than could be expected (annual decline TFC for placebo: -0.72/y; for pridopidine: -0.94/y). Similar considerations apply to the cUHDRS results.

The other secondary endpoints were not discussed for (m)ITT population. In CSR, it was indicated that none of the remaining secondary efficacy endpoints demonstrated nominally significant benefit for pridopidine over placebo in the mITT population.

PROOF-HD study is proposed and accepted as only source of pivotal evidence. Hence, the study should be compelling with respect to validity, data quality and clinical relevance (CPMP/EWP/2330/99) However, this is not the case.

For the predefined subgroup analysis, there were no evident inconsistencies, except the subgroups based on neuroleptic use. Hence, the influence of ADMs appears to be driven by neuroleptics; i.e., less by use of VMAT2i. Effects in the neuroleptic subgroups moved towards placebo over-time, and favoured placebo at Week 78 regardless of use (estimates for cUHDRS per subgroup of use: yes: -.59; no: -.14 and combined: -.27 pt.).

Investigations in patients not using neuroleptics or VMAT2 inhibitors (off ADM group)

During the initial phase of the procedure, it was assessed that, as PROOF-HD did not meet its primary endpoint in the overall population, no confirmatory claims could be made on efficacy in the off ADM group. The Guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013) states that in such cases only in rare instances there may a basis for pursuing regulatory approval without conducting additional studies.

As part of initial responses, the applicant argued per-point that the off-ADM group does meet the **guideline criteria** as per assessment scenario 3 i.e. the clinical data presented fail to establish statistically persuasive evidence in the primary analysis population but there is interest in identifying a subgroup where a relevant treatment effect and compelling evidence of a favourable risk-benefit profile can be assessed. (EMA/CHMP/539146/2013).

Noted that the guideline states that 'post-baseline covariates may be affected by treatment received and will not usually be appropriate to define subgroups for the investigation of a treatment effect'. However, the off-ADM subgroup is defined based on the use of ADM at baseline and during the trial. I.e., the definition includes a post-baseline variable - which is not appropriate.

Further, the above guideline states that under scenario 3, one or more additional trials should usually be conducted. In rare instances there may a basis for pursuing regulatory approval without conducting additional studies. If nevertheless a positive licensing decision is, exceptionally, considered in this circumstance then Section 5.3 represents the **minimum** criteria that should be fulfilled (**emphasis added** EMA/CHMP/539146/2013).

Assessment of that response is as follows: (1) External evidence should exist that the subgroup of interest is a well-defined and clinically relevant entity. Usually it would be expected that the respective subgroup has been considered when planning the trial (e.g. stratified randomisation or that it has been mentioned amongst the key subgroups) with an argument provided as to why it is a clinically relevant entity

As part of initial responses, the applicant used literature to discuss that HD is a highly heterogeneous disease with various phenotypes and prognostic factors including age, CAG repeat length, and ADM use. It is not agreed that ADM use is an established prognostic factor, but the other arguments are accepted. High disease heterogeneity complicates approval of a broad label if a benefit cannot be shown across disease subgroups. This issue was resolved because the applicant restricted the indication to adult patients with early (HD) who are not treated with ADMs. While it is agreed that HD is a heterogeneous disease, it is not agreed that the off-ADM subgroup is well-defined or a clinically relevant entity. Further, it is not agreed that the subgroup has been properly considered when planning the trial.

- *As part of the initial responses,* the applicant clarified that interest in VMAT2i analysis was specified since the first SAP (v1) in 'the 'other efficacy analysis section' ('*to explore potential impact on efficacy based on co-medication […] some will be participants taking tetrabenazine/deutetrabenazine/valbenazine vs not those not taking these medications*". It became a subgroup analysis in SAP v3. How this interest in VMAT2i was exploratively defined remains perpendicular to the importance now given to this analysis by the applicant. Further, the applicant re-iterated that the off-ADM group analysis was (also) pre-specified as it combined two pre-specified analyses (stratification factor neuroleptic use; and sensitivity analysis on VMAT2i use). This argument is not accepted. The off-ADM group has not been mentioned in the protocol or SAP, was analysed in two ways and not controlled for type I inflation (see below). This renders the ADM subgroup analysis explorative. Findings first need to be confirmed in a different credible source (e.g., RCT) before it can be accepted for regulatory decision making (see further on replication). But even then, it is uncertain if it can outbalance the fact that pridopidine formally failed to show efficacy in four HD patient studies.
- *Later during the procedure,* the applicant referred to the EMA subgroup guideline (EMA/CHMP/539146/2013) to argue that pre-specification is not a prerequisite for credibility of a subgroup The EMA guideline states that *such pre-specification, reflecting that there is plausibility for differential outcomes between subgroups, can lend credibility to positive or negative subgroup findings. Conversely, the absence of pre-specification cannot be taken as a direct argument that results in a particular subgroup lack credibility.* ***In particular, for adverse findings*** *in subgroups there should be no disincentive to properly consider and pre-specify all relevant subgroups at the planning stage. Instead, arguments for lack of credibility should focus on biological plausibility and (absence of) replication* (**emphasis added** EMA/CHMP/539146/2013). While respective section thus refers to credibility in context of adverse findings, not efficacy, it nonetheless may be true if pre-specification was an isolated issue. Indeed, as indicated in the guidance, credibility depends on the degree of well-founded, a priori definition, the biological plausibility for a particular finding and replication. In this MAA, pre-specification is an issue together with issues on biological plausibility and replication (see below). The guidance then clearly states that results 'likely are not credible' (Step 3b, EMA/CHMP/539146/2013).

*(2) A pharmacological rationale, or a mechanistically plausible explanation, should exist, why the drug under investigation could have different efficacy (or risk-benefit) in a sub-population and its complement (after considering also the scale of assessment).*It is not agreed that this criterion is met.

As part of the initial responses, literature, product information of ADMs, and PROOF-HD data were reviewed to support that ADM use exacerbates HD progression. Most of these data were assessed previously. As part of the initial responses, another published article (Tan et al. 2025) was provided, but this is a review article from the applicant covering generally the same topics as touched upon already. New submitted data during the procedure were:

a) A peer-reviewed article of the applicant (Geva et al. 2025). It discusses an analysis on the effect of ADMs in the global ongoing observational study ENROLL-HD. Impact of ADM dose was included in this analysis (further discussed below). The results support that ADMs affect endpoints in HD patients that have been measured in PROOF-HD (i.e., cUHDRS, SDMT, SWR and TFC) - albeit the magnitude of effect varies per endpoint. It is unclear if the off ADM group in ENROLL-HD is comparable to the subgroup in PROOF-HD. Either way and in agreement with previously raised concerns, the applicant acknowledges in the article that causality could not be determined, that baseline differences may have influenced results, and that results do not substitute for a balanced randomisation of patients regarding ADMs at baseline. This conclusion is shared.

b) A *post hoc* baseline propensity score weighing (PSW) analysis of patients receiving placebo, using as covariate adjustments: age and CAG repeat length (continuous), sex, region (North America, Europe), baseline CAP100 (i.e. Age × (CAG - 30)/6.49), and baseline TFC, TMS, SWR, SDMT, and Q-Motor FT-IOI mean. The analysis mostly resolved baseline known differences for the on- vs, off-ADM *placebo* subgroups, although, the PSW-corrected baseline data for the *pridopidine* subgroups were not found. Regardless, the analysis likely is data-driven and its results may have many other explanations than proposed by the applicant, rendering it highly explorative and not credible to support any type of MA. These results are not further discussed for the following reasons:

   - It is another non-prespecified *post hoc* analysis that further aims to 'correct' results of the failed study PROOF-HD, and is on top of two stratification factors and in a small subgroup which itself is already exploratory. I.e., the risk for bias is high.
   - It is unclear how the selection of the above variables in the propensity score model was performed. It is questionable why CAP100 and FT-IOI were chosen as additional covariates, and why two were needed (instead of e.g., one, or three). It is argued that both are established prognostic factors. However, age and CAG (as continuous variables) as well as key endpoint covariates such as TFC - which also relates to disease progression are already included in the PSW. In the particular case of CAP100, there is a risk of over correction as CAP100 is a formula on age and CAG repeat length. There are concerns that the analysis was data-driven, and it is questionable whether results would have been less favourable if different choices had been made.
   - There are additional issues with the analyses and data leaving several alternative explanations for what is observed. The applicant's main conclusion seems to be that, after adjustment for the selected baseline differences, patients on placebo off-ADMs progress slower than those on placebo on-ADMs at baseline or at any time during follow-up. However, the above listed variables in the PS models may be insufficient to attain conditional exchangeability among the on-ADM and off-ADM groups at baseline, leaving the possibility that remaining observed differences in progression are the result of confounders that are unknown, unmeasured or not accounted for in this analysis. The provided analysis for this reason does not guarantee that the remaining observed differences between the groups are caused by the ADM exposure. Yet it may also be that the differences between the on- and off-ADM groups are caused by strong AEs of ADMs that resemble (or worsen) HD symptoms rather than truly representing a real difference in the HD progression (as also indicated by Applicant in their response). Finally, ADM use is only discussed as a baseline confounder, but initiation of ADM(s) after baseline should have been considered an intercurrent event (and an appropriate strategy for handling this should have been predefined).

c) The article 'Boareto et al., 2025'; see 'replication of findings' below.

d) Additional PK-results for the DDI of pridopidine (CYP2D6 inhibitor) and deutetrabenazine (Austedo; metabolized by CYP2D6) were also provided to support that ADM-related side effects may be increased and so cloud efficacy assessment. The DDI could be plausible in some patients. However and as discussed previously, extrapolating results to all ADMs is not appropriate as the DDI for pridopidine with individual ADMs differs. E.g., (deu)tetrabenazine is highly metabolized by CYP2D6 but for quetiapine this is limited. Thus, the Austedo data cannot support the claim that *all ADMs* affect clinical outcomes.

(3) The treatment effect observed in the subgroup would usually be larger than in the all-randomised population. The totality of statistical evidence, based on individual trials and pooled analyses, should meet the same standards of evidence as would usually be expected for the all-randomised population indicating that the size of the treatment effect in the subgroup is substantial as compared to the variability of the problem.

As opposed to results in (m)ITT, the differences in the 65-week change from baseline in the TFC and cUHDRS were numerically in favour of pridopidine in the off-ADM group. However, clinical relevance of these results is not agreed (see further details under results in the Off-ADM group).

(4) Replication of subgroup findings from other relevant trials (internal to the MAA or external trials that are relevant). A particular challenge exists in applications based on a single pivotal study since replication is a key component of credibility. In this instance the biological plausibility and the clinical trial data from the subgroup would have to be exceptionally strong.

Meeting this criterion is <u>not agreed.</u>

As part of the responses, the applicant discussed results from a) the integrated efficacy analysis (IEA) of the 4 studies (HART, MermaiHD, PRIDE-HD and PROOF-HD); b) a new analysis: a similar IEA but only of PRIDE-HD and PROOF-HD; and c) Geva et al. 2025 from ENROLL-HD. Both IEA analyses are not useful as issues raised previously in regard to its analysis remain (see below). Moreover, being largely driven by PROOF-HD data, both IEAs cannot be considered 'independent confirmation'. Consequently, the only useful replication is from the applicant's analysis from ENROLL-HD (Geva et al. 2025). However, as discussed above, the applicant concluded in that article that its results cannot substitute for a balanced RCT. I.e., as of yet there is no replication across trials. New data were:

a) Final PROOF-HD OLE results. They, however, are not useful to support replication of findings as i) results are also from PROOF-HD, for which the double-blind phase data are not credible (see above), ii) the OLE analysis was not agreed as e.g., substantial modification were made *post hoc* (see below) and iii) interpretation of external control (ENROLL-HD) vs. trial data to distinguish placebo from drug effect may be potentially misleading (Boareto et al., 2025). Therefore, the new OLE results are not further discussed.

b) Boareto et al., 2025, which was used to support the argument that worsening of HD progression by ADM use is replicated in multiple independent studies. The other studies/articles were assessed previously. It is not agreed they are fully 'independent' as all used the ENROLL-HD dataset. I.e., Tedroff et al., 2015 used ENROLL-HD's precursor REGISTRY, Harris et al., 2020 used ENROLL-HD; Boareto et al., 2025 used ENROLL-HD + GENERATION HD1 (placebo data of an industry-sponsored RCT with tominersen), and Ghazaleh et al., 2021. also used ENROLL-HD. It is therefore logical that they arrived at comparable conclusions. Moreover, 'Boareto et al.' stated 'we cannot determine whether co-medication use causes faster progression', yet that is implied by the applicant. Thus, independent replication is still not demonstrated.

(5) The fifth criterion listed refers to safety and hence, it is not further elaborated here.

Altogether it is not agreed that the subgroup analysis follows EMA guidance. Results are 'likely not credible' (Step 3b EMA/CHMP/539146/2013). The minimum criteria as set up in the section 5.3 are not considered fulfilled (EMA/CHMP/539146/2013).

Moreover, **interpretation** of the off-ADM group remains problematic. During the procedure, the applicant provided a per-point response, which are assessed as follows:

- *Balance and reason of ADM use at baseline:* this concern is not pursued. PROOF-HD results on ADM use and why they were used, were provided. Neuroleptic use was a stratification factor and therefore balanced. VMAT2i use, however, was not stratified and was imbalanced (in mITT, placebo: n=38/15.4%; pridopidine: n=54/22.3%). It is agreed with the applicant that this explains the disbalance between treatment arms for the reason ADM use: 'chorea' at baseline (in placebo: n=43/39.4%; pridopidine: n=63/52.5%). Other reasons for ADM use at baseline were roughly comparable. No discussion on the impact of this disbalance was provided, but as comprehensive data on ADM use was provided (also see below), it is not likely that this can be further investigated.

- *Demographics and disease characteristics:* this concern remains. A new detailed breakdown of patient characteristics of subgroups based on ADM use was provided. It is agreed with the applicant that the placebo and pridopidine arms *within* the off-ADM group, and both arms *within* the on-ADM group are similar as per the included variables. However and acknowledged by the applicant, the off-ADM group is less impaired *compared to* the on-ADM group (e.g., for off-ADM vs on-ADM group disease stage HD1 was n=124/46.3% vs. n=78/34.1%; baseline cUHDRS was 9.5 vs. 8.0). The applicant's argument that the on-ADM group shows meaningful differences compared to the off-ADM group, in support of plausibility of the effects of ADMs, is therefore not readily appropriate. Moreover, patients off-ADM at baseline but who initiated an ADM during the study, i.e. were excluded from the off-ADM group (thus, the aforementioned comparison of group at baseline is also no longer valid to evaluate whether features are similar between the on and off-ADM groups defined in this MAA), also had higher chorea, irritability and psychosis scores at baseline. These data reaffirm the concern that the off-ADM group in PROOF-HD may not be a distinct subgroup but rather a selected population of less impaired patients not requiring rescue medication.

- *Composition of off-ADM group over-time:* this concern is resolved. A new detailed breakdown on ADM use in PROOF-HD was provided based on which it can be agreed that initiation of ADMs (both neuroleptics, and VMAT2i) was comparable between the placebo and pridopidine group. Reasons for initiating ADMs that differed >1 between groups were 'chorea' (placebo 13, vs pridopidine 8); 'irritability' (placebo 1, vs pridopidine 5); 'anxiety' (placebo 0, vs pridopidine 3) and 'depression' (placebo 0, vs pridopidine 2). That 'chorea' was a more common reason in the placebo group is not surprising since more patients in the pridopidine arm were already using VMAT2i at baseline (see above). These data resolve the specific concerns, but conversely further question the claimed benefit of pridopidine. I.e., in both groups a comparable number of patients initiated ADMs, seemingly as rescue medication for symptoms of HD.

- *Impact of region or site on recruitment of the off-ADM group:* this concern is resolved. A new detailed breakdown on recruitment was provided. Apart from a few discrepancies, it appears that outliers could not have biased results to a considerable extent.

- *Time-to-initiation, dose modification and dose suspension of ADMs*: this concern is resolved. A new detailed breakdown of ADM use was provided based on which it is agreed that results on time-to-initiation, dose modification and on dose suspension of ADMs were all comparable between treatment arms. Still, the data are not indicative of a treatment effect as there was no between- treatment difference in how ADMs were seemingly used as rescue medication.

- *ADM group are two subgroup analysis not controlled for type I error:* this concern remains.

- During the procedure, the applicant argued that the off-ADM group may have been underpowered and that the COVID-19 pandemic may have increase ADM use. However, those are no arguments to accept questionable findings. When evaluating multiple subgroups exploratively, there is always an increasing risk of type I error inflation and erroneously concluding efficacy in one of the subgroups where effects are tested. It is also not agreed that the totality of data is convincing and/or are persuasive enough to wave away the need for statistical rigor.
- *Additionally*, the applicant used a global statistical test (Goeman et al.) as an alternative to control for type 1 error. Results suggested significant treatment-by-subgroup interactions on cUHDRS in Week 26, 39, 52 and 78 but not Week 65. The approach is not agreed. Statistically it is not possible to 'repair' that PROOF-HD is a 'failed' trial which did not meet its primary endpoint, and/or make further formal confirmatory statistical statements (EMA/CHMP/539146/2013, scenario 3). It is not acceptable to define multiple testing corrections *post hoc*, as it cannot be ruled out that the choice is data-driven. There are many ways to adjust for multiple testing and the global test is not the most obvious choice. How it was applied, seems to focus on the aim of illustrating that there is at least one subgroup variable (related to neuroleptic, chorea medication or ADM use) that modifies the effect. Notably, there are still 5 global tests performed, across which type I error is not controlled, and the unadjusted *p*-value at the primary endpoint assessment (i.e., Week 65) is 0.12. These results are therefore of no use to contextualize how off-ADM group results would have looked with type 1 error control.

Off-ADM subgroup results are inconsistent between two analyses: this concern is not pursued. The applicant discussed details of the two ADM subgroup analyses that were reported at the time of submission. Method 1 was the VMATi subgroup analysis on top of the neuroleptic stratification-analysis; Method 2 was a MMRM analysis in the on- and off-ADM group separately. This resulted in different analysis populations and different assumptions if treatment differences were constant between groups. The applicant provided a comparison of results of both methods for it is accepted that they were roughly comparable, hence that issue is not pursued. Regardless, no explanation was provided on why two different off-ADM group analyses were reported, yet it supports the concern that the ADM subgroup analyses were explorative.

Thus, two main issues on interpretation of the off-ADM group remain. It may not be a distinct subgroup, but rather a selected population of less impaired patients not requiring rescue medication. The two analyses and uncontrolled Type 1-eror testing support investigations in the off-ADM group are explorative. These two issues question validity of the results.

Further, **extrapolation** of results in the off-ADM subgroup to the PROOF-HD population, and to the broader HD population is not straightforward. In PROOF-HD, ~42% of ITT population were part of the off-ADM group, which challenges how representative the ADM group is for the initially target population of broad HD. During the procedure, the applicant argued that pridopidine's benefit is masked only in patients that received higher-dose ADMs. I.e., pridopidine's effect is not masked in patients that were off-ADMs or on low-dose ADMs - they had similar benefit. In support, a review of regulatory labels, literature and PROOF-HD data of these three groups (off-, lower-dose-, and higher-dose-ADMs) were provided to discuss that ADMs have a narrow therapeutic window. As such, patients on-ADMs that are metabolized by CYP2D6 (e.g., (deu)tetrabenazine) may have had increased plasma levels resulting in increased side effects. This could be plausible in some patients. Though, this lower/higher-dose analysis is uninterpretable in context of treatment policy development or B/R assessment. Primarily, the ADM subgroup analysis itself is not persuasive (see above), rendering the lower/higher-dose investigations in the ADM subgroup analysis highly exploratory and with high risk for bias. Even more so as a dichotomous definition of 'lower vs higher dose' was rather arbitrary, even when accepting that cut-offs were by expert consensus, and because the PK interaction is not the same across all ADMs (e.g., tetrabenazine is highly metabolized by CYP2D6 but for quetiapine this is limited). During the procedure, the applicant restricted

the indication to adults with early HD who are not taking ADMs. However, while the restriction of the indication addresses the concern on extrapolation towards a broad HD population, it creates a new concern: restricting use to an off-ADM group is considered practically unfeasible in real life conditions. Patients with HD frequently (generally 30-40% of patients and in PROOF-HD even ~45%) require ADMs to control behavioural changes and/or chorea. Those patients would need to stop ADMs, putting themselves and their caregiver at risk for symptoms the ADMs treated (e.g., aggression). If pridopidine would be started without ADMs, as chorea appears, ADMs would need to be initiated as pridopidine does not treat chorea. Over time, these two scenarios would lead to uncontrolled behavioural changes / chorea or (re)-initiation of ADMs.

Results in the off ADM group

In both treatment arms, on TFC and cUHDRS impairment was seen.

Endpoint: TFC

For TFC, the treatment difference at any time was considerably lower than expected in the sample size calculation (treatment difference over-time was between 0.05-0.26pt; at Week 65 it was 0.05pt.; sample size calculation expected 0.7pt.)

Clinical relevance of TFC results is not demonstrated.

- *During the procedure,* a validation report of TFC was provided that included a proposed margin for what is a clinically relevant change on TFC: 0.14-0.21pt/year assuming 0.7pt/y progression. This margin was extrapolated from the clinically relevant margin on cUHDRS (0.2-0.3pt/y; Schobel et al. 2017). It is evidently lower than was expected in the sample size calculation (0.7 pt.), and not acceptable for the following reasons. It neglects the individual weighing of TFC in cUHDRS, and that 0.2-0.3pt/y was by clinical consensus assuming all four components contribute positively, i.e. not only TFC. Even when disregarding these issues, pridopidine did not meet this proposed margin Further, the applicant discussed why treatment differences were not consistent over-time: the Week 65 visit had too many assessments and a common closing study design was used. If true, this would rather point towards design issues than a treatment benefit for pridopidine. During the responses, the applicant argued that the proposed margin of 0.14pt+/y was met at Week78 by referencing to a corrected analysis (erratum of PROOF-HD CSR; 14mar2025). The erratum states that this updated analysis was performed as it was found out that virtual visit results were accidentally also included in the primary analysis, which was not intended per SAP. While timing of this analysis is peculiar when recalling that TFC was re-checked and correct post-DBL (see above), it is still not agreed that this updated analysis would show clinical relevance is met on the proposed MCID. The difference at Week78 was 0.16, i.e., 0.11pt/y.
- *Later during the procedure*, the applicant proposed a new margin for defining clinical relevance: 20%, based on the margin for cUHDRS (20-30%/y), a survey in ALS, and a NIH article on Alzheimer's disease. TFC results now curiously met the margin at Week 65 and 78. Given these previous steps it cannot be ruled out that this *post hoc* defined margin of 20% was data-driven, rendering it not credible. Even more so as it is unclear i) why 0.14-0.21/y was abandoned; ii) if the 20% margin on scales for ALS and Alzheimer's disease can be readily extrapolated to a HD-specific scale as TFC, and iii) if the 20-30% margin for cUHDRS can be readily applied to its subscale TFC without taking the individual weighing TFC in its composite cUHDRS into account (as discussed above). Altogether, TFC results remain of undemonstrated clinical relevance.
- Further, the applicant showed that the PROOF-HD patients off-ADMs that received pridopidine at Week 52 had 0.77 slower progression on TFC versus propensity-matched patients in ENROLL-HD. The matching in terms of the baseline variables could not be assessed, but a major concern is the large difference seen in the mean outcomes at Week 52 between the placebo arm in the trial and

the ENROLL-HD population in the analysis, questioning whether the 'matched' ENROLL-HD cohort is indeed comparable to the trial population. Regardless, the analysis is of limited value next to the double-blind phase results of PROOF-HD. As previously assessed, effects at Week 52 are not representative for the decreased effects at Week 65 and 78, which are of more importance because pridopidine is intended for chronic use.

- *Later during the procedure*, the applicant also discussed additional sensitivity analyses using adjustment for prognostic variables and PSW to compare pridopidine to placebo in the off-ADM group. The effect size estimate is somewhat increased compared to the analysis originally planned. However, major issues were observed related to this analysis, also see above. It may be data-driven and cannot save a failed trial where the primary endpoint was not met. Moreover, even without adjustment for multiple testing, sensitivity analyses do not show significant differences on TFC and cUHDRS at time of primary endpoint assessment (week 65).

The pre-defined responder analysis on TFC was first in the hierarchy (i.e., the first (non-key) multiple adjusted secondary endpoint). A responder was defined as 'TFC change ≥0'. Using this definition, in a post hoc analysis in the off-ADM group, the proportion responders slightly favoured placebo at Week 65 (placebo: n=65/61.3% vs pridopidine: n=55/59%) but favoured pridopidine in Week 78 (n=38/53% vs n=43/n=61%). Nevertheless, ~40% of subjects were classified as no-responders, therefore treatment policies for non-responders have been added in the proposed SmPC.

cUHDRS

cUHDRS effects at Week 65 were borderline clinically meaningful in favour of pridopidine (0.27pt difference at Week 65 = ~0.22/year; while 0.2-0.3p/year is meaningful). This difference was not maintained; it decreased at Week 78 to a difference of 0.14pt (i.e., ~0.1/year). This trend is comparable to TFC at Week 65.

Clinical relevance of cUHDRS results in patients off-ADMs is <u>not demonstrated</u>.

- *During the procedure,* the applicant emphasized relevancy of treatment differences up to Week52, which is not agreed as pridopidine is intended for chronic use. I.e. Week65 and 78 results should not be neglected yet are not persuasive in terms of relevance and effect maintenance. The applicant also argued that calculating a yearly progression from Week65 and 78, as done above, can be problematic in a progressive disorder. While debatable in contextualizing relevance of effects of Week65/78 to Week52, it either way does not resolve the issue that effects decreased over-time, were borderline clinically relevant at week 65 and decreased below relevance at week 78. This questions the foreseen chronic treatment of HD.
- *Later during the procedure,* the applicant provided an extensive discussion which appeared to propose to disregard the minimally clinically important difference reached by consensus (0.2-0.3/y; Schobel et al., 2017) in favour of focusing on correlation of cUHDRS with FAS (Functional Assessment Scale; measuring e.g., daily fatigue) and brain atrophy. In principle FAS and brain atrophy may be relevant, but both were not directly assessed in PROOF-HD, and so on itself they are no argument why the observations on cUHDRS *in PROOF-HD* are relevant. Moreover, Schobel et al., 2017 already explicitly discussed correlation of cUHDRS to brain changes, and determined a change of 0.2-0.3/y to be relevant *if all subscales contribute positively* (see below).
- Further a *post hoc* responder analysis *in patients off-ADMs* was provided using a +/-10% respond threshold margin. It was unclear why 10% was chosen; 20-30%/year appears more appropriate (Schobel et al., 2017). Nonetheless, at +10% the analysis favoured placebo at Week 78 (Figure 10), questioning clinical relevance rather than show efficacy of pridopidine over-time.

Moreover, all components of the cUHDRS should contribute positively (Schobel et al., 2017). It is not agreed with the applicant that this is the case. At Week 65, the treatment difference on TFC, SWR and SDMT favoured pridopidine, but on TMS favoured neither treatment. At Week 78, effects on TFC and SWR favoured pridopidine, but on SDMT and TMS favoured placebo. I.e., multiple domains do not contribute to the effect over-time. Also in this respect efficacy is not considered consistently demonstrated.

- *During the procedure*, the applicant used the per-protocol (PP) analysis to show that all components contribute positively in the off-ADM group. This is not agreed as PP analyses are known to be generally more optimistic than in ITT, and because the PP analysis in PROOF-HD was explorative – especially in the off-ADM group. I.e., results in PP cannot resolve the issue that not all components favoured pridopidine over-time in the off-ADM group in mITT. Moreover, the applicant argued there was a high placebo response. Even if true, that conversely does not mean that pridopidine is efficacious.
- *Later during the procedure,* the applicant argued that a) contribution of the subscales was positive at most timepoints; b) cUHDRS still tracks the underlying disease progression; c) each component is independently validated as clinically meaningful; and d) domains show change in a positive direction, but at different rates due to disease heterogeneity. This is not agreed. Ad 'a' (all subscales positively contributed at most timepoints): as discussed previously, this is not agreed especially at the more important later timepoints Week 65 and 78 (D180 LoQ Figure 13). Ad 'b' (cUHDRS tracks underlying disease): although trajectories of subscales may differ (Boareto et al., 2025) rather the assumption for a progression-slowing treatment in early HD is that scales change together over-time (also see Schobel et al., 2017). Instead, PROOF-HD results for cUHDRS and its subscales generally show decreasing treatment differences over-time. Ad 'c' (all subscales are validated and clinically meaningful, and 'd' (that HD is a heterogeneous disease): these are on itself no arguments why PROOF-HD results should be considered meaningful

Q motor

Q-motor FT IOI results are insufficient to support the broad treatment effects that are claimed (i.e., benefit not limited to motor function), or alternatively a limited claim that motor symptoms are treated.

The Q-motor endpoints tests were limited to the hands and fine motor function, whereas TMS assessed motor symptoms more globally. Effects on TMS in the off ADM group favoured neither treatment at Week 65, and favoured placebo at Week 78. Even if TMS may be prone to placebo responses, TMS results do not support that pridopidine had a relevant effect on motor symptoms in the off ADM group.

- *During the procedure*, correlations between TMS and Q motor finger-tapping results (FT IOI) were provided. It is not agreed that these are robust or allow to omit TMS results in PROOF-HD in favour of Q motor FT results (correlation Q motor and TMS r=0.35-0.62). Especially as the correlation widely varies between TMS-subdomains, e.g., is weak between Q motor FT IOI and TMS-chorea (r=0.38), -rigidity (0.17) and -dystonia (0.014). Also in Round 2, a discussion on baseline differences and possible effect modification by age was provided as that was noted in Round 1. This not further pursued considering above issues.
- *Later during the procedure,* in support of validity of Q Motor FT IOI (vs absence of effects on other endpoints, notably TMS) the applicant recited a variety of articles to repeat the argument that Q motor FT IOI is strongly correlated to clinical measures, brain atrophy and disease progression (=TFC and cUHDRS over-time). It is still not agreed that the correlations are strong. E.g., baseline FT IOI with TMS (i.e., global motor function) and with TFC (i.e., functional change) were weak (0.38 resp.

0.34) and in TRACK-HD moderate (0.56). Similar observations apply to the other correlations that were discussed.

- *Later during the procedure,* strikingly, the applicant acknowledged *that pridopidine has minimal effect on chorea*. The observation is agreed but concerning for multiple reasons:
  - it supports the concern that *restricting use to an off-ADM group likely is practically unfeasibl*e. I.e., if pridopidine does not treat chorea but alternative therapies are prohibited, then over-time this will either lead to uncontrolled chorea, or (re-)initiation of ADMs.
  - It argues against approval of the broad label 'treatment of HD', as not all aspects of the disease will be treated
  - Q motor has weak correlation to the TMS-chorea subscale (0.38), i.e., the statement supports that at least in this MAA both tests are needed to obtain a clear picture which disease aspects pridopidine potentially treats.

Altogether, it is not argued that Q motor results may not be relevant, but it cannot as a stand-alone result support benefit of pridopidine. Other endpoints.

No discussion was provided for CGI-C and HD-QoL endpoints in ITT population, but the CSR stated that none of the secondary endpoints showed a benefit of pridopidine. Also in the off ADM group in mITT population, no benefit of was observed on CGI-C or for HD-QoL. During the responses, the applicant argued that HD-QoL did show relevant effects in the off-ADM group. This is not agreed: a 3-point difference after 78 weeks on a 240-point scale without a sign of (nominal) significance and in absence of efficacy on all other endpoints is not considered persuasive. Rather, results on CGI-C and HD-QoL imply that from a clinician and patient perspective pridopidine did not achieve a noticeable benefit.

Results of the PROOF-HD OLE

During the procedure, preliminary results of the PROOF-HD OLE were discussed which included a comparison to an external control group (ENROLL-HD).

OLE results are not useful for benefit-risk assessment and thus, not further discussed. As major issues on multiple aspects of the double-blind results of PROOF-HD persistent, OLE results are also not credible. Moreover, the OLE analysis has been changed almost completely using post hoc knowledge and in favour of the off-ADM subgroup. The analysis is based on SAP addendum v2 with a date of 09may2024, which is well after the double-blind part was completed. Substantial modifications made after database lock of the double-blind part included, but were not limited to, change of primary analysis population (to the off-ADM group), inclusion of additional subgroups, update of primary endpoint, hierarchy change of efficacy endpoints, additional objectives, and addition of the external cohort-analysis.

Integrated Efficacy Analysis (IEA)

Design

The objective of the IEA was to assess consistency of pooled data of MermaiHD, HART, PRIDE-HD and PROOF-HD compared to PROOF-HD. This was assessed in all patients (ITT population) and in patients off ADMs, although the focus on the off-ADM group appears to have been added later as it was not part of the pooled analysis discussion with the German authority BfArM SA (oct 2022).

MermaiHD was a 26-week randomized (1:1:1), double-blind placebo-controlled, parallel phase III study testing 45mg bid vs 45 qd vs placebo. HART was a 12-week dose-finding study (1:1:1:1 pridopidine 10 mg bid, 22.5 mg bid, 45 mg bid or placebo). Both had a 4-week titration period.

For both studies the primary endpoint was mMS, a motor subscale of the UDHRS-TMS at Week 12 (HART) and Week 26 (MermaiHD). Both studies are notably different than in PROOF-HD, as they were designed under the hypothesis that pridopidine was a dopamine stabilizer with acute effects on motor symptoms. Compared to PROOF-HD, enrolment criteria differed mainly on the lower age limit (30+ instead of 25+) and also recruited all HD types based on TFC (TFC0-13). Patients were stratified at randomisation according to antipsychotic use; at least >50% had to be off-use due to expected differences when concomitantly used with pridopidine. This reasoning aligns with that of PROOF-HD and supports investigations in the off ADM population.

Both MermaiHD and HART failed to meet their primary endpoint.

Planned analysis

The criteria used to decide which studies were included in the IEA do not appear to be based on scientific reasoning (i.e., criterion that studies had to last ≥12 weeks although chronic treatment is envisaged, criterion that studies had to enrol at least stage HD1-2 patients while a broad HD indication is pursued). Nonetheless, the criteria practically resulted in exclusion of the phase 1 studies and the phase II study ACR0007, which is sensible.

The interpretation of the IEA is problematic as the four studies all failed to meet their primary endpoint and are only limitedly comparable in design. MermaiHD and HART are comparable but notably differ from PROOF-HD, while PROOF-HD also differs from PRIDE-HD in key design features (e.g., study duration, population, objective and endpoints, and allowed concomitant medication). Moreover, actual pooling is limited: no timepoint has contribution of all four studies. Only Week 26 has three of four studies (HART had a duration of 12 weeks) contributing, but is of limited use for predicting long-term efficacy as treatment differences notably reduced at later timepoints (see discussion of PROOF-HD, above). Similarly, cUHDRS analysis is flawed as SWR was not measured in PRIDE-HD. Across these studies pooled reporting of cUHDRS is limited to three of the four key components (TMS, TFC and SDMT; termed by the applicant as cUHDRS(-SWR)).

The applicant argues that cUHDRS(-SWR) is comparably sensitive to the 'full' cUHDRS by referencing to Schobel et al. 2017. However, from that article the contrary appears to be true. I.e., SDMT and SWR are stated to be the two key cognitive components of the cUHDRS. Considering the issues the IEA has, it is unlikely that cUHDRS(-SWR) can become of key importance for the benefit-risk balance. Hence this issue is not further pursued.

Altogether, it is considered that the IEA mostly inflates the sample size without providing additional confidence on the consistency of effects across studies. In addition, all information that IEA provides about efficacy beyond 52 weeks is from PROOF-HD study.

Results

On cUHDRS(-SWR), in ITT population irrespective of ADM use, a marginal treatment difference favouring pridopidine was observed till Week 52 (0.089 vs. placebo at Week 52). As PROOF-HD study was the only study contributing data after Week 52, as expected from its separate results the treatment difference reduced at Week 65. The effect favoured placebo at Week 78 (-0.121pt.). These findings further argue against the claim of efficacy in the broad adult HD population. This issue was resolved because the applicant restricted the indication to adult patients with early (HD) and off-ADMs

In the off ADM group, the effect consistently favoured pridopidine. As SWR was excluded from cUHDRS the clinical meaningfulness of the results are challenging to interpret. Treatment differences were variable but overall reduced over-time, in line with the observations for PRIDE-HD and PROOF-HD separately.

In the IEA only patients TFC7-13 (i.e., HD1-2) patients were studied. A post hoc analysis across stages HD1-4 was performed, but is not interpretable. The groups do not align with established TFC-based stages of Shoulson-Fahn (stage 1: 11–13, stage 2: 7–10, stage 3: 3–6, stage 4: 1–2, and stage 5: 0) or with the subgroups as used in PRIDE-HD (TFC 0-6; 7-13). Instead, the sample was increased in four steps with irregular intervals (0-8, 0-9, 0-10, 0-13). These analyses do not allow extrapolation of efficacy from early to late HD.

For TFC, comparable results to cUHDRS(-SWR) were observed and so similar considerations apply.

For Q-motor FT IOI, in ITT population as well as the off ADM group, treatment differences favouring pridopidine were observed at all timepoints. However, as discussed for PROOF-HD, there are uncertainties on the baseline difference in the off ADM group in mITT population. Moreover, the isolated finding on Q-motor cannot support a broad treatment effect, or alternatively on motor function specifically (see above concerns in connection with TMS). Moreover, the clinical relevance of the difference is uncertain.

During the procedure, a similar IEA but only based on PRIDE-HD and PROOF-HD was provided. However, this IEA is not of further use as the same issues apply as for the 4-study IEA (e.g., results are combined from studies that failed to meet their primary endpoint and based on post hoc knowledge; PRIDE-HD had major design issues; and there are major design differences between studies).

It is acknowledged that, in principle, a pooled may be useful. However, as there are multiple major methodological issues the 4-study and 2-study IEA are of no support for efficacy of pridopidine in the treatment of HD.

OLEs open PRIDE-HD and open HART

Open PRIDE-HD was an OLE in which 249 HD patients of all stages (i.e., TFC0-13) received pridopidine 45mg bid for 2 years (104 weeks + 2 week follow-up). Patients could be enrolled following completion of PRIDE-HD.

Patients treated in open PRIDE-HD did not have a better response than expected based on natural history data. TMS was increased by 7.2pt/2 years; which is comparable to 3-3.25 points/year that was observed in a broad natural history HD population. (Dorsey et al., 2013; van der Burg et al 2017). Similarly, TFC declined by 1 point/2 years. TFC declines ~1 point/year in HD stage 1-2 but 0.4 in HD stage 3 and 0.06 in HD stage 4. (Marder et al 2000; Waters et al 2018) In this likely broad HD population, 1 point decline is considered comparable to natural decline and not indicative of a treatment effect. This conclusion is in line with the CSR which concludes 'it would be challenging to conclude maintenance of efficacy in this open-label study'.

- During the procedure, a propensity score weighting and matching methodology was used to compare results of OPEN-PRIDE-HD up to Week156 versus the natural history study TRACK-HD. Patients off-ADMs that received pridopidine throughout (n=10 at Wk156) were analysed separately from patients off-ADMs transitioning from placebo-to-pridopidine (n=6 at Wk156). In both analyses (i.e., pridopidine throughout vs TRACK-HD, and placebo-to-pridopidine vs TRACK-HD) the treatment differences favoured pridopidine at all timepoints in the OLE. However, the large drop-out in both early start and delayed start pridopidine group likely cause the groups at weeks 104 and 156 to differ from the matched TRACK-HD samples. It is expected that especially those subjects with worse outcomes drop out, leading to the outcomes in especially the early and delayed pridopidine group to be overoptimistic. This in turn inflates the mean difference and introduces a bias favouring pridopidine groups. Because of this, relevance of these results for MAA are doubtful. Furthermore, the issue remains that the off-ADM group is exploratory.

In open-HART, HD patients of all stages (i.e., TFC0-13) received pridopidine 45mg bid up to 72 months; 123 patients were included in the efficacy analysis. Although there was large attrition (~70% did not complete Month 72), open HART has the most long-term efficacy data by far. Patients treated in open HART also did not have a better response on UHDRS-TMS or -TFC than expected based on natural history data (over 72 months on TMS a change of ~18pt.; on TFC ~3pt.). This conclusion was also made by the authors in the CSR.

- During the procedure, articles on 60-month results of OPEN-HART were discussed (McGarry et al. 2017 and 2020). The applicant discussed these two articles and not the CSR, because the CSR only had descriptive statistics, included late-stage HD patients and those using ADMs, and did not include an external control. This rationale is not agreed: late-stage patients and those using ADMs are important as they are part of the target population. It also neglects that the CSR included 72-month data, based on which the CSR authors concluded that patients did not have a better response than natural history.

Altogether, Open-HART data corroborate with those of PROOF-HD, open PRIDE-HD and non-clinical data, which all argue against that pridopidine can maintain an effect.

Additional efficacy data needed in the context of a conditional MA

Late during procedure, the applicant restricted the proposed indication to adult patients with HD who are not treated with ADMs, and requested CMA for pridopidine in this restricted indication. The indication was further restricted to adult patients with early HD who are not treated with ADMs to address the concern on extrapolability. Efficacy has not been demonstrated in the newly requested target population of adult patients with early HD who are not treated with ADMs Refer to section 3.7.3. for that assessment.

2.6.7. Conclusions on the clinical efficacy

A dossier based on a single pivotal study (PROOF-HD) was provided to support efficacy of pridopidine 45mg bid as treatment for adult HD. Supportive efficacy evidence was from studies PRIDE-HD, MermaiHD and HART and their OLEs. All four studies failed to meet their primary endpoint and also failed to provide confirmatory evidence on secondary endpoints. As it stands, efficacy is not demonstrated.

In the pivotal study PROOF-HD that included adult early HD patients (stage 1-2; TFC score 7-13), pridopidine 45mg bid performed worse than placebo on the primary endpoint TFC at Week 65 and 78; the same applies for the key secondary endpoint cUHDRS.

In PROOF-HD study, a treatment difference favouring pridopidine was observed in the subgroup that did not use neuroleptics or VMAT2i (patients off-ADMs) at any time. Late during the procedure, the applicant restricted the indication to this subgroup (i.e., adult patients with early HD who are not treated with ADMs). However, this subgroup analysis can be seen as exploratory only, in particular due to important methodological issues making the results of a low level of evidence. Moreover, the off-ADM group may not be a distinct subgroup, but rather a selected population of less impaired patients not requiring rescue medication. Furthermore, also in the off-ADM group efficacy is not considered demonstrated. Treatment differences were not statistically compelling, variable over-time, and the observed numerical differences were not consistently above meaningful margins at Week 65 and 78, which questions the suitability for foreseen chronic treatment.

Pooled efficacy analyses ('IEA') were presented for the four studies (PROOF-HD, PRIDE-HD, MermaiHD, HART), and for two of these four studies (PROOF-HD, PRIDE-HD). As all these studies failed to meet their primary endpoint, and because there are key design feature differences across these studies,

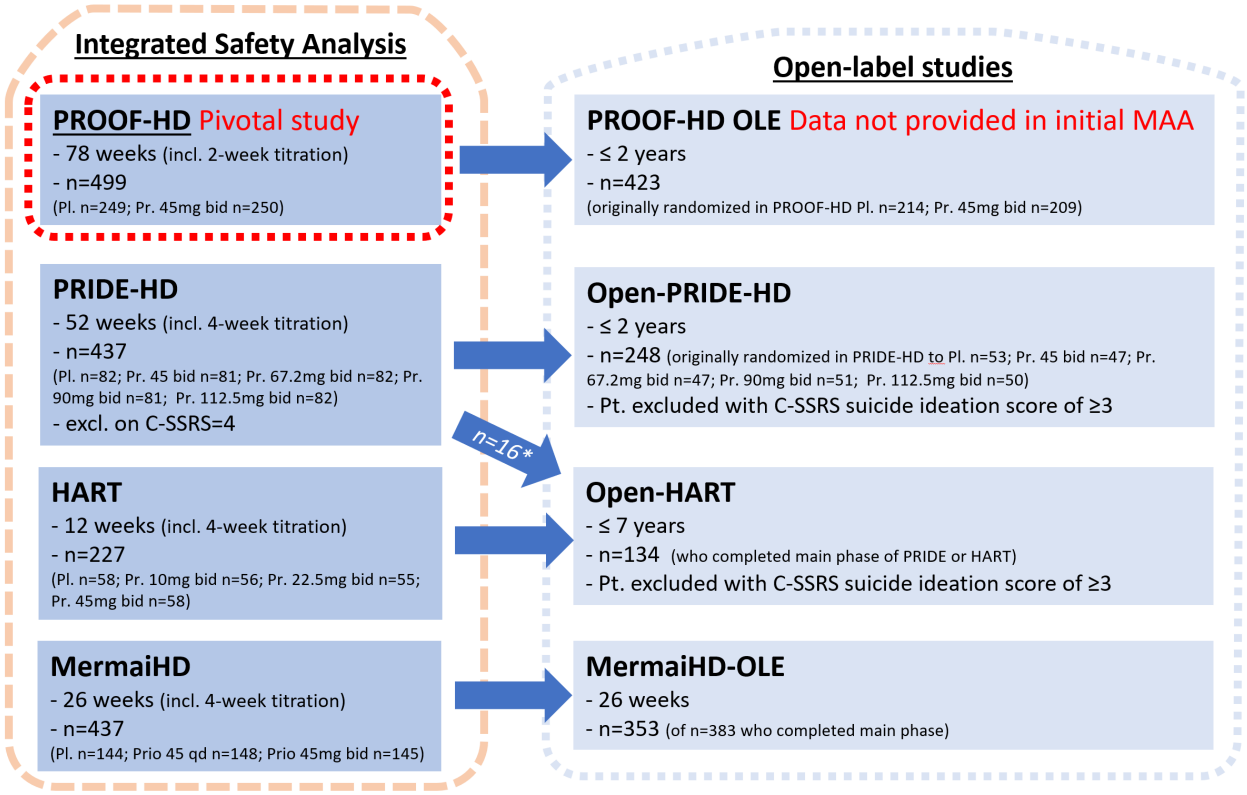
interpretation of the IEA is problematic and their results of no support for efficacy of pridopidine in the treatment of HD.

Pridopidine had no better response on TFC or TMS than expected based on natural history data as observed in the ITT populations of OLEs open-PRIDE-HD (104 weeks) and open HART (72 months). These results corroborate with those of PROOF-HD, PRIDE-HD and non-clinical data, and all argue against that pridopidine can maintain its effect.

Late during procedure, the applicant restricted the proposed indication to adult patients with HD who are not treated with ADMs, and requested CMA for pridopidine in this restricted indication. The indication was further restricted to adult patients with early HD who are not treated with ADMs to address the concern on extrapolability. Efficacy has not been demonstrated in the newly requested target population of adult patients with early HD who are not treated with ADMs Refer to section 3.7.3. for that assessment.

2.6.8. Clinical safety

The applicant proposes the integrated safety analysis (ISA) of the 4 placebo-controlled studies (PROOF-HD, PRIDE-HD, MermaiHD and HART studies) as the most relevant safety data considering the high number of subjects. This is not fully agreed, as the data is mainly driven by PROOF-HD study, which has the largest number of subjects exposed to the proposed dose of pridopidine 45 mg bid with a substantial exposure duration. In addition, the study inclusion and exclusion criteria were different (disease severity and mental status (depression)) which may have impacted the reported AE. In addition, differences in prohibited medication may hamper an adequate analysis of the concomitant medication allowed. Therefore, in the sections below the focus is not strictly on the 4 placebo-controlled studies as preferred by the applicant. This CHMP AR first starts with the pivotal study PROOF-HD, like for efficacy, PROOF-HD is also considered pivotal for the safety assessment. The ISA, individual data of MermaiHD, PRIDE-HD and HART and their respective OLE phases are also assessed as these allow assessment of dose-related adverse events and for assessment of long term exposure to pridopidine (see Figure 17).



*Source of subject numbers: Nurzigma-6261-Doc-Request-2-Flow-of-patients(2024-10-02). Classification of placebo-controlled studies: PROOF-HD (red box): pivotal; MermaiHD, PRIDE, HART: supportive for dose related effect. Integrated safety analysis (ISA): supportive (orange box). The Open Label studies/phases (light blue box) are supportive for assessment of exposure-related effect. *: transition from PRIDE-HD to open-HART was allowed per protocol. These 16 subjects were randomized in PRIDE-HD to Pl.: n=4; Pr. 45 bid n=2; Pr. 67.2mg bid n=3; Pr. 90mg bid n=3; Pr. 112.5mg bid n=4. No subjects transitioned from open-HART to open PRIDE-HD or vice versa although that was permitted per protocol. n= number of subjects, OLP: open-label-phase; Pl.: placebo; Pr.: pridopidine. C-SSRS: Columbia Suicide Severity Rating Scale, other abbreviations: see complete list at top of this document.*

Figure 17: Visualisation of the data considered for the safety analysis (made by assessor)

2.6.8.1. Patient exposure

To date, approximately 1600 participants have received at least one dose of pridopidine across multiple completed clinical studies pertinent to the HD indication, see Table 31. To date, 1278 HD patients, approximately 80% has been exposed to pridopidine in clinical studies for varying durations for a total of >1200 patient-years. The recommended clinical dose of 45 mg bid has been evaluated in over 500 HD patients across four phase 2 and phase 3 double-blind studies, with the remaining patients exposed to a daily dose ranging between 10 mg bid to 112.5 mg bid.

Table 31: Patient exposure (cut off)

	Patients enrolled	Patients exposed*	Patients exposed to proposed dose range	Patients with long term** safety data
PROOF-HD (placebo-controlled)	499	250	250	239
MermaiHD (placebo-controlled)	437	293	145	62
PRIDE-HD (placebo-controlled)	408	326	81	229
HART (placebo-controlled)	227	169	58	

	Patients enrolled	Patients exposed*	Patients exposed to proposed dose range	Patients with long term** safety data
Integrated Safety Analysis (placebo-controlled)	1067	533	533	341
MermaiHD OLE (26 weeks)	353	353	353	353
Open PRIDE-HD (2 years)	248	248	248	248
Open-HART (up to 7 years)	134	134	134	134
Post marketing	n.a.	n.a.	n.a.	n.a.
Compassionate use	n.a.	n.a.	n.a.	n.a.

** Received at least 1 dose of active treatment ** In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure. Here the long term exposure is >26 weeks (i.e. 6months) for the placebo-controlled studies. For the OLE the exposure is indicated with the name of the study.*

2.6.8.2. Adverse events

An overview of treatment emergent adverse events is provided for PROOF-HD in Table 32 and for the integrated safety analysis in Table 33.

Table 32: Overview of treatment emergent adverse events (SP) - PROOF-HD

Category	Number of patients (%)		
	Placebo (N = 249)	Pridopidine 45 mg bid (N = 250)	Total (N = 499)
All TEAEs	214 (85.9)	207 (82.8)	421 (84.4)
All SAEs	21 (8.4)	34 (13.6)	55 (11.0)
All study treatment related SAEs	1 (0.4)	0	1 (0.2)
TEAEs leading to study discontinuation	6 (2.4)	4 (1.6)	10 (2.0)
Study treatment related TEAEs leading to study discontinuation	2 (0.8)	1 (0.4)	3 (0.6)
TEAEs leading to death	1 (0.4)	3 (1.2)	4 (0.8)
Study treatment related TEAEs leading to death	0	0	0
TEAEs based on maximum severity	214 (85.9)	207 (82.8)	421 (84.4)
Missing	0	0	0
Mild	116 (46.6)	90 (36.0)	206 (41.3)
Moderate	75 (30.1)	92 (36.8)	167 (33.5)
Severe	23 (9.2)	25 (10.0)	48 (9.6)
TEAEs occurring anytime during the double-blind period leading to study drug withdrawal	18 (7.2)	26 (10.4)	44 (8.8)
TEAEs leading to study drug withdrawal during titration	6 (2.4)	3 (1.2)	9 (1.8)
TEAEs leading to study drug withdrawal during maintenance	12 (4.8)	23 (9.2)	35 (7.0)
All study treatment related TEAEs	58 (23.3)	60 (24.0)	118 (23.6)

bid = twice daily; TEAE = treatment emergent adverse event
Note: a TEAE is defined as an AE that occurred for the first time or worsened on or after initiation of treatment in the Main Study and within 14 days of stopping study treatment. Source: Table 14.3.1.1.1, Table 14.3.1.1.2

Table 33: Integrated safety analysis (ISA): overview of TEAEs (SG)

	Placebo (N=533) n (%)	Pridopidine 45 mg bid (N=534) n (%)
Patients with at least one TEAE	404 (75.8)	411 (77.0)
Patients with at least one TEAE by worst severity		
Mild	215 (40.3)	198 (37.1)
Moderate	150 (28.1)	171 (32.0)
Severe	39 (7.3)	42 (7.9)
Patients with at least one treatment-related TEAE	167 (31.3)	177 (33.1)
Patients with treatment-related TEAE by worst severity		
Mild	107 (20.1)	111 (20.8)
Moderate	51 (9.6)	56 (10.5)
Severe	9 (1.7)	10 (1.9)
Patients with at least one SAE	33 (6.2)	54 (10.1)
Patients with at least one treatment-related SAE	7 (1.3)	4 (0.7)
Patients with at least one TEAE leading to discontinuation from study treatment	41 (7.7)	57 (10.7)
Patients with at least one treatment-related TEAE leading to discontinuation from study treatment	26 (4.9)	33 (6.2)
Patients with at least one AESI[a]	8 (1.5)	9 (1.7)
Patients with at least one treatment-related AESI[a]	2 (0.4)	1 (0.2)
Patients with at least one treatment-related AEs with onset in post-treatment period	4 (0.8)	1 (0.2)
Patients with at least one TEAE leading to death	2 (0.4)	4 (0.7)

Source: ISA, Table 21
A AESIs include prolonged QTc interval defined using SMQ code 20000001 (Torsade de pointes/QT prolongation).
Note: An AE is considered as treatment-related if it was definitely, probably, or possibly related to the study drug. If a patient had multiple occurrences of the same event, then only the most severe event (mild, moderate, and severe in the increasing order of severity) was summarized for that event.
Note: One patient from PRIDE-HD's pridopidine 45 mg bid arm had an isolated AE described as "significant artifact on ECG" starting and ending on study Day 15 (end of titration period) and coded as "Defect conduction intraventricular" where severity was missing.
Note: Post-treatment-period AEs are defined as AEs that developed or worsened more than 14 days after the last dose of study drug.
Note: If a patient experienced more than one event in a given category, that patient was counted only once in that category.

PROOF-HD study

The PROOF-HD study was conducted during the Coronavirus Disease 2019 (COVID-19) pandemic which impacted the frequency of COVID-19 related TEAEs reported during this trial.

In total, 118 patients (23.6% overall) reported at least one TEAE that was considered by the investigator to be related to study medication, in a similar proportion across study groups: 58 patients (23%) from the placebo arm and 60 patients (24%) from the pridopidine 45 mg bid arm.

The most frequently reported TEAEs were reported in the infections and infestations System Organ Class (SOC), with 223 (44.7%) patients overall reporting at least one AE from this class, in a slightly higher proportion for patients on placebo: 117 (47%) patients from the placebo arm, and 106 (42.4%) from the pridopidine 45 mg bid arms, see Table 34.

The reported TEAEs in PROOF-HD were mild to moderate in most patients (mild TEAEs in 46.6% on placebo and 36% on pridopidine; moderate TEAEs in 30.1% on placebo and 36.8% on pridopidine). While moderate TEAEs occurred at a slightly higher frequency in the pridopidine arm, severe TEAEs were reported with comparable frequency in the two treatment arms: 9.2% of patients in the placebo arm and 10.0% of patients in the pridopidine arm.

Table 34: PROOF-HD: summary of common TEAEs occurring in ≥5% of patients from any treatment arm (Safety Population)

System Organ Class, Preferred Term, n (%)	**Placebo (N=249)**	**Pridopidine 45 mg bid (N=250)**	**Total (N=499)**
Infections and Infestations	**117 (47.0)**	**106 (42.4)**	**223 (44.7)**
COVID-19	58 (23.3)	60 (24.0)	118 (23.6)
Nasopharyngitis	18 (7.2)	19 (7.6)	37 (7.4)
Urinary tract infection	17 (6.8)	11 (4.4)	28 (5.6)
Injury, Poisoning and Procedural Complications	**82 (32.9)**	**79 (31.6)**	**161 (32.3)**
Fall	58 (23.3)	55 (22.0)	113 (22.6)
Contusion	14 (5.6)	12 (4.8)	26 (5.2)
Psychiatric Disorders	**70 (28.1)**	**82 (32.8)**	**152 (30.5)**
Depression	13 (5.2)	26 (10.4)	39 (7.8)
Insomnia	18 (7.2)	20 (8.0)	38 (7.6)
Anxiety	17 (6.8)	20 (8.0)	37 (7.4)
Nervous System Disorders	**70 (28.1)**	**69 (27.6)**	**139 (27.9)**
Headache	25 (10.0)	16 (6.4)	41 (8.2)
Gastrointestinal Disorders	**66 (26.5)**	**66 (26.4)**	**132 (26.5)**
Diarrhoea	22 (8.8)	21 (8.4)	43 (8.6)
Musculoskeletal and Connective Tissue Disorders	**51 (20.5)**	**38 (15.2)**	**89 (17.8)**
Back pain	14 (5.6)	13 (5.2)	27 (5.4)
Investigations	40 (16.1)	29 (11.6)	69 (13.8)
Weight decreased	7 (2.8)	13 (5.2)	20 (4.0)

Source: PROOF-HD CSR, Summary Table 14.3.2.1.1.
Note: MedDRA Version 23.0 was used for AEs coding.
AEs = adverse events; bid = twice daily; COVID-19 = Coronavirus Disease 2019; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients per arm; n = number of patients per reported event; TEAE = treatment-emergent adverse event.

MermaiHD, PRIDE and HART studies

Adverse events in the placebo arm of the 4 placebo-controlled studies were reported with a frequency ranging from 56.9% to 85.9%.

For the proposed posology of 45mg bid the reported AEs that were more commonly reported for pridopidine than for placebo were in MermaiHD study: nasopharyngitis (6.2 vs. 3.5%), fall (6.3 vs. 9%), insomnia (5.5 vs. 3.5%), and diarrhoea (6.8 vs. 3.5%).

In HART study, these were nasopharyngitis (5.2 vs. 1.7%), urinary tract infection (6.9 vs. 1.7%), fall (13.8 vs. 12.1%), dizziness (6.9 vs. 0%), nausea (8.6 vs. 6.9%), dry mouth (5.2 vs. 0%) and upper respiratory tract infection (5.2 vs. 3.4%).

In PRIDE study, this were nasopharyngitis (17 vs. 9%), fall (23 vs. 21%), contusion (7 vs. 4%), ligament sprain (5 vs. 1%), insomnia (6 vs. 4%), anxiety (7 vs. 2%), creatinine renal clearance decreased (6 vs. 1%), chorea (5 vs. 1%), constipation (4 vs. 1%), cough (6 vs. 2%) and rash (5 vs. 0%).

OLE studies: Open MermaiHD, Open PRIDE and Open HART studies

In the 3 completed OLE studies of pridopidine in HD patients, the frequency of AEs varied markedly between studies, which is expected given the different treatment durations. AEs occurring in at least

5% of patients were fall (10.8% to 34%), weight decreased (2.0% to 22%), anxiety (2.3% to 20%), insomnia (3.1% to 18%), chorea (10% to 13%), contusion (0.3% to 13%), diarrhoea (3.1% to 12%), and headache (2.3% to 9%) (Table 35).

Table 35: Open-label extension studies: common AEs occurring in ≥5% of patients in any study

System Organ Class Preferred Term, n (%)	**MermaiHD Open-label Phase**[a] (26 weeks)	**Open PRIDE-HD**[a] (2 years)	**Open-HART**[b] (up to 7 years)
	N=353	**N=248**	**N=134**
Median exposure (days) (Min; Max)	182 (6; 267)	519.0 (17; 743)	677.5 (11; 2413)
Gastrointestinal Disorders	**35 (9.9)**	**51 (21)**	**56 (42)**
Diarrhoea	11 (3.1)	12 (5)	16 (12)
Nausea	7 (2.0)	6 (2)	11 (8)
Vomiting	4 (1.1)	5 (2)	10 (7)
Dysphagia	6 (1.7)	7 (3)	9 (7)
Constipation	4 (1.1)	10 (4)	7 (5)
General disorders and administration site conditions	**41 (11.6)**	**36 (15)**	**34 (25)**
Irritability	15 (4.2)	10(4)	13 (10)
Gait disturbance	9 (2.5)	6 (2)	8 (6)
Infections and infestations	**43 (12.2)**	**77 (31)**	**56 (42)**
Nasopharyngitis	14 (4.0)	29 (12)	16 (12)
Upper respiratory tract infection	0	7 (3)	9 (7)
Urinary tract infection	6 (1.7)	10 (4)	9 (7)
Sinusitis	1 (0.3)	1 (<1)	8 (6)
Bronchitis	3 (0.8)	6 (2)	7 (5)
Injury, poisoning and procedural complications	**52 (14.7)**	**94 (38)**	**57 (43)**
Fall	38 (10.8)	77 (31)	46 (34)
Contusion	1 (0.3)	14 (6)	18 (13)
Laceration[c]	4 (1.1)	10 (4)	18 (13)
Excoriation	2 (0.6)	4 (2)	11 (8)
Investigations	**22 (6.2)**	**37 (15)**	**52 (39)**
Weight decreased	7 (2.0)	14 (6)	30 (22)
Musculoskeletal and connective tissue disorders	**16 (4.5)**	**30 (12)**	**28 (21)**
Back pain	2 (0.6)	14 (6)	7 (5)
Nervous system disorders	**68 (19.3)**	**71 (29)**	**52 (39)**
Chorea	37 (10.5)	24 (10)	18 (13)
Headache	8 (2.3)	14 (6)	12 (9)
Dizziness	10 (2.8)	5 (2)	7 (5)
Psychiatric disorders	**72 (20.4)**	**71 (29)**	**69 (51)**
Anxiety	8 (2.3)	16 (6)	27 (20)
Insomnia	11 (3.1)	20 (8)	24 (18)
Depression	15 (4.2)	9 (4)	21 (16)
Renal and urinary disorders	**9 (2.5)**	**9 (4)**	**23 (17)**
Urinary incontinence	2 (0.6)	1 (<1)	9 (7)
Hypertonic bladder	0	0	7 (5)
Skin and subcutaneous tissue disorders	**13 (3.7)**	**20 (8)**	**25 (19)**
Rash	1 (0.3)	2 (<1)	10 (7)

Source: Open PRIDE-HD CSR, Summary Table 15.15; MermaiHD Open-label Phase CSR, Summary Table 14.3.1.7; Open-HART CSR, Summary Table 15.18. [a]MedDRA version 14.1 was used for AEs coding in Open-HART. [a]MedDRA version 11.1 was used for AEs coding in MermaiHD Open-label Phase. [b]MedDRA version 17.0 was used for AEs coding in Open PRIDE-HD. [c]The term contains preferred terms of laceration and skin laceration. Note: Preferred terms are sorted by descending order of incidence within system organ class for the Open-HART group. Patients are counted only once in each preferred term category, and only once in each system organ class category. AE = adverse event; CSR = clinical study report; MedDRA = Medical Dictionary for Regulatory Affairs; Max=maximum; Min=minimum; N = number of patients per study; n = number of patients per reported event.

A draft CSR was submitted for the OLE of PROOF-HD; AEs that occurred in ≥5% of Patients were fall (17.7%), nasopharyngitis (6.1%) and Insomnia (4.%). The frequency for anxiety (4.7%), chorea (1.4%), weight decrease (1.4%) contusion and headache (2.6%) was (slightly) lower than 5%.

Integrated Safety Analysis

The most frequently reported TEAEs were reported in the infections and infestations SOC, with 161 (30.2%) patients in the placebo arm and 166 (31.1%) patients in the pridopidine 45 mg bid arm reporting at least one AE from this class. This was followed by TEAEs from the psychiatric disorders SOC (123 [23.1%] patients in the placebo arm and 150 [28.1%] patients in the pridopidine 45 mg bid arm), the injury, poisoning, and procedural complications SOC (128 [24.0%] patients in the placebo arm and 127 [23.8%] patients in the pridopidine 45 mg bid arm), the gastrointestinal disorders SOC (119 [22.3%] patients in the placebo arm and 132 [24.7%] patients in the pridopidine 45 mg bid arm), and the nervous system disorders SOC (117 [22.0%] patients in the placebo arm and 125 [23.4%] patients in the pridopidine 45 mg bid arm). Overall, the reported percentages were comparable between the study arms.

2.6.8.3. Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

PROOF-HD study

In the safety population, 55 patients reported a total of 78 SAEs, with a higher frequency in the pridopidine-treated arm: 21 patients in the placebo arm (8.4%) reported 32 SAEs, while 34 patients in the pridopidine arm (13.6%) reported 46 SAEs.

The most common SAEs were reported within SOC psychiatric disorders. In the pridopidine arm, 10 (4.0%) patients reported at least 1 AE in this SOC compared with 6 (2.4%) patients in the placebo arm, see Table 36. Most SAEs were reported in 1 patient only.

Table 36: PROOF-HD: SAEs by system organ class and preferred term (Safety Population)

System Organ Class Preferred Term, n (%)	**Placebo (N=249)**	**Pridopidine 45 mg bid (N=250)**
At Least 1 SAE	**21 (8.4)**	**34 (13.6)**
Psychiatric Disorders	**6 (2.4)**	**10 (4.0)**
Suicidal ideation	2 (0.8)	2 (0.8)
Anxiety	2 (0.8)	1 (0.4)
Suicide attempt	0	3 (1.2)
Delusion	1 (0.4)	1 (0.4)
Paranoia	1 (0.4)	1 (0.4)
Psychotic disorder	1 (0.4)	1 (0.4)
Anxiety disorder	0	1 (0.4)
Depression	1 (0.4)	0
Irritability	0	1 (0.4)
Injury, Poisoning and Procedural Complications	**5 (2.0)**	**4 (1.6)**
Fall	2 (0.8)	0
Accident	1 (0.4)	0
Brain contusion	1 (0.4)	0
Facial bones fracture	0	1 (0.4)
Fibula fracture	1 (0.4)	0
Head injury	0	1 (0.4)

System Organ Class Preferred Term, n (%)	Placebo (N=249)	Pridopidine 45 mg bid (N=250)
Limb injury	0	1 (0.4)
Patella fracture	1 (0.4)	0
Road traffic accident	1 (0.4)	0
Spinal cord injury cervical	1 (0.4)	0
Subdural haematoma	0	1 (0.4)
Tibia fracture	1 (0.4)	0
Infections and Infestations	**2 (0.8)**	**4 (1.6)**
COVID-19	1 (0.4)	1 (0.4)
COVID-19 pneumonia	0	2 (0.8)
Appendicitis perforated	0	1 (0.4)
Bronchitis	1 (0.4)	0
Pneumonia	0	1 (0.4)
Sepsis	0	1 (0.4)
Neoplasms Benign, Malignant and Unspecified (incl cysts and polyps)	**1 (0.4)**	**5 (2.0)**
Breast cancer	0	2 (0.8)
Meningioma	0	1 (0.4)
Spinal cord neoplasm	1 (0.4)	0
Transitional cell carcinoma	0	1 (0.4)
Uterine leiomyoma	0	1 (0.4)
Gastrointestinal Disorders	**1 (0.4)**	**4 (1.6)**
Dysphagia	1 (0.4)	1 (0.4)
Gastrointestinal haemorrhage	0	1 (0.4)
Gastrointestinal polyp haemorrhage	0	1 (0.4)
Haematemesis	0	1 (0.4)
Nervous System Disorders	**2 (0.8)**	**3 (1.2)**
Syncope	2 (0.8)	0
Ataxia	0	1 (0.4)
Chorea	0	1 (0.4)
Radiculopathy	0	1 (0.4)
Cardiac Disorders	**3 (1.2)**	**1 (0.4)**
Acute myocardial infarction	3 (1.2)	0
Aortic valve incompetence	0	1 (0.4)
Musculoskeletal and Connective Tissue Disorders	**1 (0.4)**	**2 (0.8)**
Back pain	0	1 (0.4)
Intervertebral disc protrusion	0	1 (0.4)
Spinal stenosis	1 (0.4)	0

System Organ Class Preferred Term, n (%)	Placebo (N=249)	Pridopidine 45 mg bid (N=250)
General Disorders and Administration Site Conditions	**0**	**2 (0.8)**
Death	0	1 (0.4)
Gait disturbance	0	1 (0.4)
Metabolism and Nutrition Disorders	**1 (0.4)**	**1 (0.4)**
Hyponatraemia	1 (0.4)	0
Malnutrition	0	1 (0.4)
Blood and Lymphatic System Disorders	**1 (0.4)**	**0**
Microcytic anaemia	1 (0.4)	0
Hepatobiliary Disorders	**0**	**1 (0.4)**
Cholecystitis	0	1 (0.4)
Investigations	**0**	**1 (0.4)**
Weight decreased	0	1 (0.4)
Respiratory, Thoracic and Mediastinal Disorders	**0**	**1 (0.4)**
Epistaxis	0	1 (0.4)
Vascular Disorders	**0**	**1 (0.4)**
Haematoma	0	1 (0.4)

Source: PROOF-HD CSR, Summary Table 14.3.2.3
Note: MedDRA Version 23.0 was used for AEs coding.
Note: COVID-19 SAEs were exclusively reported in PROOF-HD, as it was the only one of the 4 studies contributing data to the ISA that was conducted during the pandemic.
AE = adverse event; bid = twice daily; COVID-19 = Coronavirus Disease 2019; CSR = clinical study report; ISA = integrated safety analysis; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients per treatment arm; n = number of patients per reported event; SAE = serious adverse event.

Integrated Safety Analysis

Thirty three (6.2%) and 54 (10.1%) patients in the placebo and pridopidine 45 mg bid arms, respectively, reported having at least one SAE. SAEs reported in at least two patients in the ISA in either treatment arm are presented by preferred term (PT) in Table 37.

Table 37: Integrated safety analysis [ISA]: SAEs reported in ≥2 patients in either treatment arm by preferred term

Preferred Term, n (%)	Placebo (N=533)	Pridopidine 45 mg bid (N=534)
At least one SAE	**33 (6.2)**	**54 (10.1)**
Suicide attempt	1 (0.2)	6 (1.1)
Fall	2 (0.4)	4 (0.7)
Head injury	0 (0.0)	3 (0.6)
Suicidal ideation	3 (0.6)	2 (0.4)
Psychotic disorder	1 (0.2)	2 (0.4)
Dysphagia	1 (0.2)	2 (0.4)
COVID-19 pneumonia	0 (0.0)	2 (0.4)
Pneumonia	0 (0.0)	2 (0.4)
Breast cancer	0 (0.0)	2 (0.4)
Anxiety	2 (0.4)	1 (0.2)
Acute myocardial infarction	3 (0.6)	0 (0.0)
Depression	2 (0.4)	0 (0.0)
Syncope	2 (0.4)	0 (0.0)
Disease progression	2 (0.4)	0 (0.0)

OLE: Open MermaiHD, Open PRIDE and Open HART studies

In the OLE studies of PRIDE-HD, MermaiHD and HART, additional SAEs were reported:

OLE of PRIDE-HD: 31 (13%) patients reported at least 1 SAE. Most common SAEs were fall, reported in 4 patients, and chorea and suicidal ideation reported in 3 patients each. Three patients had SAEs deemed related to study drug: suicidal ideation in one patient, squamous cell carcinoma in another patient, and anaemia and death in another patient.

OLE of MermaiHD: 35 (9.9%) patients reported at least 1 SAE; 15 SAEs were considered as possibly related to study drug. Among possibly related SAEs, the majority were reported in a single patient each (head injury, constipation, disease progression, agitation, menorrhagia, cholangitis, psychotic disorder, syncope, dizziness, nausea, chest pain, overdose, and abnormal behaviour), except for major depression, reported in two patients.

OLE of HART: 31 (23%) patients reported at least 1 SAE (including death). Most common SAEs were fall and subdural haemorrhage reported in 4 patients each, and aspiration pneumonia reported in 3 patients. Few SAEs were considered related to study drug and included single events of convulsion, delirium, loss of consciousness, subdural hematoma, retinal detachment, and anxiety.

Adverse events of special interest

Note to the reader:

Cardiac impairment and renal impairment are discussed under the heading 'safety in special populations'. ADRs of special interest which are discussed here are QT interval prolongation, depression and suicidality.

QT interval prolongation

The risk of QTc prolongation has been characterized through the ISA of the 4 placebo-controlled studies in HD patients (PROOF-HD, PRIDE-HD, MermaiHD and HART). For exposure-response analysis based on PRIDE-HD data, please refer to the PD section.

In the ISA, no patient had QTcF prolongation >500 msec. None of the patients in the placebo arm and 4 (0.7%) patients in the pridopidine 45 mg bid arm had QTcF prolongation of 480 msec to <500 msec. Nine (1.7%) patients in the placebo arm and 25 (4.7%) patients in the pridopidine 45 mg bid arm had QTcF prolongation of 450 msec to ≤480 msec.

Approximately half of these events occurred during the first 12 weeks of treatment with the study drug.

Table 38: ISA: TEAEs under the SMQ 20000001 (Torsade de pointes/QT prolongation) by preferred term (SG)

Preferred Term, n (%)	Placebo (N=533)	Pridopidine 45 mg bid (N=534)
At least one TEAE under the SMQ 20000001 (Torsade de pointes/QT prolongation)	8 (1.5)	9 (1.7)
Syncope	4 (0.8)	7 (1.3)
Electrocardiogram QT prolonged	2 (0.4)	2 (0.4)
Electrocardiogram repolarisation abnormality	1 (0.2)	0 (0.0)
Loss of consciousness	1 (0.2)	0 (0.0)

Source: ISA report.
Note: If a patient experienced more than one event in a given category, that patient was counted only once in that category.
Note: Preferred terms are sorted in decreasing frequency in the pridopidine 45 mg bid arm.
Note: MedDRA Dictionary (Version 23.0) is used for coding AEs.
AE = adverse event; bid = twice daily; ISA = integrated safety analysis; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients per treatment arm; n = number of patients per reported event; SG = primary safety group; TEAEs = treatment-emergent adverse events.

Regarding treatment-related TEAEs under the SMQ "Torsade de pointes/QT prolongation", these were reported for 2 patients (0.4%) in the placebo arm of MermaiHD study and one patient (0.2%) in the pridopidine 45 mg bid arm of PRIDE-HD study, and all led to study treatment discontinuation. The reported PTs included two events of "Electrocardiogram QT prolonged", one moderate and one severe, in the placebo arm, and one mild event of "Electrocardiogram QT prolonged" in the pridopidine 45 mg bid arm. The latter was an isolated measurement of 487 msec (60.6 msec increase from baseline) at Week 52 of PRIDE-HD, which did not recur through the 52 weeks of the OLE study (Open PRIDE-HD) with the same dose. A single treatment-related SAE under the AESI "QT interval prolongation" was reported in one patient in the placebo arm ("Electrocardiogram QT prolonged").

Depression

PROOF-HD study

In PROOF-HD, depression was reported in 13 (5.2%) patients on placebo and in 26 (10.4%) patients on pridopidine, see Table 39. Most events were mild to moderate in severity, with 2 severe TEAEs of depression, one in each arm.

MermaiHD, PRIDE and HART studies

In MermaiHD, depression was reported in 8 (5.6%) patients in the placebo arm, 6 (4.1%) patients each in the pridopidine 45 mg qd arm and pridopidine 45 mg bid arm.

In PRIDE-HD, depression was reported in 4 (5%) patients in the placebo arm, in 2 (2%) patients each in the pridopidine 67.5 mg bid and 90 mg bid arms, and in 4 (5%) patients in the pridopidine 112.5 mg bid arm. There was no event of depression in the pridopidine 45 mg bid arm.

In HART, depression was reported in 4 (6.9%) patients in the placebo arm, in 2 (3.6%) patients in the pridopidine 10 mg bid arm, in 3 (5.5%) patients in the pridopidine 22.5 mg bid arm, and in 2 (3.4%) patients in the pridopidine 45 mg bid arm.

Integrated Safety Analysis

In the ISA, there was a comparable incidence of depression between patients on placebo (30 [5.6%]) and those on pridopidine 45 mg bid (33 [6.2%]). The overall incidence of severe TEAEs of depression was similar (1 [0.2%]) in both arms. Depressed mood was reported with higher frequency in the pridopidine 45 mg bid (6 [1.1%]) compared to the placebo arm (1 [0.2%]). There were no TEAEs of suicidal depression or major depression among participants taking pridopidine 45 mg bid, while one (0.2%) patient on placebo suffered a TEAE of moderate suicidal depression.

Table 39: Depression-related AEs in the PROOF-HD, PRIDE-HD, MermaiHD, and HART studies (45 mg bid vs placebo) (Safety Population)

Preferred Term	**Incidence/ Severity/ Seriousness/ Relationship**	**Double-Blind, Placebo-Controlled Studies with Pridopidine (n, %)**									
		PROOF-HD		**PRIDE-HD**		**MermaiHD**		**HART**		**4 Studies Integrated**	
		Placebo (N=249)	**Prido 45 mg bid (N=250)**	**Placebo (N=82)**	**Prido 45 mg bid (N=81)**	**Placebo (N=144)**	**Prido 45 mg bid (N=145)**	**Placebo (N=58)**	**Prido 45 mg bid (N=58)**	**Placebo (N=533)**	**Prido 45 mg bid (N=534)**
Depression	**All**	13 (5.2)	26 (10.4)	4 (5)	0	8 (5.6)	6 (4.1)	4 (6.9)	2 (3.4)	30 (5.6)	33 (6.2)
	Severe	1 (0.4)	1 (0.4)	0	-	0	0	0	0	1 (0.2)	1 (0.2)
	SAE(s)	1 (0.4)	0	0	-	1 (0.7)	0	0	0	2 (0.4)	0
	Relationship to Study Drug										
	Possibly Related	-	-	-	-	5 (3.5)	3 (2.1)	4 (6.9)	1 (1.7)	10 (1.9)	6 (1.1)
	Related	0	3 (1.2)	1 (1)	0	-	-	-	-		
Depressed Mood	**All**	1 (0.4)	2 (0.8)	0	1 (1)	0	3 (2.1)	0	0	1 (0.2)	6 (1.1)
	Severe	0	0	**-**	1 (1)	**-**	0	**-**	**-**	0	1 (0.2)
	SAE(s)	0	0	-	0	**-**	0	**-**	**-**	0	0
	Relationship to Study Drug										
	Possibly Related	-	-	**-**	-	**-**	2 (1.4)	**-**	**-**	0	3 (0.6)
	Related	0	0	**-**	1 (1)	**-**	-	**-**	**-**		
Depression Suicidal	**All**	1 (0.4)	0 (0)	0	0	0	0	0	0	1 (0.2)	0
	Severe	0	0	-	-	-	-	-	-	0	-
	SAE(s)	0	0	-	-	-	-	-	-	0	-
	Relationship to Study Drug										
	Possibly Related	0	-	**-**	**-**	**-**	**-**	**-**	**-**	0	-

	Related	0	-	-	-	-	-	-	-		
Major Depression	**All**	0	0	0	0	0	0	0	0	0	0

Source: PROOFHD CSR Section 12.3.1.4.1, PRIDEHD CSR Section 12.6.1, Section 12.2.2.2, Section 12.2.2.3, Section 12.3.1.2, Summary Table 15.1.32.2a, Summary Table 15.1.32.3a; MermaiHD CSR Summary Table 14.3.1.4, Summary Table 14.3.1.7, Summary Table 14.3.1.9, Summary Table 14.3.1.22; HART CSR Summary Table 14.3.1.4, Summary Table 14.3.1.7, Summary Table 14.3.1.8, Summary Table 14.3.2.1; ISA Summary Table 1.4.3, Summary Table 1.4.6, Summary Table 1.4.7, Summary Table 1.4.9, Summary Table 1.4.13.
Note: "All" refers to all reported cases of the specific TEAE, regardless of severity, seriousness or relationship to study drug.
Note: If an AE was reported, the frequencies and percentages of the relevant categories are listed. If it does not fall within a certain category, that category is marked with a zero.
Note: If the incidence of an AE was reported as zero (i.e., did not occur), all the categories beneath it are marked with a hyphen to denote they are not relevant.
Note: For relationship to study drug – only relevant categories are populated. The rest are marked with a hyphen. Where applicable, "Related or Possibly related" are considered one category and are therefore merged.
Note: For AEs of depression, one placebo patient originally coded as 'depression' in PRIDE-HD was recoded to 'mixed anxiety and depressive disorder' in MedDRA up-versioning; two placebo patients in original MermaiHD study data were allocated to the open label extension period but were re-allocated to double-blind, placebo-controlled period based on AE start date and double-blind period start and end dates; one pridopidine patient in HART study with the depression event occurring 40 days after last dose (originally classified as TEAE) was re-classified as NOT an TEAE in the integrated analysis.

Suicidality

PROOF-HD, MermaiHD, PRIDE and HART studies

Overall, in the four HD studies, suicidality events were generally comparable between the placebo and the pridopidine 45 mg bid arms. There was a comparable incidence of suicidal ideation between patients on placebo (n=8, 1.5%, deemed related or possibly related in 2 [0.4%] patients) and those on pridopidine 45 mg bid (n=12, 2.2%, deemed related or possibly related in 1 [0.2%] patient), see Table 40.

The overall incidence of severe TEAEs of suicidal ideation was the same (n=2, 0.4%) in both arms. Similarly, the rate of SAEs of suicidal ideation was comparable: 3 (0.6%) patients in the placebo arms and 2 (0.4%) in the pridopidine 45 mg bid arms. TEAEs of suicidal attempt were slightly more frequent in the pridopidine 45 mg bid arm (n=6, 1.1%, deemed related or possibly related in 2 [0.4%] patients) than in the placebo arm (n=1, 0.2%, deemed possibly related), as were severe TEAEs (n=5, 0.9% vs. none) and SAEs (n=6, 1.1% vs. 1, 0.2%) of suicidal attempt.

Among the 534 patients receiving pridopidine 45 mg bid in the 4 double-blind HD studies, there was one (0.2%) report of suicidal behaviour (deemed not related) and there were no TEAEs of completed suicide. Across the placebo arms, there were no TEAEs of suicidal behaviour, and there was one (0.2%) completed suicide.

Table 40: Suicidality-related AEs in the PROOF-HD, PRIDE-HD, MermaiHD, and HART studies (45 mg bid vs placebo) (Safety Population)

Preferred Term	Incidence/ Severity/ Seriousness/ Relationship	Double-Blind, Placebo-Controlled Studies with Pridopidine (n, %)									
		PROOF-HD		PRIDE-HD		MermaiHD		HART		4 Studies Integrated	
		Placebo (N=249)	Prido 45 mg bid (N=250)	Placebo (N=82)	Prido 45 mg bid (N=81)	Placebo (N=144)	Prido 45 mg bid (N=145)	Placebo (N=58)	Prido 45 mg bid (N=58)	Placebo (N=533)	Prido 45 mg bid (N=534)
Suicidal ideation	**All**	6 (2.4)	9 (3.6)	0	2 (2.4)	1 (0.7)	0	1 (1.7)	1 (1.7)	8 (1.5)	12 (2.2)
	Severe	1 (0.4)	2 (0.8)	-	0	1 (0.7)	-	0	0	2 (0.4)	2 (0.4)
	SAE	2 (0.8)	2 (0.8)	-	0	1 (0.7)	-	0	0	3 (0.6)	2 (0.4)
	Relationship to Study Drug										
	Possibly Related	-	-	-	-	-	-	1 (1.7)	-	2 (0.4)	1 (0.2)
	Related	1 (0.4)	1 (0.4)	-	0		-	-			
Suicidal attempt	**All**	0	3 (1.2)	0	1 (1)	1 (0.7)	2 (1.4)	0	0	1 (0.2)	6 (1.1)
	Severe	-	3 (1.2)	0	1 (1)	0	1 (0.7)	0	0	0	5 (0.9)
	SAE	-	3 (1.2)	0	1 (1)	1 (0.7)	2 (1.4)	0	0	1 (0.2)	6 (1.1)
	Relationship to Study Drug										
	Possibly Related	-	-	-	-	1 (0.7)	1 (0.7)	-	-	1 (0.2)	2 (0.4)
	Related	0	0	0	1 (1)	-	-	-	-		
Suicidal behaviour	**All**	0	1 (0.4)	0	0	0	0	0	0	0	1 (0.2)
	Severe	-	0	-	-	-	-	-	-	-	0
	SAE	-	0	-	-	-	-	-	-	-	0
	Relationship to Study Drug										
	Possibly Related	-	0	-	-	-	-	-	-	-	-
	Related	-	0	-	-	-	-	-	-		
Completed suicide	**All**	0	0	0	0	1 (0.7)	0	0	0	1 (0.2)	0
	Severe	0	0	0	0	1 (0.7)	0	0	0	1 (0.2)	0
	SAE	0	0	0	0	1 (0.7)	0	0	0	1 (0.2)	0
Completed suicide (continued)	**Relationship to Study Drug**										
	Possibly Related	0	0	0	0	1 (0.7)	0	0	0	1 (0.2)	0

Preferred Term	Incidence/ Severity/ Seriousness/ Relationship	Double-Blind, Placebo-Controlled Studies with Pridopidine (n, %)									
		PROOF-HD		PRIDE-HD		MermaiHD		HART		4 Studies Integrated	
		Placebo (N=249)	Prido 45 mg bid (N=250)	Placebo (N=82)	Prido 45 mg bid (N=81)	Placebo (N=144)	Prido 45 mg bid (N=145)	Placebo (N=58)	Prido 45 mg bid (N=58)	Placebo (N=533)	Prido 45 mg bid (N=534)
	Related	-	-	-	-	-	-	-	-		

Source: PROOFHD CSR, Section 12.3.1.4.2; PRIDEHD CSR, Section 12.6.1, Section 12.2.2.2, Section 12.2.2.3, Section 12.3.1.2, Summary Table 15.1.32.2a, Summary Table 15.1.32.3a; MermaiHD CSR, Summary Table 14.3.1.4, Summary Table 14.3.1.7, Summary Table 14.3.1.9; Summary Table 14.3.1.22; HART CSR, Summary Table 14.3.1.4, Summary Table 14.3.1.7, Summary Table 14.3.1.8, Summary Table 14.3.2.1; ISA, Summary Table 1.4.3, Summary Table 1.4.6, Summary Table 1.4.7, Summary Table 1.4.9, Summary Table 1.4.13.
Note: If an AE was reported, the frequencies and percentages of the relevant categories are listed. If it does not fall within a certain category, that category is marked with a zero.
Note: If the incidence of an AE was reported as zero (i.e., did not occur), all the categories beneath it are marked with a hyphen to denote they are not relevant.
Note: For relationship to study drug – only relevant categories are populated. The rest are marked with a hyphen.
AE = adverse event; bid = twice weekly; CSR = clinical study report; N = number of patients analysed; n = number of patients with reported event; prido = pridopidine; SAE = serious adverse event; - = as described in notes above, relatedness cells not populated as there were no events.

Across the performed HD studies, the incidence of adverse events related to depression and suicidality was low. The incidence of apathy across the studies was 2.2% in the pridopidine 45 mg BID arm as compared to 1.3% in the placebo arm. The incidence of crying was 0.4% in the pridopidine 45 mg BID arm as compared to 0 in the placebo arm. Mood swings and dysphoria occurred in 0.2% of patients in the pridopidine arm as compared to none in the placebo arm. The majority of these events were not considered related to the study drug and only one was considered severe (in placebo arm).

Deaths

PROOF, MermaiHD, PRIDE and HART studies

Eleven patients died in the four Phase 2 and Phase 3 randomized, placebo-controlled studies (PROOF-HD, PRIDE-HD, MermaiHD, and HART studies). Among those, the relation to the study drug was considered possible for one patient (assigned to placebo) who completed suicide after 3-4 months of starting the study. Further, a case of death due to aspiration pneumonia in a patient assigned to pridopidine 112.5mg bid and enrolled in the study for at least 5 month was considered related to the study drug by the investigator.

OLE: Open MermaiHD, Open PRIDE and Open HART studies

In the three OLE studies with pridopidine, 12 deaths were reported:

MermaiHD-OLP: 1 death (completed suicide), was considered as unlikely related to pridopidine. The patient started study medication (randomised to pridopidine 45mg) and attended visit 6 (week 12) and visit 7 (week 26); study drug was interrupted for 1 week 6 months later due to worsening of HD and the patient was admitted to hospital. Whilst in hospital for treatment of worsening HD, visit 13 was completed but the patient died on the same day.

Open PRIDE-HD: 3 deaths, all were considered not related to pridopidine by both investigator and sponsor (cachexia most probably related to HD, poisoning most probably accidental and anaemia and weight loss).

Open-HART study: 8 deaths, all were considered not related to pridopidine.

2.6.8.4. Laboratory findings

Haematology

PROOF-HD, MermaiHD, PRIDE and HART studies

In PROOF-HD study, clinically significant values were observed in no more than 5% of patients at any time point. The proportion of patients with clinically significant haematology values and shifts from baseline was similar between treatment arms.

In MermaiHD study, there were no clinically significant changes in haematology values from baseline by treatment.

In PRIDE-HD study, between 2% and 10% of patients showed clinically significant haematology values post-baseline, and the proportions were similar across treatment arms and lowest in the highest pridopidine dosing arm (placebo: 7%; pridopidine 45 mg bid: 10%; pridopidine 67.5 mg bid: 10%; pridopidine 112.5 mg bid: 2%). Shifts from baseline were comparable between treatment arms.

In HART study, no clinically significant changes in haematology values from baseline by treatment were observed.

Chemistry

PROOF-HD, MermaiHD, PRIDE and HART studies

In PROOF-HD study, clinically significant values (based on principle investigator assessment) were recorded in several serum chemistry parameters measured. However, these findings were sporadic with no trends in shift from baseline for any of the serum chemistry parameters. The incidence of shifts of values from normal to clinically significant was comparable between treatment arms.

In PRIDE-HD study, the proportion of patients with at least 1 potentially clinically significant abnormal chemistry value post baseline varied between 3% and 9%, and was similar between treatment arms. The most frequent post-baseline abnormality was blood urea nitrogen increased, reported in 4 (5%) out of 81 patients in the pridopidine 90 mg bid arm. However, only 1 to 2 patients in the other treatment arms (including placebo) had a potentially clinically significant event of blood urea nitrogen increased.

In MermaiHD study, no clinically significant mean change from baseline to the last assessment attributed to study drug was observed. Shifts in serum chemistry values were observed for several chemistry measures and occurred at similar frequency across treatment arms. The most common shifts observed in more than 10% of patients overall occurred in glucose (normal/high to low; 54 [12.4%] out of 434 patients).

In HART study, no clinically significant mean change from baseline to the last assessment attributed to study drug was observed. Shifts in serum chemistry values were observed for several chemistry measures and occurred at similar frequency across treatment arms. The most common shifts observed in more than 10% of patients overall occurred in glucose (normal/high to low; 36 [16.1%] out of 223 patients) and prolactin (normal/low to high; 23 [10.3%] out of 223 patients).

In the Phase 1 Study ACR16C007, there were minor changes in serum chemistry values over time. There was a transient increase in mean glucose levels in both treatment arms and an increase in prolactin levels in the pridopidine arm. Prolactin levels above normal range during the study were mostly associated with concomitant use with risperidone (known to cause hyperprolactinemia) and independent of treatment arm.

OLE: Open-MermaiHD, Open-PRIDE and Open-HART studies

In the OLE studies, shifts occurred at low frequency. In the OLE phase of PRIDE-HD, none of the shifts were considered clinically significant. In the OLE of HART studies, several abnormal laboratory values were recorded as AEs, i.e., blood potassium increased/ hyperkalaemia (3 patients), blood potassium decreased/hypokalaemia (6 patients), magnesium deficiency and blood calcium decreased in 1 patient each.

2.6.8.5. In vitro biomarker test for patient selection for safety

Not applicable

2.6.8.6. Safety in special populations

Safety profile by renal / hepatic impairment

Subjects with severe renal impairment or severe hepatic impairment were excluded. However, use in mild to moderate renal or hepatic impairment was permitted. Upon request, the applicant has provided additional information concerning patients with mild or moderate renal or hepatic impairment (Table 41).

Table 41: Safety profile in subjects with mild or moderate renal or hepatic impairment.

	Pridopidine 45 mg bid				**Placebo**			
MedDRA Terms	**Hepatically impaired* n (%)**		**Renally impaired** n (%)**		**Hepatically impaired* n (%)**		**Renally impaired** n (%)**	
	Mild hepatic imp.	**Moderate hepatic imp.**	**Mild renal imp.**	**Moderate renal imp.**	**Mild hepatic imp.**	**Moderate hepatic imp.**	**Mild renal imp.**	**Moderate renal imp.**
Total AEs	20 (90.9)	1 (100.0)	149 (80.5)	22 (73.3)	14 (73.7)	1 (100.0)	155 (76.4)	17 (85.0)
Serious AEs – Total	1 (4.5)[c]	0 (0.0)	25 (13.5)	1 (3.3)	2 (10.5)[d]	0 (0.0)	14 (6.9)	1 (5.0)
- Fatal	0 (0.0)	0 (0.0)	1 (0.5)	1 (3.3)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)
- Hospitalisation/prolong existing hospitalisation	0 (0.0)	0 (0.0)	12 (6.5)	0 (0.0)	1 (5.3)	0 (0.0)	8 (3.9)	1 (5.0)
- Life-threatening	0 (0.0)	0 (0.0)	3 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
- Disability/incapacity	0 (0.0)	0 (0.0)	3 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)	0 (0.0)
- Other (medically significant)	0 (0.0)	0 (0.0)	6 (3.2)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.5)	0 (0.0)
AE leading to drop-out	1 (4.5)	0 (0.0)	26 (14.1)	2 (6.7)	2 (10.5)	0 (0.0)	17 (8.4)	1 (5.0)
Alanine aminotransferase increased			2 (1.1)	0 (0.0)			0 (0.0)	0 (0.0)
Anxiety	0 (0.0)	0 (0.0)	2 (1.1)	0 (0.0)	1 (5.3)	0 (0.0)	2 (1.0)	0 (0.0)
Aspartate aminotransferase increased			2 (1.1)	0 (0.0)			0 (0.0)	0 (0.0)
Liver function test increased	1 (4.5)	0 (0.0)			0 (0.0)	0 (0.0)		
Depression			2 (1.1)	0 (0.0)			1 (0.5)	0 (0.0)
Diarrhoea			2 (1.1)	0 (0.0)			2 (1.0)	0 (0.0)
Gait disturbance			2 (1.1)	0 (0.0)			0 (0.0)	0 (0.0)
Suicide attempt			2 (1.1)	0 (0.0)			0 (0.0)	0 (0.0)
Disorientation			0 (0.0)	1 (3.3)			0 (0.0)	0 (0.0)
Sedation			0 (0.0)	1 (3.3)			0 (0.0)	0 (0.0)
Delusion	0 (0.0)	0 (0.0)			1 (5.3)	0 (0.0)		
Electrocardiogram QT prolonged	0 (0.0)	0 (0.0)			1 (5.3)	0 (0.0)		

* Hepatic impairment is defined as having Child-Pugh score B or C
** Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)
bid = twice daily; MedDRA = Medical Dictionary for Regulatory Affairs; AE = adverse event.

Safety profile in the elderly population

The age of HD subjects in the 4 placebo-controlled studies ranges from 22 up to 86 years of age. The applicant provided safety subgroup analysis based on age at entry. However, 54 years and 65 years were used as cut-off. Upon request, the applicant has provided additional information for patients above 65 years (Table 42).

Table 42: Safety profile in subjects older than 65 years

	Pridopidine 45 mg bid				**Placebo**			
MedDRA Terms	**Age <65 n (%)**	**Age 65-74 n (%)**	**Age 75-84 n (%)**	**Age 85+ n (%)**	**Age <65 n (%)**	**Age 65-74 n (%)**	**Age 75-84 n (%)**	**Age 85+ n (%)**
Total AEs	352 (76.7)	52 (77.6)	5 (83.3)	2 (100.0)	356 (74.9)	41 (82.0)	7 (87.5)	0 (0.0)
Serious AEs – Total	41 (8.9)	11 (16.4)	1 (16.7)	1 (50.0)	27 (5.7)	6 (12.0)	0 (0.0)	0 (0.0)
- Fatal	3 (0.7)	0 (0.0)	0 (0.0)	1 (50.0)	1 (0.2)	1 (2.0)	0 (0.0)	0 (0.0)
- Hospitalisation/prolong existing hospitalisation	18 (3.9)	9 (13.4)	0 (0.0)	0 (0.0)	15 (3.2)	5 (10.0)	0 (0.0)	0 (0.0)
- Life-threatening	4 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (2.0)	0 (0.0)	0 (0.0)
- Disability/incapacity	6 (1.3)	2 (3.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (4.0)	0 (0.0)	0 (0.0)
- Other (medically significant)	12 (2.6)	3 (4.5)	0 (0.0)	0 (0.0)	5 (1.1)	2 (4.0)	0 (0.0)	0 (0.0)
AE leading to drop-out	49 (10.7)	8 (11.9)	0 (0.0)	0 (0.0)	36 (7.6)	4 (8.0)	1 (12.5)	0 (0.0)
Psychiatric disorders	126 (27.5)	21 (31.3)	3 (50.0)	0 (0.0)	115 (24.2)	6 (12.0)	2 (25.0)	0 (0.0)
Nervous system disorders	107 (23.3)	16 (23.9)	2 (33.3)	0 (0.0)	101 (21.3)	14 (28.0)	2 (25.0)	0 (0.0)
Accidents and injuries	104 (22.7)	19 (28.4)	3 (50.0)	1 (50.0)	107 (22.5)	17 (34.0)	4 (50.0)	0 (0.0)
Cardiac disorders	14 (3.1)	1 (1.5)	0 (0.0)	0 (0.0)	21 (4.4)	4 (8.0)	1 (12.5)	0 (0.0)
Vascular disorders	20 (4.4)	5 (7.5)	1 (16.7)	0 (0.0)	22 (4.6)	4 (8.0)	0 (0.0)	0 (0.0)
Cerebrovascular disorders	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	138 (30.1)	26 (38.8)	1 (16.7)	1 (50.0)	141 (29.7)	17 (34.0)	3 (37.5)	0 (0.0)
Anticholinergic syndrome	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Quality of life decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures	97 (21.1)	21 (31.3)	4 (66.7)	1 (50.0)	94 (19.8)	19 (38.0)	3 (37.5)	0 (0.0)
Fatigue	10 (2.2)	5 (7.5)	1 (16.7)	0 (0.0)	28 (5.9)	1 (2.0)	1 (12.5)	0 (0.0)
COVID-19	48 (10.5)	12 (17.9)	0 (0.0)	0 (0.0)	51 (10.7)	6 (12.0)	1 (12.5)	0 (0.0)
Diarrhoea	28 (6.1)	12 (17.9)	0 (0.0)	0 (0.0)	35 (7.4)	2 (4.0)	2 (25.0)	0 (0.0)

	Pridopidine 45 mg bid				Placebo			
MedDRA Terms	**Age <65 n (%)**	**Age 65-74 n (%)**	**Age 75-84 n (%)**	**Age 85+ n (%)**	**Age <65 n (%)**	**Age 65-74 n (%)**	**Age 75-84 n (%)**	**Age 85+ n (%)**
Contusion	15 (3.3)	6 (9.0)	0 (0.0)	0 (0.0)	17 (3.6)	2 (4.0)	0 (0.0)	0 (0.0)
Skin abrasion	9 (2.0)	4 (6.0)	1 (16.7)	0 (0.0)	7 (1.5)	2 (4.0)	1 (12.5)	0 (0.0)
Constipation	7 (1.5)	4 (6.0)	0 (0.0)	0 (0.0)	8 (1.7)	2 (4.0)	0 (0.0)	0 (0.0)
Cough	11 (2.4)	4 (6.0)	0 (0.0)	0 (0.0)	10 (2.1)	3 (6.0)	0 (0.0)	0 (0.0)
Dysphagia	7 (1.5)	3 (4.5)	0 (0.0)	0 (0.0)	8 (1.7)	3 (6.0)	0 (0.0)	0 (0.0)
Gait disturbance	5 (1.1)	3 (4.5)	0 (0.0)	0 (0.0)	4 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)

bid = twice daily; MedDRA = Medical Dictionary for Regulatory Affairs; AE = adverse event.

Safety profile by HD stage (from ISA)

HD stage is defined as follow: baseline TFC: 7 to 13 (HD stage 1 and 2) and baseline TFC: 0 to 6 (HD stage 3 and 4)

Treatment-related TEAEs were more frequently reported in patients with baseline HD3-4 (patients with at least one treatment-related TEAE: 32 [37.6%] and 37 [43.5%] in the placebo and pridopidine arms, respectively) as compared to patients with baseline HD1-2 (patients with at least one treatment-related TEAE: 135 [30.1%] and 140 [31.2%] in the placebo and pridopidine arms, respectively). This difference stems mainly from more frequently reported treatment-related TEAEs under the SOC Psychiatric disorders (HD1-2: 6.3% and 9.4% of patients in the placebo and pridopidine arms, respectively; HD3-4: 15.3% and 21.2% of patients in the placebo and pridopidine arms, respectively) and Gastrointestinal disorders (HD1-2: 7.4% and 9.8% of patients in the placebo and pridopidine arms, respectively; HD3-4: 4.7% and 17.6% of patients in the placebo and pridopidine arms, respectively).

Table 43: Treatment-related TEAEs reported with a higher incidence in participants treated with pridopidine 45 mg bid compared to placebo, for participants HD1-2 vs HD3-4

PT	**Placebo (n = 533)**		**Pridopidine 45 mg bid (n = 534)**	
	HD1-2 (n = 448)	**HD3-4 (n = 85)**	**HD1-2 (n = 449)**	**HD3-4 (n = 85)**
All treatment-related TEAEs	**135 (30.1)**	**32 (37.6)**	**140 (31.2)**	**37 (43.5)**
Decreased appetite	0 (0%)	0 (0%)	4 (0.9%)	0 (0%)
Dizziness postural	1 (0.2%)	0 (0%)	4 (0.9%)	0 (0%)
Dysgeusia	0 (0%)	0 (0%)	3 (0.7%)	0 (0%)
Hot flush	0 (0%)	0 (0%)	3 (0.7%)	0 (0%)
Abdominal pain upper	1 (0.2%)	0 (0%)	4 (0.9%)	1 (1.2%)
Pruritus	0 (0%)	0 (0%)	3 (0.7%)	0 (0%)
Back pain	0 (0%)	0 (0%)	3 (0.7%)	0 (0%)
Apathy	2 (0.4%)	0 (0%)	2 (0.4%)	3 (3.5%)
Diarrhoea	14 (3.1%)	0 (0%)	11 (2.4%)	4 (4.7%)
Huntington’s disease	8 (1.8%)	1 (1.2%)	8 (1.8%)	5 (5.9%)

Proposed ADR in SmPC				
Insomnia	6 (1.3%)	1 (1.2%)	11 (2.4%)	4 (4.7%)
Sleep disorders	1 (0.2%)	1 (1.2%)	8 (1.8%)	1 (1.2%)
Anxiety	1 (0.2%)	2 (2.4%)	8 (1.8%)	2 (2.4%)
Vomiting	1 (0.2%)	0 (0%)	6 (1.3%)	1 (1.2%)
Electrocardiogram QT prolonged	1 (0.2%)	1 (1.2%)	0 (0%)	1 (1.2%)
Creatinine renal clearance decreased	1 (0.2%)	1 (1.2%)	3 (0.7%)	0 (0%)

bid = twice daily; PT = Preferred term; ADR = Adverse drug reaction; TEAE = treatment-emergent adverse event; SmPC = Summary of product characteristics; HD= Huntington's disease

Overall, some treatment-related TEAEs were more frequently reported in patients HD1-2 treated with pridopidine 45 mg bid than placebo: decreased appetite, dizziness postural, dysgeusia, hot flush, abdominal pain upper, pruritus and back pain. Others were more frequently reported in patients HD3-4 treated with pridopidine 45 mg bid than placebo: apathy, diarrhoea and Huntington's disease.

When comparing patients treated with pridopidine by HD stage, decreased appetite, dizziness postural, dysgeusia, hot flush, abdominal pain upper, pruritus, back pain and diarrhoea were more reported in patients HD1-2 than HD3-4. However, patients HD1-2 treated with pridopidine 45 mg bid represent 449 patients vs 85 patients HD3-4, and the mentioned events were "only" reported in 3 to 4 patients HD1-2 among the 449 (expect for diarrhoea: 11 patients). No specific trend could be identified regarding treatment-related TEAEs (individual PTs) reported by HD stage.

Regarding treatment-related SAEs and treatment-related TEAEs leading to study drug discontinuation, no specific trend could either be identified by HD stage.

2.6.8.7. Immunological events

Not applicable

2.6.8.8. Safety related to drug-drug interactions and other interactions

Tricyclic antidepressants and class I antiarrhythmics

Concomitant treatment with tricyclic antidepressants and class I antiarrhythmics was generally prohibited as these drugs were considered to prolongate the QTc or were considered CYP2D6 substrates. In fact, it was observed in PK studies that exposure of metoprolol, a probe substrate of CYP2D6, is significantly increased when given concomitantly with pridopidine (at steady state), i.e., Cmax of metoprolol increased 3.50-fold and AUC0-t increased 6.64-fold. Pridopidine may potentially increase the exposure of concomitant CYP2D6-metabolised drugs.

Table 44: Permitted/prohibited concomitant medications with CYP2D6 substrates in clinical studies in HD patients

Study	**Concomitant medications with CYP2D6 substrates**
PROOF-HD	Caution statement*
MermaiHD	Permitted except for tricyclic antidepressants, class I antiarrhythmics and strong CYP2D6 inhibitors
PRIDE-HD	Prohibited if reducing seizure threshold*
HART	Permitted except for tricyclic antidepressants and class I antiarrhythmics
Open PRIDE-HD	Permitted except for tricyclic antidepressants
Open MermaiHD	Permitted except for tricyclic antidepressants and class I antiarrhythmics
Open HART	Permitted except for tricyclic antidepressants and class I antiarrhythmics

** Caution should be exercised with medications that are mainly eliminated via the CYP2D6 -dependent pathway.*

ADM

Participants were stratified according to neuroleptic use at baseline in PROOF-HD, PRIDE-HD, MermaiHD, and HART studies. Neuroleptic use had to be constant for at least 4 weeks prior to baseline as specified in the respective protocols. The overall safety profile observed in HD patients treated with neuroleptics was similar to that seen in patients without concomitant neuroleptics.

In the ISA, the frequency of AEs was analysed by ADM use at baseline or at any timepoint during the study. The frequency of treatment-related TEAEs was comparable between the placebo and pridopidine treatment arms (reported in 31.3% and 33.1% of patients, respectively). The frequency of treatment-related TEAEs was the same regardless of the ADM usage.

Among patients not taking ADMs, the incidence of treatment-related TEAEs in the placebo and pridopidine 45 mg bid arms, respectively, were:

Off ADMs at baseline: 30.7% and 33.5%

Off ADMs all the time: 31.9% and 34.7%

Among patients taking ADMs, the incidence of treatment-related TEAEs in the placebo and pridopidine 45 mg bid arms, respectively, were:

On ADMs at baseline: 32.4% and 32.6%

On ADMs at any time: 30.7% and 31.3%

Table 45: Treatment-related TEAEs reported with a significantly higher incidence in participants treated with pridopidine 45 mg bid compared to placebo, for participants on ADMs vs off ADMs (at any time)

PT	**Placebo (n = 533)**		**Pridopidine 45 mg bid (n = 534)**	
	ADM yes (n = 238)	**ADM no (n = 295)**	**ADM yes (n = 243)**	**ADM no (n = 291)**
All treatment-related TEAEs	**73 (30.7)**	**94 (31.9)**	**76 (31.3)**	**101 (34.7)**
Somnolence	1 (0.4%)	5 (1.7%)	5 (2.1%)	2 (0.7%)
Huntington's disease	3 (1.3%)	6 (2.0%)	7 (2.9%)	6 (2.1%)
Weight decreased	0 (0%)	1 (0.3%)	3 (1.2%)	0 (0%)
Dizziness	5 (2.1%)	8 (2.7%)	1 (0.4%)	14 (4.8%)
Dizziness postural	*1 (0.4%)*	*0 (0%)*	*3 (1.2%)*	*1 (0.3%)*
Abdominal pain upper	0 (0%)	1 (0.3%)	1 (0.4%)	4 (1.4%)
Dry mouth	1 (0.4%)	1 (0.3%)	1 (0.4%)	4 (1.4%)
Pruritus	0 (0%)	0 (0%)	0 (0%)	3 (1.0%)
Back pain	0 (0%)	0 (0%)	0 (0%)	3 (1.0%)
Proposed ADR in SmPC				
Insomnia	4 (1.7%)	3 (1.0%)	6 (2.5%)	9 (3.1%)
Sleep disorders	0 (0%)	2 (0.7%)	5 (2.1%)	4 (1.4%)
Anxiety	2 (0.8%)	1 (0.3%)	5 (2.1%)	5 (1.7%)
Vomiting	1 (0.4%)	0 (0%)	2 (0.8%)	5 (1.7%)
Electrocardiogram QT prolonged	2 (0.8%)	0 (0%)	0 (0%)	1 (0.3%)
Creatinine renal clearance decreased	1 (0.4%)	1 (0.4%)	3 (1.2%)	0 (0%)

bid = twice daily; ADM = Antidopaminergic medications; PT = Preferred term; ADR = Adverse drug reaction; TEAE = treatment-emergent adverse event; SmPC = Summary of product characteristics; HD= Huntington's disease

No specific trend could be identified regarding treatment-related TEAEs and ADMs use status (at any time and at baseline). Some PTs were more reported in participants taking ADMs, and others in

participants not taking ADMs. Nevertheless, the SOC "psychiatric disorders" was more represented among participants treated with pridopidine than with placebo, regardless of ADM use status.

Treatment-related SAEs were reported in a comparable frequency between treatment arms, in 7 (1.3%) patients in the placebo arm and 4 (0.7%) in the pridopidine 45 mg bid arm. Due to the overall low frequency of treatment-related SAEs, the number of patients reporting these events in each ADM usage category was very low.

Among patients not taking ADMs, the incidence of treatment-related SAEs in the placebo and pridopidine 45 mg bid arms, respectively, were:

- Off ADMs at baseline: 0% and 0.6%
- Off ADMs all the time: 0% and 0.3%

Among patients taking ADMs, the incidence of treatment-related SAEs in the placebo and pridopidine 45 mg bid arms, respectively, were:

- On ADMs at baseline: 3.3% and 0.9%
- On ADMs at any time: 2.9% and 1.2%

No specific trend could be identified regarding treatment-related SAEs and ADMs use status (at baseline or at any time).

The overall frequency of treatment-related TEAEs leading to discontinuation from the study treatment was comparable across study arms (26 [4.9%] and 33 [6.2%] patients in the placebo and pridopidine 45 mg bid arms, respectively). Among patients not taking ADMs, the frequency of treatment-related TEAEs leading to discontinuation from the study treatment was low, with a slightly higher frequency in the pridopidine 45 mg bid arm. The incidence in the placebo and pridopidine 45 mg bid arms, respectively, were:

- Off ADMs at baseline: 3.7% and 7.8%
- Off ADMs all the time: 4.1% and 8.2%

Among patients taking ADMs, the frequency of treatment-related TEAEs leading to discontinuation from the study treatment was low, with a slightly higher frequency in the placebo arm. The incidence in the placebo and pridopidine 45 mg bid arms, respectively, were:

- On ADMs at baseline: 6.7% and 3.7%
- On ADMs at any time: 5.9% and 3.7%

While among patients not taking ADMs the frequency of overall treatment-related TEAEs leading to discontinuation was higher in participants treated with pridopidine 45 mg bid than in participants receiving placebo, no specific trend could be identified from individual (and grouping of) PTs. Nevertheless, the SOC "Psychiatric disorders" was more represented among participants not using ADMs (at baseline or at any time) with pridopidine than with placebo.

No other specific trend could be identified regarding treatment-related TEAEs leading to drug discontinuation in participants taking ADMs (at baseline or at any time).

Effects on Ability to Drive or Operate Machinery or Impairment of Mental Ability

No specific studies have been conducted to evaluate the influence of pridopidine treatment on the ability to drive or operate heavy machinery. CNS-related TEAEs potentially related to the ability to drive of insomnia, dizziness, fatigue, sleep disorder, somnolence, dizziness postural, vertigo, and vision disorder, observed in the ISA are summarised in Table 46. There was no clinically meaningful difference between the pridopidine and placebo arm for these CNS-related TEAEs.

Table 46: Integrated Safety Analysis (ISA): selected CNS-related TEAEs by preferred term potentially associated with ability to drive or operate heavy machinery

Preferred Term, n (%)	Placebo (N=533)	Pridopidine 45 mg bid (N=534)
Insomnia	26 (4.9)	34 (6.4)
Dizziness	19 (3.6)	24 (4.5)
Fatigue	30 (5.6)	16 (3.0)
Sleep disorder	6 (1.1)	15 (2.8)
Somnolence	13 (2.4)	12 (2.2)
Dizziness postural	1 (0.2)	4 (0.7)
Vertigo	2 (0.4)	3 (0.6)
Vision blurred	1 (0.2)	0 (0.0)

Source: ISA, Summary Table 1.4.3
Note: TEAEs were defined as AEs that developed or worsened during the period from the first administered dose up to the earlier date of the end date of DBP or 14 days after the last dose of study drug in DBP.
Note: If a patient experienced more than 1 event in a given category, that patient was counted only once in that category.
Note: MedDRA Dictionary (Version 23.0) is used for coding AEs.
AE = adverse event; bid = twice daily; CNS = central nervous system; DBP = double-blind period; ISA = integrated safety analysis; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients per arm; n = number of patients per category; SG = primary safety group; TEAE = treatment-emergent adverse event.

2.6.8.9. Discontinuation due to adverse events

Discontinuation in the placebo-controlled studies

PROOF-HD study

In total, 44 patients (8.8%) experienced a TEAE that led to study drug discontinuation: 18 (7.2%) patients in the placebo arm and 26 (10.4%) in pridopidine arm. The most frequent TEAEs leading to permanent study drug discontinuation (reported for ~ >1% of patients overall) were anxiety and suicidal ideation, each reported in 3 (1.2%) patients on placebo and 2 (0.8%) patients on pridopidine.

Other TEAEs leading to study drug discontinuation and occurring in more than 2 patients included suicidal attempt (none in the placebo arm and 3 [1.2%] patients in the pridopidine arm), acute myocardial infarction (3 [1.2%] in the placebo arm and none in the pridopidine arm), diarrhoea (1 [0.4%] in the placebo arm and 2 [0.8%] in the pridopidine arm) and gait disturbance (none in the placebo arm and 3 [1.2%] in the pridopidine arm).

PRIDE-HD study

The rate of AEs leading to discontinuation was higher in the 45 mg bid treatment group than in the placebo group, followed by increased rates of discontinuation at the higher treatment doses, indicating a dose-dependent decrease in tolerability. A total of 59 (14%) patients discontinued from the study because of AEs; 6 (7%) patients in the placebo group, 10 (12%) patients in the 45 mg bid treatment group, 16 (20%) patients in the 67.5 mg bid treatment group, 12 (15%) patients in the 90 mg bid treatment group, and 15 (18%) patients in the 112.5 mg bid treatment group.

The most frequent reasons (occurring in ≥2% of patients in any treatment arm) for study drug discontinuation were creatinine renal clearance decreased, electrocardiogram QT prolonged, akathisia, chorea, irritability, anxiety, suicidal ideation, suicide attempt, and urinary retention. None were reported as a reason for drug discontinuation in more than 2 patients per arm. All other events leading to withdrawal were reported in 1 patient each.

MermaiHD study

The number of patients who discontinued study drug due to a TEAE was similar across treatment arms: 13 (9%) patients in the placebo arm, 9 (6%) patients in the pridopidine 45 mg qd arm and 15 (10%) patients in the pridopidine 45 mg bid arm.

The most frequently reported AEs that led to study drug withdrawal were from the SOC of Psychiatric disorders (e.g., depression, suicidal attempt, insomnia), followed by gastrointestinal Disorders (e.g., nausea) and Nervous system disorders (e.g., dizziness). However, there was no marked difference between treatment arms observed nor a clear dose-dependency or trend regarding AEs leading to study drug discontinuation.

HART study

Overall, 16 (7%) patients interrupted or discontinued study drug due to an AE (including death); 3 (5.2%) patients in the placebo arm, 5 (8.9%) in the pridopidine 10 mg bid arm, 2 (3.6%) patients in the 22.5 mg bid arm, and 6 (10.3%) patients in the pridopidine 45 mg bid arm. Most AEs were reported in one patient each, except for Huntington's chorea (reported in 3 patients), fall and depression (reported in 2 patient each). No clear dose-dependency or trend regarding AEs leading to treatment interruption or discontinuation was observed.

TEAEs leading to study drug discontinuations occurred in 3 (5.2%) patients in the pridopidine 10 mg bid arm and in 4 (7%) patients in the pridopidine 45 mg bid arm. No patient in the placebo or pridopidine 22.5 mg bid arms had a TEAE that lead to study drug discontinuation.

Integrated Safety Analysis

Forty-one (7.7%) and 57 (10.7%) patients in the placebo and pridopidine 45 mg bid arms, respectively, had at least one TEAE that led to discontinuation from the study treatment. TEAEs leading to discontinuation from the study treatment reported in at least 2 patients in either treatment arm are presented by PT in Table 47.

Excluding anxiety, which led to discontinuation from study treatment in 5 (0.9%) patients in the placebo arm and 2 (0.4%) patients in the pridopidine 45 mg bid arm, and diarrhoea which led to discontinuation in 3 (0.6%) patients in the placebo arm and 5 (0.9%) patients in the pridopidine 45 mg bid arm, no TEAE led to discontinuation from study treatment in more than 4 (0.8%) patients in either arm.

No meaningful differences were observed between the treatment arms in the general frequency of TEAEs leading to discontinuation from the study treatment.

Table 47: ISA: TEAEs leading to discontinuation from the study treatment reported in ≥2 patients from either treatment arm by preferred term (SG)

Preferred Term, n (%)	Placebo (N=533)	Pridopidine 45 mg bid (N=534)
At least one TEAE leading to discontinuation from the study treatment	**41 (7.7)**	**57 (10.7)**
Diarrhoea	3 (0.6)	5 (0.9)
Insomnia	3 (0.6)	4 (0.7)
Irritability	2 (0.4)	4 (0.7)
Suicide attempt	0 (0.0)	4 (0.7)
Dizziness	2 (0.4)	3 (0.6)
Gait disturbance	1 (0.2)	3 (0.6)
Anxiety	5 (0.9)	2 (0.4)
Suicidal ideation	4 (0.8)	2 (0.4)
Depression	2 (0.4)	2 (0.4)
Sleep disorder	0 (0.0)	2 (0.4)
Muscle spasms	0 (0.0)	2 (0.4)
Alanine aminotransferase increased	0 (0.0)	2 (0.4)
Aspartate aminotransferase increased	0 (0.0)	2 (0.4)
Head injury	0 (0.0)	2 (0.4)

Preferred Term, n (%)	Placebo (N=533)	Pridopidine 45 mg bid (N=534)
Huntington's disease	4 (0.8)	1 (0.2)
Psychotic disorder	2 (0.4)	1 (0.2)
Electrocardiogram QT prolonged	2 (0.4)	1 (0.2)
Acute myocardial infarction	3 (0.6)	0 (0.0)
Hallucination	2 (0.4)	0 (0.0)
Disturbance in attention	2 (0.4)	0 (0.0)
Nausea	2 (0.4)	0 (0.0)

Source: ISA report.
Note: If a patient experienced more than one event in a given category, that patient was counted only once in that category.
Note: MedDRA Dictionary (Version 23.0) is used for coding AEs.
Note: Preferred terms are presented in descending order in the pridopidine 45 mg bid arm.
AEs = adverse events; bid = twice daily; ISA = integrated safety analysis; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients per treatment arm; n = number of patients per reported event; SG=primary safety group; TEAEs=treatment-emergent adverse events.

OLE studies

In the OLE studies of PRIDE-HD, HART, and MermaiHD studies, the following AEs led to study drug discontinuation.

OLE of PRIDE-HD: 21 patients (8%) withdrew from the study due to AEs. The most frequent reasons for withdrawal were suicidal ideation (5 patients), weight decreased (3 patients), and creatinine renal clearance decreased (2 patients). These AEs were considered related to treatment with study drug for 9 of the 21 patients who withdrew from the study. All other events leading to withdrawal were reported in 1 patient each.

OLE of MermaiHD: 27 (7.6%) patients discontinued study drug due to an AE during the OLE of MermaiHD. Most frequent AEs leading (≥2 patients) to study drug discontinuation were Huntington's chorea (6 patients), insomnia, asthenia, irritability (3 patients each), and apathy (2 patients). All other events leading to withdrawal were reported in 1 patient each.

OLE of HART: 30 (22%) patients discontinued study drug due to an AE. The most frequent reasons for withdrawal were chorea (4 patients [3%]) and irritability, agitation, and aspiration pneumonia (2 patients each [1%]). All other events leading to withdrawal were reported in 1 patient each.

2.6.8.10. Post marketing experience

Not applicable.

2.6.9. Discussion on clinical safety

Safety data package

The clinical program is extensive and comprises 22 clinical studies. Approximately 1600 subjects were exposed to at least one dose of pridopidine, including 1278 HD subjects. The exposure to pridopidine in the HD patients has a varying duration with a total of >1200 patient-years. The safety data base on pridopidine can be considered sufficient to allow for conclusions on safety.

The applicant proposes the pooled analysis of the 4 placebo-controlled studies as the most relevant safety data considering the high number of subjects, i.e. a total of 533 in the 45mg bid arm and 534 in the placebo arm. This is not fully agreed, as study inclusion and exclusion criteria were different (disease severity and mental status (depression)) which may have impacted the reported AE. In addition, differences in prohibited medication may hamper an adequate analysis of the concomitant

medication allowed. PROOF is considered the pivotal study for safety. The individual data of the other 3 studies MermaiHD, PRIDE and HART including their OLE's, are considered supportive as these studies allow assessment of dose-related AEs as the exposure ranged between 10 mg bid to 112.5 mg bid. The studies are therefore also discussed separately if deemed necessary.

The long term exposure safety data currently comprises 735 HD subjects from 3 OLE studies. However, approximately half of these subjects, i.e. 353 HD subjects were followed for up to 26 weeks. Thus, 382 HD subjects remain for analysis of long term exposure. These subjects had a median exposure of 2 years. 28 (21%) of the 134 subjects included in Open-HART had a follow up of up to 7 years. Data of the OLE phase of PROOF-HD study was not initially submitted, while this is considered pivotal for assessment/confirmation of the long term exposure safety. Upon request, a draft CSR of the OLE phase of PROOF-HD study was submitted.

Frequency and severity of reported adverse events

In PROOF-HD study, the incidence of mild AEs is higher in the placebo arm (46.6 vs 36%). Moderate AEs were more common under pridopidine (36.8% vs 30.1% on placebo) and the incidence of severe AEs was comparable (9.2% on placebo vs 10% on pridopidine). SAE's were more common for pridopidine (8.4% on placebo vs 13.6%). The number of TEAE's leading to discontinuation was higher for pridopidine. Also, more deaths in the pridopidine arm were reported. Number of treatment related TEAEs was comparable between arms. In the ISA, a similar picture is observed.

Common adverse events (including drug related adverse reaction)

PROOF-HD study

In the PROOF-HD study the following AEs were reported more frequently in pridopidine arm compared to the placebo arm, and thus, likely related to pridopidine: depression (13 [5.2%] placebo vs. 26 [10.4%] pridopidine), anxiety (17 [6.8%] placebo vs. 20[8.0%] pridopidine) and weight decrease (7 [2.8%] placebo vs. 13 [5.2%] pridopidine). Particularly, depression and weight decrease are of concern as these AEs are reported approximately twice more frequent in the pridopidine arm as compared to placebo. The reporting of these events corresponds with the non-clinical toxicology data.

Integrated safety analysis

The ISA of pridopidine 45mg bid in the placebo controlled studies showed a generally comparable safety profile to that of placebo as only minor differences (i.e. difference of 0.5%-2.2%) are observed. Nevertheless, several TEAEs reported at least 2 times higher in patients treated with pridopidine 45 mg bid than placebo, in terms of number of patients:

- "Rash": 12 participants (2.2%), including 1 related (placebo: 5 participants (0.9%), including 1 related)

- "Abdominal pain upper": 9 participants (1.7%), including 5 related (placebo: 5 participants (0.9%), including 1 related)

- "Haematuria": 7 participants (1.3%), none related (placebo: 1 participant (0.2%), not related)

- "Gastrooesophageal reflux disease": 6 participants (1.1%), including 4 related (placebo: 1 participant (0.2%), related)

- "Erectile dysfunction": 4 participants (0.7%), none related (placebo: 0)

The applicant provided data on the AE Rash that indicates that no causal association is seen as (i) rash was considered possibly treatment related by investigators with comparable frequency, (ii) rash was generally reported after several weeks up to months of safe exposure, (iii) rash resolved without chance in pridopidine exposure, (iv) causative factors were evident for several subjects. Also for abdominal pain upper, haematuria, gastrooesophageal reflux disease and erectile dysfunction similar

discussions were provided, i.e. (i) additional pertinent information indicates that other causative factors in the pridopidine group, (ii) no clear relation between time of onset and exposure and (iii) event resolved without dose chance. It is agreed that the current data does not support an inclusion of rash, abdominal pain upper, haematuria, gastrooesophageal reflux disease and erectile dysfunction in section 4.8 of the proposed SmPC.

SAEs include suicide attempt, fall, characteristics of HD progression.

Malignancies were reported in 1 patient under placebo and 5 under pridopidine. A causal relationship between pridopidine and malignancies could not be established. The clinical data presented by the applicant, indicates no clear risk for a specific type of malignancy. There was also no dose or exposure related increase in malignancies seen. Therefore it is agreed that from the current data, malignancies can be excluded from section 4.8 of the proposed SmPC. This event can be followed with regular PSURs, and therefore no additional studies are needed.

3 OLE studies (MermaiHD, PRIDE and HART)

The reported AEs in the long term safety follow up from the 3 OLE studies correspond with the short-term safety. The following AEs occurred in at least 5% of the patients in the OLE's: fall (range of frequency 3 OLE's: 10.8% - 34%), weight decreased (2.0% - 22%), anxiety (2.3% - 20%), insomnia (3.1% - 18%), chorea (10% - 13%), contusion (0.3% - 13%), and diarrhoea (3.1% - 12%). Fall, weight decrease, chorea, contusion and diarrhoea were not initially proposed to be included in section 4.8 of the proposed SmPC. A discussion was requested, particularly as several of these AEs correspond with the non-clinical toxicity findings and are also present with a higher frequency following longer exposure. More specifically:

A) Fall and gait disturbances; as these may indicate muscle weakness, an AEs which was also related to exposure in the non-clinical studies. Furthermore, in the pivotal PROOF-HD study, the TEAE of "Gait disturbance" was reported 3.5 times higher in participants treated with pridopidine (7 participants: 2.8%, including 2 related: 0.8%) compared to placebo (2 participants: 0.8%, none related). Based on additional safety data, particularly regarding ADM concomitant use and subjects with moderate renal impairment where an increase in plasma levels is seen, fall occurs with a higher frequency, indicating that this event is not purely related to HD and elderly age of the subjects. However, no clear causal association is seen in the cases reported. Contusions appeared to be age related, rather than treatment related as they occurred more frequently in elderly subject. .

B) In the pivotal PROOF-HD study, the TEAE of "weight decreased" was reported 2 times higher in participants treated with pridopidine (13 participants: 5.2%, including 2 related: 0.8%) compared to placebo (7 participants: 2.8%, none related). Across the 4 placebo-controlled studies in HD patients (PROOF-HD, PRIDE-HD, MermaiHD and HART), the TEAE of "weight decreased" was reported in 17 participants (3.2%, including 3 related: 0.6%) treated with pridopidine 45 mg bid; this TEAE was reported in 11 participants (2.1%, including 1 related: 0.2%) receiving placebo across the 4 studies. Furthermore, in the pivotal PROOF-HD study, the TEAE of "Decreased appetite" was reported in 3 participants (1.2%) treated with pridopidine and was considered related for all 3 patients; this TEAE was not reported in participants receiving placebo in this study. Across the 4 placebo-controlled studies in HD patients (PROOF-HD, PRIDE-HD, MermaiHD and HART studies), the TEAE of "Decreased appetite" was reported in 8 participants (1.5%, including 4 related: 0.7%) treated with pridopidine 45 mg bid; this TEAE was reported in 1 participant (0.2%, not related) receiving placebo across the 4 studies.

The applicant further provided data indicating that in the placebo arm there was a mean loss of 3.91 kg (change from baseline of -5.32%), which was highly comparable and not significantly different (p=0.978) from the pridopidine 45 mg bid arm, where the mean weight loss was 4.00 kg (change from

baseline of -5.51%). Though the frequency for weight loss and the amount of weight loss is comparable between the two arms, on individual level difference may be present. For "Decreased appetite", no clear relationship to pridopidine could be determined based on the provided data.

Furthermore, vomiting and diarrhoea may contribute to the weight loss seen particularly in HART study. The weight loss is of concern as this may contribute to several AEs noted. Moreover, the occurrence of these gastrointestinal disorders is in line with the weight loss seen in the non-clinical studies. Additional data is submitted where comparable frequencies were noted for gastrointestinal disorders between placebo and pridopidine (expect for "Diarrhoea"; see after). Supportive data from pridopidine in amyotrophic lateral sclerosis subjects indicate no effect on weight. However, concomitant treatment with ADMs indicate an additive effect for the AE weight decrease. Therefore, the applicant agreed to add this AEs as ADR in section 4.8 of the proposed SmPC. Adding weight loss to the safety specifications is not recommended as HD also has an effect on weight loss making it difficult to establish causality in an open-label setting.

C) Moreover, "Diarrhoea" seems to be dose-related to pridopidine. Furthermore, a clear difference was seen from placebo at higher dosages. In addition, in patients who experienced a clinically meaningful weight loss, "Diarrhoea" as a TEAE was significantly more reported in patients treated by pridopidine than in those receiving placebo. The applicant agreed to include "Diarrhoea" as ADR in section 4.8 of the proposed SmPC.

D) Upon request, the applicant provided additional arguments for not including chorea as ADR in section 4.8 of the proposed SmPC. First, the applicant claimed that pridopidine alone (i.e., without ADMs) is not associated with an increased frequency of chorea as seen by a 1% frequency of TEAEs of chorea in both the placebo and pridopidine 45 mg bid arms (ISA). Furthermore, there were no related TEAEs of chorea in either the placebo or pridopidine arms. In those patients who used ADMs at any time during the study, the TEAE rate for chorea was comparable with 8/238 patients on placebo (3.4%) and 11/243 patients on pridopidine (4.5%) reporting chorea. Importantly, treatment-related TEAEs of chorea were equivalent between placebo and pridopidine treated patients with one patient in each group (0.4%). As an additional argument, AMD medications i.e. VMAT2 inhibitors (e.g., tetrabenazine) and neuroleptic medications are used effectively to treat chorea (note the applicant claimed that the use of neuroleptic medications is off label but haloperidol is approved in various EU countries to treat chorea). Ultimately, the applicant acknowledged that the table with AEs stratified to placebo and pridopidine off-ADM during the DB phase of PROOF-HD study showed that concomitant use with ADMs resulted in a higher frequency for chorea 4.5% vs 1.0%. Accordingly, the applicant agreed to add chorea as ADR in section 4.8 of the proposed SmPC.

In the pivotal PROOF-HD study, the TEAE of "Depression" was reported 2 times higher in participants treated with pridopidine (26 participants: 10.4%, including 3 related: 1.2%) compared to placebo (13 participants: 5.2%, none related). Furthermore, in the pivotal PROOF-HD study, the TEAE of "Suicide attempt" was reported in 3 participants (1.2%, none related) treated with pridopidine and was not reported in participants receiving placebo. Across the 4 placebo-controlled studies in HD patients (PROOF-HD, PRIDE-HD, MermaiHD and HART studies), the TEAE of "Suicide attempt" was reported in 6 participants (1.1%, including 2 related: 0.4%) treated with pridopidine 45 mg bid; this TEAE was reported in 1 participant (0.2%, related) receiving placebo across the 4 studies. These AEs are not listed in the proposed SmPC. It is acknowledged that depression and suicidal thoughts are common in HD and it may therefore be difficult to disentangle these events from HD progression. However, in view of the higher reported incidence of these TEAEs with pridopidine than placebo and the dose proportional effect, a thorough discussion on suicide (ideation, attempt, behaviour) and depression was requested, also taking into account exposure duration and dose. It was requested that the discussion also includes the depression and suicidality related AEs apathy, crying, mood swings and dysphoria, and the concomitant use of VMAT2 inhibitors. After the assessment, it is not irrefutable concluded that

pridopidine does not affect mood/depression in HD patients. Particularly for apathy and depressed mood a dose related effect is seen. Exposure related effects are masked by the way the data are presented (on group level rather than on PT level). Upon request, the applicant agreed to add apathy and depressed mood as ADR in section 4.8 of the proposed SmPC. Furthermore, suicidality-associated events should be closely monitored in the PSURs.

AEs of chorea, tremors, muscle weakness, behaviour change as well as Huntington's disease required discussion. Particularly the latter of HD as it is unclear what symptoms let to this AE, i.e. both chorea and behavioural change are signs of HD progression. The applicant was requested to clarify what events occurred that were considered HD (progression), as an increase in chorea, tremors, muscle weakness or behaviour change are also indicative for HD progression. The applicant indicates that as the clinical program spans from 2008 up to 2024 and for each clinical study the most recent version available of the MedDRA dictionary at the time were used, minor difference in terminology may have occurred. However the PTs Huntington's disease and Huntington's chorea were consistently used to indicate an increase or worsening of chorea.

The applicant used the data from the ISA to substantiate the need for a warning/precaution regarding the effect of pridopidine on driving and/or operating (heavy) machinery. Insomnia (34 (6.4%) vs. 26 (4.9%)), dizziness (24 (4.5% vs. 19(3.6%)) and sleep disorders (15 (2.8%) vs. 6 (1.1%) are reported in a slightly higher frequency in the pridopidine group compared to the placebo group, respectively. Though no clear dose or exposure related increase in frequency of TEAEs effecting the CNS is seen for pridopidine, a clear difference from placebo is seen. Particularly for Insomnia. Therefore, section 4.7 of the proposed SmPC includes a warning not to drive or operate heavy machinery when experiencing sleep disturbance (including insomnia) or dizziness when on prodipine treatment, until these have resolved.

Dizziness (postural)

In the pivotal PROOF-HD study, the TEAE of "Dizziness postural" was reported in 2 participants (0.8%) treated with pridopidine and was considered related for both patients; this TEAE was not reported in participants receiving placebo in this study. Across the 4 placebo-controlled studies in HD patients (PROOF-HD, PRIDE-HD, MermaiHD and HART studies), the TEAE of "Dizziness postural" was reported in 4 participants (0.7%) treated with pridopidine 45 mg bid and was considered related for all 4 patients; this TEAE was reported in 1 participant (0.2%, related) receiving placebo across the 4 studies.

Furthermore, in the pivotal PROOF-HD study, the TEAE of "Dizziness" was reported in 12 participants (4.8%, including 5 related: 2.0%) treated with pridopidine and in 11 participants (4.4%, including 6 related: 2.4%) receiving placebo. Across the 4 placebo-controlled studies in HD patients (PROOF-HD, PRIDE-HD, MermaiHD and HART studies), the TEAE of "Dizziness" was reported in 24 participants (4.5%, including 15 related: 2.8%) treated with pridopidine 45 mg bid and in 19 participants (3.6%, including 13 related: 2.4%) receiving placebo. The frequency of dizziness and dizziness postural is reported more frequently in pridopidine group as compared to placebo. Though there is no clear increase with exposure or dose as seen for insomnia, dizziness and dizziness postural should be included as dizziness has a high (though comparable) frequency in all pridopidine dose groups and the frequency of dizziness postural increased at least 4x. Dizziness postural is included in section 4.8 of the proposed SmPC.

Adverse events of special interest

The AESI included depression and suicide. The applicant concludes that these events are reported with comparable frequencies between placebo and the pridopidine 45mg bid arms in the integrated safety analysis of the 4 HD studies and studies in amyotrophic lateral sclerosis do not indicate suicidal

behaviour. This is not agreed, as both the SAEs and the individual studies data show that suicide and depression is reported more frequently in the pridopidine treatment arm (see above).

In the ISA, across the 4 placebo-controlled studies in HD patients (PROOF-HD, PRIDE-HD, MermaiHD and HART studies), the TEAE of "Syncope" was reported nearly 2 times higher in participants treated with pridopidine 45 mg bid (7 participants: 1.3%) compared to placebo (4 participants: 0.8%). None of the TEAE of "Syncope" was considered related across the 4 studies in both treatment arms; however, this TEAE was more reported in patients treated with pridopidine. Furthermore, this event could be a manifestation of QT interval prolongation, which is listed in section 4.8 of the proposed SmPC. The applicant was asked to discuss the relatedness of this TEAE to pridopidine and the need to update the PI. In its response, the applicant highlighted that "syncope" is common in the general population, and that the frequency observed across the 4 placebo-controlled studies was lower than the incidence described for the general population. This is acknowledged. In addition, the applicant stated that none of these events of "syncope" were associated with TEAEs of QT interval prolongation, and that the ECGs did not reflect any meaningful QT changes, which is reassuring. Therefore, it is agreed that the occurrence of these events of "syncope" is unlikely linked to QT interval prolongation. Of note, all these events of "syncope" resolved without study drug modification. As these events were considered not related to pridopidine by the Investigator, were not associated with QT interval prolongation, and resolved spontaneously, it is agreed that the current data does not support an inclusion of "syncope" in sections 4.4, 4.7 and 4.8 of the proposed SmPC. The true effect of pridopidine on QT prolongation remains unclear, as there are concerns on the quality of the popPK model that was used to estimate the effect. The applicant was requested to conduct a QT study. However, the applicant committed to perform full PK sampling to allow for a better estimation of the C_{max} and AUC in HD patients and to inform whether specific situations, such as various degrees of renal impairment, are expected to lead to clinically relevant changes in QT. This was considered acceptable. Further, 'arrhythmias including torsades de points' has been included in the proposed RMP as important potential risk.

Seizures were identified as a potential safety signal in animal studies (rats and dogs) at high pridopidine exposures (~10-fold higher than the anticipated mean peak plasma concentrations at 45 mg bid at steady state). Across all completed clinical studies in HD patients with pridopidine, 6 participants experienced seizures/convulsions. Of these, 4 patients (4/1158, 0.3%) received the clinically recommended dose of pridopidine 45 mg bid during the OLEs, 1 received pridopidine 22.5 mg bid, and 1 received pridopidine 67.5 mg bid. The applicant was requested to discuss this concern and the potential impact on the proposed SmPC and/or proposed RMP. Review of the 6 cases did not allow to establish a clear causal role of pridopidine regarding the occurrence of seizures/convulsions, as these cases presented several confounding factors. However, as seizures/convulsions were observed in non-clinical studies at high doses revealing a potential dose-dependent effect, and as these events can have severe consequences, "Seizures/convulsions" will be closely monitored in the PSURs.

Decline in creatinine clearance and increase in serum creatinine were anticipated, therefore patients with severe renal impairment were excluded. A shift in creatinine clearance is observed in the clinical studies, which was reversible when terminating the treatment. Though this effect is uncommon, a warning is included in proposed SmPC section 4.4. which is agreed. Subjects with severe renal impairment or severe hepatic impairment were excluded. However, use in mild to moderate renal or hepatic impairment was permitted. The applicant provided the requested information to complete the table adverse events for subjects with mild and moderate renal or hepatic impairment. Renal impairment is a factor which could potentially lead to increased exposure of pridopidine, which could exacerbate the QT prolongation risk as well as other AEs. This is also evident from the frequency of the most common reported AEs in moderate renal impaired patients. Therefore, patients with severe renal impairment are contraindicated (proposed SmPC section 4.3). A warning and precaution for use is

included for patients with moderate renal impairment which also highlight that other AEs may increase in frequency with increased exposure.

Regarding hepatic impairment, it should be noted that pridopidine does not seem to cause hepatotoxic effects. Indeed, in all the safety population of 1067 HD patients in the 4 placebo-controlled studies, only 2 TEAEs were reported in the SOC *Hepatobiliary disorders* for patients treated with pridopidine, and 3 TEAEs in this SOC for patients receiving placebo. In the SOC *Investigations*, PTs which could be related to hepatotoxicity (i.e. *Alanine aminotransferase increased*, *Aspartate aminotransferase increased*, *Blood bilirubin increased*, *Gamma-glutamyltransferase increased*, *Liver function test increased*, *Blood cholesterol increased*) were all reported in the same proportion in patients treated with pridopidine and in patients not treated; furthermore, each PT was only reported 1 to 3 times in each group. No further action is deemed necessary regarding patients with hepatic impairment.

Discontinuation

A higher proportion of subjects on pridopidine discontinued compared to placebo in all 4 placebo controlled studies as well as in the integrated safety analysis. In PROOF-HD study, TEAEs leading to study drug discontinuation were reported for 18 (7.2%) patients in the placebo arm and 26 (10.4%) patients in the pridopidine arm. The most frequent TEAEs leading to permanent study drug discontinuation (reported for ~ >1% of patients overall) were anxiety and suicidal ideation, each reported in 3 (1.2%) patients on placebo and 2 (0.8%) patients on pridopidine.

The number of patients who discontinued study drug due to a TEAE in MermaiHD study was: 13 (9%) patients in the placebo arm, 9 (6%) patients in the pridopidine 45 mg qd arm and 15 (10%) patients in the pridopidine 45 mg bid arm.

In HART study 3 (5.2%) patients in the placebo arm, 5 (8.9%) in the pridopidine 10 mg bid arm, 2 (3.6%) patients in the 22.5 mg bid arm, and 6 (10.3%) patients in the pridopidine 45 mg bid arm discontinued study drug due to an AE.

In PRIDE study, a total of 59 (14%) patients discontinued from the study because of adverse events; 6 (7%) patients in the placebo group, 10 (12%) patients in the 45 mg bid treatment group, 16 (20%) patients in the 67.5 mg bid treatment group, 12 (15%) patients in the 90 mg bid treatment group, and 15 (18%) patients in the 112.5 mg bid treatment group.

In the ISA, 26 subjects (4.9%) in the placebo arm and 33 (6.2%) in the pridopidine 45mg bid arm discontinued from study treatment due to treatment-related TEAEs.

Overall in the ISA, 41 (7.7%) and 57 (10.7%) patients in the placebo and pridopidine 45 mg bid arms, respectively, had at least one TEAE that led to discontinuation from the study treatment.

Adverse events related to pridopidine treatment leading to discontinuation were similar across the 4 placebo-controlled studies. The AEs were from the SOC of psychiatric disorders (e.g., depression, anxiety, suicidal ideation, suicidal attempt, insomnia, irritable), followed by gastrointestinal Disorders (e.g., nausea) and nervous system disorders (e.g., dizziness.) Huntington's chorea and fall were also reasons for discontinuation. Two subjects (0.4%) discontinued due to alanine aminotransferase (ALT) increased and aspartate aminotransferase (AST) increased. These events were not seen previously and may indicate hepatic impairment. The applicant was requested to provide further discussion on the pridopidine treated subjects who discontinued treatment due to elevated ALT and AST levels. A total of 3 subjects discontinued following elevated ALT or AST levels. ALT was moderately increased in all these 3 subjects. The events occurred after 16 weeks, 34 weeks or 52 weeks. Further concomitant medication may have caused these elevations in ALT or AST. It is agreed with the applicant that in the context of the large, accumulated safety database and extensive pridopidine exposure, these findings are consistent with pridopidine not demonstrating hepatotoxic concerns.

As the frequency of AEs increased in patients with mild and moderate renal impairment, and because the popPK model indicates that pridopidine in severe renal impaired patients may reach plasma levels associated with a clinically meaningful change in QT prolongation, a contraindication was added for pridopidine in patients with severe renal impairment, as well as a warning for pridopidine use in patients with moderate renal impairment.

The treatment related AEs leading to withdrawal during the OLE phase were similar to the common AEs related to pridopidine treatment in the placebo-controlled studies.

Deaths

A total of 20 subjects died during the HD clinical program, 8 in one of the placebo-controlled studies and 12 in during the OLE phases.

The causes for death in the pridopidine group during the placebo controlled phases of the studies were pneumonia, head injury, fall, aspiration pneumonia, urosepsis and subarachnoid haemorrhage. It is agreed that these appear unrelated to the pridopidine treatment. One subject tabulated as 'unknown cause', actually had as reported cause of death complication from HD, type 2 diabetes mellitus with chronic kidney disease. Considering the effects of pridopidine on creatine clearance and the unexplained transient effected glucose level, the applicant was requested to provide a detailed narrative. The patient blood glucose levels were reasonably well controlled and no decline in renal function was seen. It is unlikely that the renal and metabolic factors may have contributed to this patient's death.

The causes of death for the 12 cases reported in the OLE studies were completed suicide (n=2), pneumonia (n=3), accidental poisoning (n=1), cachexia (n=1), anaemia & weight loss (n=1), multiple myeloma (n=1), cardiac failure (n=1), starvation (n=1) and endocarditis (n=1). It is agreed that the majority of these are unrelated to treatment with pridopidine and appear to be either related to the age of the patient or HD progression. However, the cases of cachexia and anaemia with weight loss and cardiac failure requires further discussion:

- Cachexia can indeed be caused by HD. However, extreme weight loss may have also contributed to this event. The narrative provided indicates that the patient with cachexia had late-stage HD and who had substantial weight gain while on pridopidine. Therefore, cachexia can be considered unrelated to pridopidine in this patient.

- The subject wo died of anaemia was a patient with moderately severe HD, complicated by multiple gastrointestinal symptoms suggestive of an underlying more serious disease, with likely ensuing weight loss. Following prolonged dosing with pridopidine (> 2 years), the patient had a relatively short period of severe anaemia, likely on the basis of a gastrointestinal bleed. The patient shortly thereafter developed respiratory depression associated with midazolam usage and died. Causality is unlikely.

- Minor cardiac effects are observed in treatment with pridopidine, e.g. QT prolongation. Therefore a discussion on exposure duration an cardiac failure (including underlying condition or concomitant medication) was requested to allow assessment of the contributing effect of pridopidine. The subject who died following myocardial infarction, suffered acute myocardial infarction complicated by acute congestive heart failure after 342 days of receiving pridopidine. The patient had multiple long-standing cardiovascular risk factors. Furthermore, the autopsy confirmed the presence of pre-existing cardiovascular conditions. Five days prior to this event, the patient was evaluated and did not have symptoms of congestive heart failure. Furthermore, evaluation of the ECG showed a normal QTcF interval. Thus, it is unlikely that pridopidine was the main contributing factor to the patient's death.

Special populations

The age of HD subjects in the 4 placebo-controlled studies ranged from 22 up to 86 years of age. The applicant was requested to provide safety data per age range i.e. <65 years, 65-74 years, 75-84 years, and 85+ year-old patients. The largest proportion of subjects is seen in the <65 years of age group (459 in the pridopidine arm and 475 in the placebo arm). For the subgroup 65-74, 67 subjects were included in the pridopidine arm and 50 in the placebo arm. Frequency data of psychiatric disorders, nervous system disorders, accidents and injuries, cardiac disorders, vascular disorders, cerebrovascular disorders and infections and infestations for these age groups were provided. The majority of these events were age related and showed no difference from placebo. Other serum chemistry changes were also noted, i.e. changes in prolactin level or glucose levels. Changes in prolactin levels were generally related to the concomitant medication allowed in the studies, risperidone to be more specific. However for the shift glucose (though transient) limited data was provided. The newly provided data suggest that the change in glucose level is not clinically meaningful and at this time there are no signs for increased risks for the development of hypoglycaemic episodes nor for the development of diabetes (hyperglycaemia).

Regarding safety by HD stage in the 4 placebo-controlled studies, no specific trend could be identified regarding the reported events when comparing for patients HD1-2 vs patients HD3-4.

Patients that are CYP2D6 poor metabolisers and have renal impairment are at higher risk of QTc prolongation. Therefore, the proposed SmPC contains a warning and precaution for use in section 4.2 and 4.4 regarding this aspect.

Concomitant treatment

Concomitant treatment with tricyclic antidepressants and class I antiarrhythmics was prohibited as these drugs were considered to prolongate the QTc or were considered CYP2D6 substrates. Since tricyclic antidepressants and class I antiarrhythmics were not allowed in the 4 placebo-controlled studies, the applicant therefore included a warning on concomitant use in section 4.5 of the proposed SmPC.

Participants were stratified according to neuroleptic use at baseline in PROOF-HD, PRIDE-HD, MermaiHD, and HART studies. To gain more insight on whether there is relationship between 'any time ADM' and 'no ADM at all' and 'ADM use at baseline yes versus no group' and AEs, a table with AEs stratified to placebo and pridopidine off-ADM during the complete double-blind phase of PROOF-HD study was provided by the applicant. Concomitant use with ADMs results in a higher frequency for the following AEs: Insomnia (9.1% vs 4.1%), Anxiety (8.6% vs 3.1%), Chorea 4.5% vs 1.0%), Somnolence (4.1% vs 0.7%) Gait disturbance (2.1% vs 1.0% for pridopidine on and off ADMs); weight decrease (5.8% vs 1%).

On the other hand, regarding safety by ADM use in the 4 placebo-controlled studies, no specific trend could be identified regarding treatment-related TEAEs, treatment-related SAEs and treatment-related TEAEs leading to study drug discontinuation when comparing the reported events for patients on-ADM vs off-ADM (at baseline or at any time).

The applicant provided an integrated safety table and thorough analysis of all TEAEs (not just treatment-related TEAEs) by SOC and PT, for the Safety Population - Primary Safety Group, for the subgroups "Use of ADM at Any time: No" and "Use of ADM at Any time: Yes" (with these two populations in the same table, to allow an easier comparison by ADM use). And the same for the subgroups "Use of ADM at Baseline: No" and "Use of ADM at Baseline: Yes". The same with all serious TEAEs and all TEAEs leading to discontinuation in these subgroups. As certain AEs are exacerbated with concomitant use of pridopidine and AMDs a statement is included in the proposed SmPC.

Additional monitoring/ safety concerns

Section 4.6 of the proposed SmPC was amended to include a statement that pridopidine should not be used during lactation. Therefore, the safety concerns use in lactation is removed from the safety specifications.

It was initially discussed whether embryo-foetal toxicity should be included as a safety concern. It was finally agreed to remove this safety concern because there will be no additional PhV activities nor additional risk minimisation measures (see below). However, use in pregnancy should be closely monitored in regular PSURs.

- There is an advice for two effective methods of contraception including a barrier method based on results from non-clinical data concluding a potential risk of teratogenicity (section 4.6 of the proposed SmPC). However, an absolute contraindication for use in pregnancy was not considered appropriate as a contraindication for use in pregnancy should only be proposed when teratogenicity is found in 2 species or the mechanism related will be relevant for humans which is not the case in this MAA. It was agreed not to include additional risk minimisation measures as a patient alert card is reserved for exceptional cases.
- It was also agreed that a post-authorisation safety study to evaluate pregnancy outcomes is not feasible.

Additional safety data needed in the context of a conditional MA

The applicant proposed to restrict the population late during procedure, to adult patients with HD who are not treated with ADMs and further restricted to adult patients with early HD who are not treated with ADMs to address the concern on extrapolability. Refer to section 3.7.3. for that assessment. From a safety perspective, the SmPC, the proposed risk minimisation measures, additional pharmacological activities and commitments (i.e. full PK sampling) are sufficient to manage safe use in adults with early HD who are not using ADMs.

2.6.10. Conclusions on the clinical safety

The applicant provided an elaborate analysis of the safety of pridopidine in HD patients. Most AEs were of mild to moderate severity It has been agreed that the section 4.8 of the proposed SmPC includes the following ADR: Insomnia/sleep disorders, anxiety, apathy and depressed mood, dizziness postural, chorea, diarrhoea, vomiting, weight decreased, electrocardiogram QT prolonged and decrease in creatinine clearance.

Furthermore, long term safety data of the single pivotal PROOF-HD study confirmed the AEs seen in Open-HART, Open-PRIDE and MermaiHD-OLE studies. Chorea, apathy and depressed mood are included in section 4.8 with a foot note indicating that these AEs are exacerbated in patients treated with ADMs concomitantly. Moreover, apathy and depressed mood show a exposure effect relationship. Taking into account that use with ADMs is not a contraindication and the exposure effect relationship, inclusion of these AEs is considered appropriate.

Pridopidine is contraindicated in patients with severe renal impairment and a warning for use is included for patients with moderate renal impairment.

For the true effect on QT prolongation additional studies are needed as the popPK model is inadequate to reliably estimate the effect size. The applicant committed to perform full PK sampling to allow for a better estimation of the C_{max} and AUC in HD patients and to inform whether specific situations, such as various degrees of renal impairment, are expected to lead to clinically relevant changes in QT. Further,

'arrhythmias including torsades de points' has been included in the proposed RMP as important potential risk.

Moreover, mandatory CYP2D6 genotyping was requested as HD patients who are also poor CYP2D6 are at risk for a higher pridopidine exposure thus not only a risk for more frequent reported AEs, but also at risk for QT-prolongation. The applicant proposed warning with strong recommendation in section 4.4 of the proposed SmPC which is considered acceptable.

Adverse events seen in animal studies that cannot be confirmed in the clinical studies due to confounding factors, will be followed closely in the PSURs as clinical studies are not feasible. These events include seizures/convulsion and malignancies.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 48: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Arrhythmias including TdP
Missing information	• None

2.7.2. Pharmacovigilance plan

No additional pharmacovigilance activities

2.7.3. Risk minimisation measures

Table 49: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	**Risk minimisation measures**	**Pharmacovigilance activities**
Important potential risk: Arrhythmias including TdP	Routine risk minimisation measures: • SmPC, Sections 4.2, 4.3, 4.4, 4.5 and 4.8 • PL, Sections 2, 4 Additional risk minimisation measures: No risk minimisation measures	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: None Additional pharmacovigilance activities: None.

ECG = electrocardiogram; PL = package leaflet; SmPC = summary of product characteristics.

2.7.4. Conclusion

The CHMP, having considered the data submitted in the application was of the opinion that due to the concerns identified with this application, the risk management plan cannot be agreed at this stage.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

N/A

2.9. Product information

In light of the negative recommendation, a satisfactory summary of product characteristics, labelling and package leaflet cannot be agreed at this stage.

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

HD is a rare, chronic progressive and fatal neurodegenerative disorder. HD results from CAG trinucleotide repeat expansion in the HTT gene, which encodes for the HTT protein. Without a curative treatment available the pathophysiology has not been fully confirmed, but is currently thought to be due to toxicity of mHTT.

CAG repeat length is inversely correlated with disease onset. Unaffected individuals have <35 CAG repeats; HD carriers have 36+ CAG repeats, although those with 36-39 repeats may or may not eventually develop HD. Patients with 36-55 CAG repeats usually have adult-onset HD where patients with >60 CAG repeats often have juvenile-onset HD by showing symptoms before the age of 20. (Medina et al., 2020; Serranilla et al., 2022)

HD is characterised by variable disease manifestation but includes movement-, psychiatric, and cognitive problems that worsen over-time. Chorea is a key sign of HD; other often reported symptoms are abnormal eye movements, irritability, depression and suicidal behaviour (McAllister et all., 2021). Following onset, symptoms steadily worsen over the ensuing 15 to 20 years, leading to an overall decline in ability to function and perform activities of daily living, ultimately leading to a state of immobility, severe cognitive and global functional impairment and death (Ross et al 2014; Ross and Tabrizi 2011).

3.1.2. Available therapies and unmet medical need

In the EU, tetrabenazine and haloperidol are currently approved for symptomatic management of chorea in HD. In addition, a variety of therapies are used (on- and off-label) to treat motor, cognitive, behavioural and psychiatric symptoms.

There is no approved therapy that modifies HD disease progression, indicating an unmet medical need.

The initially proposed indication was

Nurzigma is indicated in adults for the treatment of Huntington´s disease (HD).

The latest proposed indication is

Nurzigma is indicated in adults for the treatment of early Huntington´s disease (HD) in adults who are not treated with antidopaminergic medicinal products (ADMs; see section 4.4. and 5.1).

3.1.3. Main clinical studies

The pivotal efficacy data are from **PROOF-HD**, a 78-week randomised (1:1), double-blind, placebo-controlled, parallel-arm, global Phase III study that evaluated pridopidine 45mg bid vs. placebo in 499 HD patients aged >25 years, with >36 CAG repeats and TFC score 7-13. The study was followed by a 2-year OLE phase.

3.2. Favourable effects

PROOF-HD study did not meet its primary endpoint, which was the change-from baseline on UHDRS-TFC (TFC) at Week 65 in ITT population. The LS mean treatment difference was -0.23 pts. numerically favouring placebo (95% CI: -0.55, 0.09; p=0.16). At Week 78 the effect in mITT population favoured placebo with -0.26 pts. (95% CI: -0.62, 0.10; nominal p=0.16).

The key secondary endpoint, change-from-baseline cUHDRS at Week 65 in mITT population, numerically favoured placebo with a LS mean treatment difference of -0.11 pts. (95% CI: -0.40, 0.18; nominal p=0.45). At Week 78 the effect in mITT numerically favoured placebo with -0.27 pts. (95% CI: -0.62, 0.07; nominal p=0.12).

Patients off-ADMs

In a late phase during the procedure, the applicant restricted the indication from the broad population 'adult patients with HD', to the population 'adult patients with early HD who are not treated with ADMs' (i.e., off-ADM group). In PROOF-HD Study, patients off-ADMs at all times (mITT population), the primary endpoint TFC at Week 65 numerically favoured pridopidine with a LS mean treatment difference of 0.05 pts. (95% CI: -0.38, 0.47; nominal p=0.82), and at Week 78 with 0.12 pts (95% CI: -0.33, 0.58; nominal p=0.59).

In that study, the key secondary endpoint cUHDRS at Week 65 numerically favoured pridopidine with a LS mean treatment difference of 0.27 pts. (95% CI: -0.12, 0.66; nominal p=0.17), and at Week 78 with 0.14 pts. (95% CI: -0.30, 0.58; nominal p=0.53).

3.3. Uncertainties and limitations about favourable effects

The overall results are from a failed pivotal Phase 3 study (PROOF-HD), in the context of three previous failed studies (PRIDE-HD (phase 2), MermaiHD (phase 3), and HART (phase 2).

In the PROOF-HD study, pridopidine performed worse than placebo in (m)ITT population on the primary endpoint (TFC) and on the key secondary endpoint (cUHDRS). There was no benefit of pridopidine on any of the remaining secondary endpoints.

The supportive studies PRIDE-HD, MermaiHD, and HART are also of limited value as they either were short-term and focussed on motor symptoms (HART – 12 weeks; MermaiHD – 26 weeks; primary endpoint in both was mMS) or are challenging to interpret due to concerns on data quality (PRIDE-HD – study extended to 52 week while ongoing).

Maintenance of efficacy is unclear as it was not shown by the available OLE results in open-HART or open-PRIDE studies. In ITT population, patients had a comparable decline of TFC and TMS to natural history in a timeframe up to 72 months. PROOF-HD OLE efficacy results are not credible, because

credibility of the double-blind phase data of PROOF-HD itself is questioned (see above), and because the OLE analysis has been substantially changed using post-hoc knowledge and in favour of the off-ADM subgroup.

Furthermore, for TFC there is no generally accepted clinical meaningful treatment margin. Those proposed by the applicant during the procedure (0.14-0.21pt/y) and 3 (20%) are not of use as the assumptions underlying those margins are considered questionable. Altogether, TFC results remain of undemonstrated clinical relevance.

The claim of benefit in early HD adult patients who are not using ADM is not agreed due to the following major issues as:

- The investigations in the off-ADM subgroup are exploratory and not in accordance with applicable guidance (EMA/CHMP/539146/2013). The guideline states that '*post-baseline covariates may be affected by treatment received and will not usually be appropriate to define subgroups for the investigation of a treatment effect'.* However, the off-ADM subgroup is defined based on the use of ADM at baseline *and* during the trial. I.e., the definition includes a post-baseline variable - which is not appropriate. Further, the applicant claimed that scenario 3 as explained in the guidance applies in this MAA. However, results in this group are 'likely not credible' (Step 3b). Credibility depends on the degree of well-founded, a priori definition, the biological plausibility for a particular finding and replication. None of them applies in this MAA: biological plausibility has not been shown in context of PROOF-HD study, the findings have not been independently replicated, and the off-ADM subgroup was not predefined in PROOF-HD study. Additionally, the minimum criteria as set up in the section 5.3 are not considered fulfilled (EMA/CHMP/539146/2013). Even if the off-ADM group could have been considered a credible group, validity of the results in this group is not agreed. First, patients off-ADM at baseline but who initiated an ADM during the study were excluded from the off-ADM group, also had higher chorea, irritability and psychosis scores at baseline. These data reaffirm the concern that the off-ADM group in PROOF-HD may not be a distinct subgroup but rather a selected population of less impaired patients not requiring rescue medication. Additionally, the ADM group is composed of two subgroup analyses (neuroleptics on/off, chorea medications on/off) that were not controlled for inflation of the Type I error rate. This increases the probability of false positive findings in the off-ADM group;
- Even if results would have been considered valid, it is not agreed that these results are sufficient to demonstrate efficacy. For cUHDRS results were mostly below meaningful margins at Week 65 and 78 in the off-ADM group (mITT population). Moreover, not all cUHDRS components contributed to effects consistently, although a critical assumption for cUHDRS to support that a therapy targets disease progression (Schobel et al., 2017). The endpoint that was most consistently in favour of pridopidine was Q-motor FT IOI mean. However, the Q-motor endpoints tests were limited to the hands and fine motor function, whereas TMS assessed motor symptoms more globally but could not show a benefit for pridopidine over placebo.
- Additional concerns was raised during the procedure about extrapolability of the results observed in the off-ADM group in PROOF-HD study to the target population of adults with HD (as per the initial indication) and also appliable to the target population of adults with HD who are not treated with ADMs. In PROOF-HD study, HD patients aged >25 years, and with a TFC score of 7-13 (HD stage 1-2) were enrolled. Most patients were above 44 years. Extrapolation to adults ~18-20 years and late disease (TFC score <7; HD stage 3-5) is not clear-cut in a progressive disease as HD. Late in the procedure, the applicant further restricted the indication to adult patients with early HD who are not taking ADM. While the newly requested indication addresses the concern on extrapolability, it creates another concern: restricting use to an off-ADM group is likely unfeasible in real life. There was high concomitant use of ADMs across pridopidine trials, which questions if pridopidine was

efficacious enough to HD treat symptoms, and challenges how representative the ADM group is for real-life situations. This uncertainty is further substantiated by the applicant's statement that pridopidine has minimal effect on chorea. I.e., if pridopidine does not treat chorea and alternative therapies are prohibited, then over-time this will either lead to uncontrolled chorea, or (re-)initiation of prohibited ADMs.

3.4. Unfavourable effects

The clinical program is extensive and approximately 1600 subjects were exposed to at least one dose of pridopidine, including 1278 HD subjects. The exposure to pridopidine in the HD patients has a varying duration with a total of >1200 patient-years. The PROOF study is considered pivotal with support of the pooled safety analysis including PROOF, MermaiHD, PRIDE and HART studies.

In PROOF-HD study, the incidence of mild AEs is higher in the placebo arm (46.6 vs 36%). Moderate AEs were more common under pridopidine (36.8% vs 30.1% on placebo), the incidence of severe AEs was comparable (9.2% on placebo vs 10% on pridopidine). SAE's were more common for pridopidine (8.4% on placebo vs 13.6%). In the ISA, a similar picture is observed.

Adverse events reported in PROOF-HD study with a frequency >5% in the 45mg pridopidine group were: depression (n=13 [5.2%] placebo vs. 26 [10.4%] pridopidine), insomnia (18 [7.2%] placebo vs. 20 [8.0%] pridopidine), anxiety (17 [6.8%] placebo vs. 20 [8.0%] pridopidine) and weight decrease (7 [2.8%] placebo vs. 13 [5.2%] pridopidine).

In the ISA the following AEs were reported with a ≥1.5% higher frequency in the 45mg bid pridopidine as compared to placebo: nasopharyngitis (32 [6.0%] vs. 44 [8.2%]), insomnia (26 [4.9%] vs. 34 [6.4%]), anxiety (22 [4.1%] vs. 30 [5.6%]) and sleep disorders (6 [1.1%] vs. 15 [2.8%]).

SAEs that were reported in PROOF-HD study as well as in the ISA include suicide attempt, fall, characteristics of HD progression and malignancies.

In the 3 long term exposure studies (MermaiHD-OLE, Open-PRIDE, Open-HART studies) the following AEs occurred with a frequency of at least 5% in one of the studies (frequency ranges of the 3 studies are presented): fall (10.8% to 34%), weight decreased (2.0% to 22%), anxiety (2.3% to 20%), insomnia (3.1% to 18%), chorea (10% to 13%), contusion (0.3% to 13%), diarrhoea (3.1% to 12%), and headache (2.3% to 9%).

In the pivotal PROOF-HD study, a total of 44 patients (8.8%) experienced a TEAE that led to study drug discontinuation: 18 (7.2%) patients in the placebo arm and 26 (10.4%) in pridopidine arm. The most frequent TEAEs leading to permanent study drug discontinuation (reported for ~ >1% of patients overall) were anxiety and suicidal ideation, each reported in 3 (1.2%) patients on placebo and 2 (0.8%) patients on pridopidine. In the ISA 26 subjects (4.9%) in the placebo arm and 33 (6.2%) in the pridopidine 45mg bid arm discontinued from study treatment due to treatment-related TEAEs. AEs related to pridopidine treatment leading to discontinuation were similar across the 4 placebo-controlled studies as well as the OLE studies. The AEs were from the SOC of psychiatric disorders (e.g., depression, anxiety, suicidal ideation, suicidal attempt, insomnia, irritable), followed by gastrointestinal disorders (e.g., nausea) and nervous system disorders (e.g., dizziness.). Huntington's chorea and fall were also reasons for discontinuation.

A total of 20 subjects died during the HD clinical program, 8 during the placebo-controlled phase of the 4 studies (PROOF, MermaiHD, PRIDE, HART studies) and 12 in during the OLE phase of 3 studies (MermaiHD-OLE, Open-PRIDE, Open-HART studies). The cause of death was pneumonia (n=5), completed suicide (n=3), head injury (n=1), fall (n=1), urosepsis (n=1), subarachnoid haemorrhage (n=1), complication of HD & type 2 diabetes mellitus witch chronic kidney disease (n=1), cachexia

(n=1), poisoning (n=1), anaemia & weight loss (n=1), multiple myeloma (n=1), cardiac failure (n=1), starvation (n=1), and endocarditis (n=1).

3.5. Uncertainties and limitations about unfavourable effects

The data of the ISA should be interpreted with caution as studies had different inclusion and exclusion criteria (severity of the disease, concomitant medication), different titration regimens, some included multiple doses of pridopidine and there was variety in study length. For the ISA, the main contribution comes from PROOF-HD study.

Data from the OLE of MermaiHD, PRIDE and HART studies should be interpreted with caution. For the OLE studies, subjects with a poor depression score or suicidal thoughts were excluded. Subjects from PRIDE were allowed to enter Open-HART study. Approximately half of all the subjects from the 3 OLE studies (353/735 HD subjects) were followed for 26 weeks and 28 (21%) of the 134 subjects included in Open-HART study had a follow up of up to 7 years. The applicant submitted a CSR for the OLE data of PROOF HD. These data were consistent with the data from the other 3 OLEs studies. Supporting the need to include depressed mood, apathy, chorea, and weight decrease. Depressed mood and apathy show a high dose low dose effect, i.e. these events are reported more frequently in the higher dose as compared to the lower dose of pridopidine or placebo. These AE were included in the ADR table in section 4.8 of the proposed SmPC.

The AEs 'malignancies' and 'convulsions/seizures' that were observed in HD patients, align with observations in the animal studies. No firm conclusions on relatedness of these AEs to pridopidine could be drawn as the clinical data are confounded. However, it cannot be excluded that these AEs are drug-related. As additional studies in patients are not feasible, these AEs need close monitoring in PSURs.

The true effect of pridopidine on QT prolongation remains unknown. The popPK model that was used to support the QT prolongation assessment, had too sparse sampling to adequately estimate/simulate if the clinically relevant threshold will be met. It is also considered that patients with renal impairment may be at even further increased risk. Though sufficient measures are in place to allow safe use in severe and moderate renal impairment, the applicant committed to perform full PK sampling to update the popPK model and appropriately estimate Cmax and AUC in HD patients. This will inform whether specific situations, such as various degrees of renal impairment, are expected to lead to clinically relevant changes in QT.

The proposed SmPC is updated to include a warning for use in patients who are CYP2D6 poor metabolisers are and thus at risk for QT prolongation and other adverse events. A statement regarding genotyping is recommended in the proposed SmPC.

3.6. Effects table

Table 50: Effects table for pridopidine for the treatment of HD

Effect	Short Description	Unit	Treatment ***Pridopidine 45mg bid***	Control ***Placebo***	Uncertainties/ Strength of evidence	References
Favourable Effects						
UHDRS-TFC (primary variable)	Change from Baseline in TFC score	LSM (SE), in points	 -1.17 (1.82) -1.24 (0.13) -0.49 (0.16) -0.42 (0.17)	 -0.94 (1.72) -0.98 (0.13) -0.54 (0.15) -0.54 (0.16)	*Unc:* **-PEP not met** -there is no generally accepted clinical meaningful treatment margin -effect claimed in subgroup off-ADMs, but there are uncertainties on composition of this group in PROOF-HD, validity and meaningfulness of results in this group, and how it relates to the target population / *SoE:* **Irrespective of ADM use:** LSM difference in **ITT** at Week **65 (PEP)**: -0.23 (95% CI -0.55; 0.09; p = 0.16) LSM difference in **mITT*** at Week **78**: -0.26 (95% CI -0.62; 0.10; nom. p = 0.16) **Subgroup off-ADMs:**** LSM difference in **mITT** at Week **65**: 0.05 (95% CI -0.38; 0.47; nom. p=0.82) LSM difference in **mITT*** at Week **78**: 0.12 (95% CI -0.33; 0.58; nom. p=0.59)	PROOF-HD CSR Table 14.2.01.1.2 Table 14.2.01.3.1 Table 14.2.01.5.21.3 Table 14.2.01.5.22.3

Effect	Short Description	Unit	Treatment *Pridopidine 45mg bid*	Control *Placebo*	Uncertainties/ Strength of evidence	References
cUHDRS (key secondary variable)	Change from Baseline in TFC score	LSM (SE), in points	 -0.99 (0.11) -1.26 (0.13) -0.26 (.14) -0.4 (0.16)	 -0.88 (0.11) -0.98 (0.13) -0.53 (.14) -0.54 (.16)	*Unc:* -effect claimed in subgroup off-ADMs, but there are uncertainties on composition of this group in PROOF-HD, validity and meaningfulness of results in this group, and how it relates to the target population -separate cUHDRS components did not all favour pridopidine at Week 65 and 78 in off-ADM group / *SoE:* **Irrespective of ADMs:** LSM difference **mITT** at Week **65**: -0.11 (95% CI -0.40; 0.18; nom. p=0.45) LSM difference **mITT** at Week **78**: -0.27 (95% CI -0.62; 0.07; nom. p=0.12) **Subgroup off-ADMs:**** LSM difference **mITT** at Week **65**: 0.27 (95% CI -0.12; 0.66; nom. p=0.17) LSM difference **mITT** at Week **78**: 0.14 (95% CI -0.3; 0.58; nom. p=0.53)	PROOF-HD CSR Table 14.2.02.1.1 Table 14.2.02.1.5 Table 14.2.02.1.10.3 Table 14.2.02.1.11.3
Unfavourable Effects						
Psychiatric disorders	Depression	N (%)	n=26/250 (10.4%)	n=13/249 (5.2%)	Unc. Common effect seen in HD (may be related to disease progression) Not as prominent in OLE as patients with poor scores were excluded.	PROOF-HD
Investigation	Weight decrease	N (%) % range	n=12/533 (5.2%) 2% - 22%	n=7/534 (2.8%)	SoE: Exposure related effect. Corresponds with animal toxicity Unc.:	PROOF-HD / OLE's of PRIDE, MermaiHD and HART

Effect	Short Description	Unit	Treatment *Pridopidine 45mg bid*	Control *Placebo*	Uncertainties/ Strength of evidence	References
Death	Death	n	N=3 N=8 N=12	N=1 N=3 n.a.	Unc.: May be related to disease progression. Unc: Stronger warnings/precautions may be needed pending outcome of discussion	PROOF / ISA / OLE's of PRIDE, MermaiHD and HART

*Abbreviations: see full list at beginning of document; PEP: primary endpoint. Notes: decreasing TFC and cUHDRS scores indicate worsening. *: no tabular data for TFC at Week 78 in ITT could be found. **based on MMRM Analysis by Concomitant Medicine for Chorea Management and Visit, Excluding Participants on Neuroleptics taken anytime in the study.*

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Favourable effects

Pridopidine (S1R agonist) has a novel mechanism of action in the treatment of HD. S1R is indicated to have broad neuroprotective effects, and the link between to HD specifically appears limited.

The efficacy claim for pridopidine is not substantiated. The results were nor statistically significant, nor clinically relevant. The pivotal study (PROOF-HD study) and the supportive studies (PRIDE-HD, MermaiHD and HART) all failed to meet their primary endpoints.

Moreover, in PROOF-HD in (m)ITT, pridopidine performed worse than placebo on both TFC and cUHDRS through Week 78. There was disease progression in both arms. No benefit of pridopidine was shown on any of remaining efficacy endpoints. As the PROOF-HD OLE analysis has been substantially changed using post hoc knowledge and changes were made that favour the off-ADM subgroup, related analyses are not credible.

Results of the OLE studies open-PRIDE HD and open-HART in (m)ITT also did not support that pridopidine had meaningful long-term effects in adult HD (all disease stages) based on TFC and TMS results up to 72 months.

The above-mentioned results in the off-ADM group did not demonstrate efficacy in the proposed indication. The latest requested restricted indication for adult early HD patients who are not using ADM is not agreed. As per the EMA EMA/CHMP/539146/2013, 'post-baseline covariates may be affected by treatment received and will not usually be appropriate to define subgroups for the investigation of a treatment effect.' However, the off-ADM subgroup is defined based on the use of ADM at baseline and during the trial. I.e., the definition includes a post-baseline variable. Further, the off ADM group is likely not credible. The minimum set of criteria for a positive licensing decision are not fulfilled. Additionally, CHMP is concerned about the validity of the results. Moreover, even if considered valid, efficacy is not demonstrated based on the provided results. Furthermore, CHMP is concerned about the feasibility of restricting the indication in the real life conditions.

Altogether, the body of evidence is far from compelling with respect to internal and external validity, clinical relevance, statistical significance, and internal consistency. These aspects are expected to be met in the context of a single pivotal study.

Unfavourable effects

Most AEs were of mild to moderate severity. Pridopidine treatment seems to be associated with depression and weight loss, which corresponds with non-clinical findings. The AEs 'malignancies' and 'seizures/convulsions' also correspond with non-clinical pridopidine findings. Relatedness of these AEs to pridopidine could not be fully confirmed (or denied) by the clinical data. As additional studies to investigate this are not feasible, these AEs would need close monitoring in the PSURs.

Gastrointestinal disorders may contribute to the weight loss, which was a dose related non-clinical finding and were also clinically associated with a longer exposure to pridopidine. The safety profiles of pridopidine by ADM use indicate an increased risk for AEs. The safety in subgroups was also submitted, indicating an increased risk for patients with moderate renal impairment, leading to a contraindication for use in severe renal impaired patients. The subgroup analysis by age group indicate no greater risks for pridopidine related AEs as most events were related to age, e.g. increased risk for infections.

SAEs that were reported in the pivotal study as well as in the ISA include suicide attempt, fall, characteristics of HD progression. Long term safety data of the pivotal study indicate a greater risk for fall, gait disturbance and chorea. These AEs increase in frequency when pridopidine is used concomitantly with ADMs. The warning in section 4.4 was updated and chorea was added as ADR in section 4.8 of the proposed SmPC.

Overall, the safety profile is considered manageable with the proposed risk minimisation measures, additional pharmacological activities and commitments (i.e. full PK sampling).

3.7.2. Balance of benefits and risks

The efficacy of pridopidine as a treatment for adult HD has not been demonstrated. The pivotal study PROOF-HD failed to show a benefit of pridopidine over placebo on any efficacy endpoint in the mITT population.

The latest requested restricted indication for adult early HD patients not using ADM is not agreed. The off-ADM group is defined partially using a post-baseline variable (use of ADM while on treatment), the group is not considered credible as per EMA/CHMP/539146/2013 and the minimum set of criteria for a positive licensing decision are not fulfilled. Additionally, CHMP is concerned about the validity of the results. Yet, even if they would have been considered valid, efficacy is not demonstrated in the provided results. There are also concerns on the feasibility of the restriction in real life conditions.

The overall evidence lacks compelling internal and external validity, clinical relevance, statistical significance, and internal consistency, which are typically expected in a single pivotal study.

From the safety point of view, concerns have been raised regarding the risk of several drug-related AEs, such as anxiety, insomnia, QT prolongation, depression and weight loss, of which the latter is consistent with non-clinical findings. In addition, it remains unclear if the observed depression is related to HD or related to pridopidine use, as subjects with poor depression scores were excluded when entering the OLE phase. Further, the AEs 'malignancies' and 'convulsions/seizures' were seen in the animal studies. It is unclear if pridopidine also caused/increased these events and need close monitoring via PSURs, because additional studies to address these risks are not considered feasible. Finally, the true effect of pridopidine on the QT interval remains unclear as there are unresolved issues related to the popPK model that was used to estimate the effect on QT prolongation effect and its clinical sequel. Though sufficient warnings and precautions for use are included in the proposed SmPC, the applicant committed to perform full PK sampling to update the popPK model and appropriately estimate Cmax and AUC in HD patients. This will inform whether specific situations, such as various degrees of renal impairment, are expected to lead to clinically relevant changes in QT.

No therapeutic window can be determined and therefore it can also not be determined if the covariates patients status, CYP2D6 phenotype, renal impairment, hepatic impairment, gender, body weight, ethnic origin, and age are clinically relevant. Patients that are CYP2D6 poor metabolisers and have renal impairment are at higher risk of QTc prolongation. The applicant does not want to include mandatory CYP2D6 genotyping, but due to safety in all patient populations (not only Caucasians) mandatory genotyping could be considered. However, instead a strong warning is included in the proposed SmPC section 4.4, indicating that if the CYP2D6 status of the patient is not known then genotyping is strongly recommended. This can be considered appropriate.

Overall, the safety profile is considered manageable with the proposed risk minimisation measures, additional pharmacological activities and commitments (i.e. full PK sampling).

In conclusion, given the lack of demonstrated efficacy, the benefit-risk balance of pridopidine for the treatment of early Huntington's disease in adults who are not treated with antidopaminergic medicinal products is negative.

3.7.3. Additional considerations on the benefit-risk balance

Patient and healthcare professional engagement

Patient perspective

Information on the patient perspective was obtained from the European Huntington Association (EHA). It encompassed a literature review on HD symptom presentation and therapeutic needs, survey results over the years, Round Table meetings and interviews from patients with HD across severity stages.

Aspects that were felt not understood or sufficiently considered were that HD is more than a disease as it affects all life aspects and major decisions. As HD is hereditary, most families have several affected members. Patients need to live with the chance they also develop the disease which deteriorates their family, which exponentially increases the burden of HD.

An online survey was recently conducted by EHA to characterise and benchmark the health care and social support available to HD families in Europe. 48.5% of the 637 HD family members who completed the survey aid with symptom management as one of their top priorities and desired services. The survey also indicated that proper referral and understanding of HD specificities seem to be missing in Europe.

The expectations for future treatments were consensual: medicines that can reduce the disease impact, enhance their quality of life and prolong their well-being. The EHA believes it to be crucial to have therapies that address real-life hurdles of individuals affected by HD and have a tangible positive impact on their functional status, quality of life and well-being.

Healthcare professionals

Response was received from healthcare professional organisation European Academy of Neurology, and from the European Reference Network for Rare Neurological Diseases.

An overview HD care and strategies was provided, including reflection on the high economic burden. The great variability in clinical presentation is a concern as patients from different ages and disease stages may respond differently. This supports the need for multimodal treatment strategies (i.e., by multiple types of healthcare professionals) are needed. Pregnancy is a complex topic in this inheritable disease as manifestation in women is often only after pregnancy. Similarly, the disease can lead to social disruption as there is a large 'fear of knowing' if they have HD.

Absence of disease modifying therapies is sometimes seen as a deterrent to case as patients are discouraged to follow a similar future as their relatives that died from HD. HD patients are indicated to tolerate important side effects if disease progression could be slowed. ERN-RND proposed to propose to implement a stepwise approach for a new treatment by monitoring of AEs and long-term real-world evaluation. An indirect benefit of a new HD medication may also be that HD patients are more likely to visit expert centres.

For pridopidine specifically it was indicated that it may have a potential based on recently presented data.

Reflection of the patient and healthcare perspective on clinical results

The insights are valuable and are taken into account.

The patient perspective highlights that for a HD therapy to be of use it does not have to be curative, I.e., also therapies that enhance functional status and quality-of-life are needed. Symptom management was indicated to be the top priority.

PROOF-HD data do not support that pridopidine is a therapy that meets those wishes. Results indicate that patients receiving pridopidine progressed faster on functional capacity than placebo as measured on TFC, and had no gain in quality-of-life as measured on HD-QoL. The results in the off-ADM group are not considered to be alternatively suitable to address this medical need, as there are uncertainties on composition of this group in the study, validity of results in the group and how representative it is for the target population. In contrast, it is considered that the patient perspective on the need for symptom management reinforces the concern that keeping patients off ADMs while treated with pridopidine may not be preferable.

The healthcare professional response support that there is an unmet medical need, that pregnancy in HD is a topic that requires attention, and that a therapy with a broad label may be challenging in HD.

Conditional marketing authorisation

As comprehensive data on the product are not available, a CMA was requested by the applicant during the assessment.

The CHMP considers that the product cannot be recommended for a CMA as the benefit-risk balance is negative (as discussed), the applicant is unlikely to be able to provide comprehensive data after authorisation, it has not been demonstrated that the product will address an unmet medical need, and the benefits to public health of the immediate availability do not outweigh the risks inherent in the fact that additional data are still required.

Regarding 'a positive benefit risk balance' (criterion #1)

Benefit is claimed in the early HD off-ADM group as i) effects favoured pridopidine over placebo up to at least one year; ii) effects were seen across endpoints on disease progression; function, motor and cognition; iii) effects were consistent across (m)ITT and PP in those off-ADMs; iv) efficacy persisted in the OLE vs external control (ENROLL-HD), and was repeatable as shown by effects in patients that switched from placebo to pridopidine in the OLE.

The arguments are not agreed:

- Ad i, iv): by claiming effects last 'up to at least one year' (i) and 'are persistent in the OLE' (iv), the applicant carefully omits the key issue of undemonstrated relevance of TFC and cUHDRS up to Week 78. However, for a chronic treatment, undemonstrated relevance of effects vs placebo at Week 65 and 78 should not be disregarded for possibly more favourable results at earlier timepoints (e.g., Week 52), and/or for results of the OLE of which the analysis is not credible.
- Ad ii) it is not agreed that effects of pridopidine are consistent across endpoints, let alone consistently reached clinically relevant levels.
- Ad iii) consistency across (m)ITT, ITT and PP in patients off-ADMs is acknowledged. However, consistency on itself is no reason for CMA, especially as the off-ADM rather seems a selected population of less impaired patients not requiring rescue medication

Further, the following issues remain and argue against a positive benefit-risk balance (and consequently, against CMA):

- The results of the off-ADMs group do not follow the guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013). The group is likely not credible. Additionally, the minimum set of criteria as outlined in the guidance for licensing are not met.

- Additionally, CHMP is concerned about the validity of the results. Even if considered valid, efficacy is not demonstrated in the provided results.
- Practical feasibility of the off-ADM group in real-life is questioned. HD patients often use ADMs: generally 30-40% of patients and in PROOF-HD even ~45%. Those patients would need to stop ADMs, putting themselves and their caregiver at risk for symptoms the ADMs treated (e.g., aggression). Moreover, pridopidine has minimal effect on chorea symptoms. Keeping patients off-ADMs thus likely seems not feasible. At the same time, efficacy has (also) not been demonstrated in patients using pridopidine with ADMs, which has been acknowledged by the applicant.

Altogether, efficacy is not demonstrated in mITT or in the off-ADM group. There are, however, risks associated with pridopidine as specified in the proposed SmPC section 4.8. Therefore, the B/R balance for pridopidine remains **negative**, both in mITT and in the off-ADM subgroup. It is acknowledged that the safety aspects could have been managed with the provisions in the proposed SmPC and RMP.

As a benefit is not demonstrated, criterion #4 also is also not met (i.e., the benefit does not outweigh inherent risks that additional data are needed).

Regarding 'provision of comprehensive data after authorisation' (criterion #2)
The applicant committed to perform a confirmatory study (SOB) in patients not receiving ADMs.

The applicant proposes a 6-month double-blind period, followed by a 2,5y OLE.

This would not have been acceptable as confirmatory evidence because week 26 data were not predictive for later timepoints in PROOF-HD study. This is a major concern. The double-blind period would have been expected to be at least 65-78 weeks to allow comparing to PROOF-HD, and yield particularly compelling results as they should outweigh the fact that all four previous HD trials are formally failed studies. Thus, the currently proposed design is not considered appropriate to render comprehensive evidence. Fulfilment of the second criterion is therefore, not agreed.

It is noted that the study plans to enrol only early HD patients (TFC score ≥7), yet extrapolation to more severe HD has not been demonstrated (TFC <7, also see above). The applicant addressed this major concern late in the procedure by restricting the indication to patients with early HD.

Regarding 'the product addresses an unmet medical need' (criterion #3)

The unmet medical need in HD is evident. However, the arguments provided by the applicant are not sufficient and had deserved further discussion if the other criteria would have been met.

In support to meeting this criterion, the applicant indicated that currently available therapies are only supportive, specifically ADMs (note: in the EU pharmacological and approved options are tetrabenazine and haloperidol). According to Regulation (EC) No 507/2006, in that case major therapeutic advantage of (in this case) pridopidine over ADMs should have been justified. Currently the applicant based the arguments of treatment benefit on PROOF-HD results, for which it was not agreed that they can support an efficacy claim (discussion criterion #1; above).

Later during the procedure, the applicant restricted the label to patients off-ADMs. I.e., ADMs are not a therapy-option, although practical feasibility of keeping patients off-ADMs is questioned (discussion criterion #1; above). Thus, formally, there are no pharmacological therapies approved for the restricted population of patients off-ADMs, and hence meeting this criterion potentially could have been agreed. The unmet medical need in the target population is agreed but without a demonstration of efficacy, it is not agreed that Nurzigma addresses it. Consequently, this criterion is not considered fulfilled at the time of this opinion.

Regarding the benefits to public health of the immediate availability do not outweigh the risks inherent in the fact that additional data are still required (criterion #4)

In the view of efficacy not being demonstrated, it is not agreed that this criterion is fulfilled.

Conclusion on eligibility for CMA: *meeting criteria for CMA in line with the requirements of Regulation (EC) No 507/2006 is not agreed, as detailed* above.

3.8. Conclusion

The overall benefit/risk balance of Nurzigma for the treatment of early Huntington´s disease in adults who are not treated with antidopaminergic medicinal products is negative.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy for Nurzigma in the treatment of early Huntington´s disease (HD) in adults who are not treated with antidopaminergic medicinal products (ADMs; see section 4.4. and 5.1), the CHMP considers by consensus that the efficacy of the above-mentioned medicinal product is not sufficiently demonstrated, and, therefore recommends the refusal of the granting of the conditional marketing authorisation for the above-mentioned medicinal product.

The CHMP considers that:

- The PROOF-HD pivotal trial failed its primary objective. The *post hoc* subgroup analyses in the proposed off-ADM patients are not in accordance with the Guideline on the investigation of subgroups in confirmatory clinical trials. Moreover, results in the off-ADM subgroup are of undemonstrated validity and clinical relevance. Hence, efficacy of Nurzigma (pridopidine) has not been established in the proposed population of adult patients with early HD who are not treated with antidopaminergic medicinal products.
- Conditional marketing authorisation is not agreed, as the requirements of Article 4 of Commission Regulation (EC) No. 507/2006 are not fulfilled. As efficacy has not been demonstrated, it is considered that the first, the third, and the fourth criteria are not met. The 2nd criterion is also not met as the proposed - still to be initiated - confirmatory study is unlikely to provide the required comprehensive data.

Due to the aforementioned concerns a satisfactory summary of product characteristics, labelling, package leaflet, pharmacovigilance system, risk management plan and post-authorisation measures to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, following review of the available data in the context of the applicant’s claim of new active substance status, the CHMP position at the time of this report is reflected in Appendix 1.

New active substance status

Based on the review of available data on the active substance, the CHMP considers that pridopidine hydrochloride is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.