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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Branaplam (LMI070)

Trial Indication(s)

Huntington's disease

Protocol Number

CLMI070C12203

Protocol Title

A Randomized, Double-Blind, Placebo-Controlled Dose Range Finding Study with Open-Label Extension to Evaluate the Safety, Pharmacokinetics and Pharmacodynamics of LMI070/branaplam Administered as Weekly Oral Doses in Participants with Early Manifest Huntington's Disease

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

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Study Start/End Dates

Study Start Date: December 08, 2021 (Actual)
Primary Completion Date: October 27, 2023 (Actual)
Study Completion Date: October 27, 2023 (Actual)

Reason for Termination (If applicable)

The clinical trial for the drug branaplam was halted prematurely due to signs and symptoms that suggested the possibility of peripheral neuropathy, a condition involving nerve damage outside the brain and spinal cord, observed in the initial cohort dosed at 56mg. However, all participants who received branaplam continued to undergo routine (safety) evaluations for up to a year following their final dose.

Study Design/Methodology

This study was a randomized, double-blind, placebo-controlled study with a variable duration (between approximately 17 weeks to approximately 53 weeks) for the core period and a one-year open label extension (OLE) in early-stage manifest Huntington's disease (HD) participants.

After screening period and baseline assessments, the following two Treatment Periods were planned:

- The core period consisted of a 17-week double-blind, placebo-controlled, Dose Range Finding (DRF) portion of the study, followed by a blinded extension (BE) of variable duration (up to approximately 53 weeks). The DRF Period was to evaluate the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics (PD) of branaplam, as well as determine the optimal dose(s) to explore in further clinical evaluations.

  The core period was planned to consist of 3 treatment arms:

  - Cohort 1: Treatment Arm A: branaplam 56 mg oral solution or matching placebo, once weekly
  - Cohort 2: Treatment Arm B: branaplam 112 mg oral solution or matching placebo, once weekly

- Cohort 3:

  Treatment Arm C: branaplam 154 mg oral solution or matching placebo, once weekly

  or

  Treatment Arm X: branaplam 84 mg oral solution or matching placebo, once weekly

  or

  Treatment Arm Y: branaplam 28 mg oral solution or matching placebo, once weekly

- The OLE was a one-year open-label extension to assess both long-term safety and tolerability, as well as the efficacy of the recommended optimal dose(s) for branaplam.

Due to safety concerns an urgent safety measure (USM) follow-up notification dated 06-Dec-2022 was issued to permanently discontinue the study treatment in all participants. At that point, only cohort 1 was enrolled. Therefore, only cohort 1 data is available for analysis (Treatment Arm A: branaplam 56 mg oral solution or matching placebo, once weekly). Participants who received active treatment (branaplam) were to remain in the study for follow-up for approximately one year following initial treatment discontinuation. The OLE part was not opened.

Centers

12 centers in 5 countries: Germany(3), Hungary(2), Spain(3), France(3), Canada(1)

Objectives:

The primary objectives of the trial were:

- To assess the dose response relationship of branaplam administered over 16 weeks on mutant Huntingtin (mHTT) protein change from baseline in cerebrospinal fluid (CSF)

- To evaluate the safety and tolerability of branaplam when administered for 16 weeks or longer in participants with Huntington's disease (HD)

The secondary objectives were:

- To assess the pharmacodynamics of branaplam in participants with HD on clinical, imaging, and biomarker endpoints relevant to HD
- To assess pharmacokinetics of branaplam and its metabolite UFB112 in plasma and CSF

Test Product (s), Dose(s), and Mode(s) of Administration

The treatments administered in this study included:

- Cohort 1: Treatment Arm A: branaplam 56 mg oral solution or matching placebo, once weekly.

Branaplam was administered up to maximum 22 weeks.

Other treatment arms and cohorts were not opened due to the USM follow-up notification.

Statistical Methods

Analysis of the primary endpoints:

As per USM, the primary estimand and statistical modelling for dose-response relationship was no longer applicable. Primary endpoint of mHTT protein in CSF was summarized descriptively. No sensitivity analysis or supplementary analysis was performed.

All safety endpoints were summarized by treatment group for all participants in the safety analysis set.

Analysis of secondary endpoints:

The clinical endpoints (Unified Huntington's Disease Rating Scales (UHDRS)-Total Functional Capacity (TFC), UHDRS-Total Motor Scale (TMS) and UHDRS-Independence Scale (IS)) were summarized with appropriate descriptive tables by visit and treatment group.

Volumetric MRI: Summary tables were provided to present the change over time by brain region of interests (ROIs): ventricular, caudate and total brain volume.

PK analysis: Descriptive summary statistics for the plasma and CSF concentrations of both analytes (branaplam and UFB112) were provided by analyte, treatment, and visit/sampling time point. Concentrations below the lower limit of quantification (LLOQ) were treated as zero in summary statistics and for pharmacokinetic (PK) parameter calculations.

Biomarkers analysis: Descriptive summary statistics for the CSF concentrations of mHTT protein were provided by treatment and visit/sampling time point.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria

- Signed informed consent must be obtained prior to participation in the study
- Clinically diagnosed Stage 1 or 2 Huntington's disease with a diagnostic confidence level (DCL) = 4 and a United Huntington's Disease Rating Scale (UHDRS) Total Functional Capacity (TFC) >8 at screening
- Genetically confirmed Huntington's disease, with presence of ≥40 cytosine-adenineguanine (CAG) repeats in the huntingtin gene
- Male and female participants between 25 to 75 years of age, inclusive, on the day of Informed Consent signature

Exclusion Criteria

- Prior participation in clinical trial investigating a huntingtin-lowering therapy (unless participant received only placebo)
- Participants taking medications prohibited by the protocol

- Any medical history, lumbar surgery or condition that would interfere with the ability to complete the protocol specified assessments
- Participant has other severe, acute or chronic medical conditions including unstable psychiatric conditions, or laboratory abnormalities that in the opinion of the Investigator may increase the risk associated with study participation, or that may interfere with the interpretation of the study results
- Any surgical or medical condition which might put the participant at risk in case of participation in the study. The Investigator should make this determination in consideration of the participant's medical history and/or clinical or laboratory evidence at the Screening visit

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Participant Flow Table

Overall Study

	Placebo	Branaplam 56 mg	Total
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly	
Started	5	21	26
Completed	4	13	17
Not Completed	1	8	9
Lost to Follow-up	0	2	2
Physician Decision	0	1	1
Participant decision	1	5	6

Baseline Characteristics

	Placebo	Branaplam 56 mg	Total
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly	
Number of Participants [units: participants]	5	21	26
Baseline Analysis Population Description			
Age Continuous (units: years) Analysis Population Type: Participants Mean ± Standard Deviation			
	52.8±15.30	49.6±10.06	50.2±10.96

Sex: Female, Male (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	1	10	11
Male	4	11	15
Race/Ethnicity, Customized (units: participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
White	5	18	23
Unknown	0	3	3

Primary Outcome Result(s)

Percentage change from baseline to Week 17 in mHTT protein in CSF

Description	Mutant Huntingtin (mHTT) protein was measured in cerebrospinal fluid (CSF) obtained via lumbar puncture. The percentage change from baseline to Week 17 in mHTT protein in CSF was calculated with the following formula: (mHTTweek17 - mHTTbaseline)/ mHTTbaseline * 100. Baseline value for mHTT is the last evaluable measurements prior to the first administration of study drug.
Time Frame	Baseline, Week 17
Analysis Population Description	Participants in the Safety Analysis Set (SAF) who had an available value for the outcome measure at baseline and Week 17. SAF included all participants who received at least one dose of study drug.

	Placebo	**Branaplam 56 mg**
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	4	9

Percentage change from baseline to Week 17 in mHTT protein in CSF (units: % change in mHTT protein)	**Mean** **± Standard Deviation**	**Mean** **± Standard Deviation**
	-1.38 ± 20.517	-26.61 ± 22.354

Number of participants with adverse events (AEs) and serious adverse events (SAEs)

Description	Incidence of AEs (any AEs regardless of seriousness) and SAEs, including changes in vital signs, neurological examination, electrocardiograms (ECGs) and laboratory parameters qualifying and reported as AEs. Participants received study treatment up to maximum Week 20 (placebo) and Week 22 (branaplam).
Time Frame	From first dose of study treatment up to Week 69
Analysis Population Description	Safety Analysis Set including all participants who received at least one dose of study drug.

	Placebo	**Branaplam 56 mg**
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	5	21
Number of participants with adverse events (AEs) and serious adverse events (SAEs) (units: participants)	**Count of Participants** **(Percentage)**	**Count of Participants** **(Percentage)**
AEs	2 (40%)	18 (85.71%)
Study drug-related AEs	1 (20%)	14 (66.67%)
SAEs	0 (%)	4 (19.05%)
Study drug-related SAEs	0 (%)	3 (14.29%)

Secondary Outcome Result(s)

Percentage change from baseline in total brain volume

Description	Three-dimensional magnetic resonance imaging (MRI) data was acquired and used to measure brain volume at each time point and changes in brain volume longitudinally. Brain MRI scans were performed at each time point without gadolinium contrast. Changes in volumetric MRI were measured in regions of interests: ventricular, caudate (left and right) and total brain volume. The baseline MRI scan was obtained within 6 days prior to the first dose of study treatment.
Time Frame	Baseline, Week 17, Week 33, Week 53, Week 69
Analysis Population Description	Participants in the Safety Analysis Set (SAF) who had an available value for the outcome measure at baseline and the corresponding study visit. SAF included all participants who received at least one dose of study drug.

	Placebo	**Branaplam 56 mg**
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	4	17
Percentage change from baseline in total brain volume (units: % change in total brain volume)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Week 17 (n=4, 17)	-0.20 ± 0.332	-0.43 ± 2.362
Week 33 (n=3, 17)	-0.67 ± 0.352	-0.88 ± 0.681
Week 53 (n=1, 12)	-0.25	-1.34 ± 0.848
Week 69 (n=0, 12)		-1.63 ± 0.877

Percentage change from baseline in total brain volume excluding patients with subdural hematoma

Description	Three-dimensional magnetic resonance imaging (MRI) data was acquired and used to measure brain volume at each time point and changes in brain volume longitudinally. Brain MRI scans were performed at each time point without gadolinium contrast. Changes in volumetric MRI were measured in regions of interests: ventricular, caudate (left and right) and total brain volume. The baseline MRI scan was obtained within 6 days prior to the first dose of study treatment.

Time Frame	Baseline, Week 17, Week 33, Week 53, Week 69
Analysis Population Description	Participants in the Safety Analysis Set (SAF) who had an available value for the outcome measure at baseline and the corresponding study visit, and who did not have subdural hematoma. SAF included all participants who received at least one dose of study drug.

	Placebo	**Branaplam 56 mg**
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	4	15
Percentage change from baseline in total brain volume excluding patients with subdural hematoma (units: % change in total brain volume)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Week 17 (n=4, 15)	-0.20 ± 0.332	-1.09 ± 0.599
Week 33 (n=3, 15)	-0.67 ± 0.352	-0.80 ± 0.675
Week 53 (n=1, 10)	-0.25	-1.30 ± 0.748
Week 69 (n=0, 10)		-1.68 ± 0.751

Percentage change from baseline in lateral ventricles volume

Description	Three-dimensional magnetic resonance imaging (MRI) data was acquired and used to measure brain volume at each time point and changes in brain volume longitudinally. Brain MRI scans were performed at each time point without gadolinium contrast. Changes in volumetric MRI were measured in regions of interests: ventricular, caudate (left and right) and total brain volume. The baseline MRI scan was obtained within 6 days prior to the first dose of study treatment.
Time Frame	Baseline, Week 17, Week 33, Week 53, Week 69
Analysis Population Description	Participants in the Safety Analysis Set (SAF) who had an available value for the outcome measure at baseline and the corresponding study visit. SAF included all participants who received at least one dose of study drug.

	Placebo	**Branaplam 56 mg**

Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	3	17
Percentage change from baseline in lateral ventricles volume (units: % change in lateral ventricles volume)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Week 17 (n=3, 17)	1.63 ± 1.392	8.84 ± 11.599
Week 33 (n=3, 17)	5.51 ± 1.772	11.73 ± 9.799
Week 53 (n=1, 12)	3.43	15.77 ± 10.842
Week 69 (n=0, 12)		17.40 ± 10.182

Percentage change from baseline in lateral ventricles volume excluding patients with subdural hematoma

Description	Three-dimensional magnetic resonance imaging (MRI) data was acquired and used to measure brain volume at each time point and changes in brain volume longitudinally. Brain MRI scans were performed at each time point without gadolinium contrast. Changes in volumetric MRI were measured in regions of interests: ventricular, caudate (left and right) and total brain volume. The baseline MRI scan was obtained within 6 days prior to the first dose of study treatment.
Time Frame	Baseline, Week 17, Week 33, Week 53, Week 69
Analysis Population Description	Participants in the Safety Analysis Set (SAF) who had an available value for the outcome measure at baseline and the corresponding study visit, and who did not have subdural hematoma. SAF included all participants who received at least one dose of study drug.

	Placebo	**Branaplam 56 mg**
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	3	15
Percentage change from baseline in lateral ventricles volume excluding patients with subdural hematoma (units: % change in lateral ventricles volume)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Week 17 (n=3, 15)	1.63 ± 1.392	9.47 ± 6.061

Week 33 (n=3, 15)	5.51 ± 1.772	9.43 ± 5.673
Week 53 (n=1, 10)	3.43	12.38 ± 6.193
Week 69 (n=0, 10)		14.45 ± 6.040

Percentage change from baseline in left caudate volume

Description	Three-dimensional magnetic resonance imaging (MRI) data was acquired and used to measure brain volume at each time point and changes in brain volume longitudinally. Brain MRI scans were performed at each time point without gadolinium contrast. Changes in volumetric MRI were measured in regions of interests: ventricular, caudate (left and right) and total brain volume. The baseline MRI scan was obtained within 6 days prior to the first dose of study treatment.
Time Frame	Baseline, Week 17, Week 33, Week 53, Week 69
Analysis Population Description	Participants in the Safety Analysis Set (SAF) who had an available value for the outcome measure at baseline and the corresponding study visit. SAF included all participants who received at least one dose of study drug.

	Placebo	**Branaplam 56 mg**
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	4	17
Percentage change from baseline in left caudate volume (units: % change in left caudate volume)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Week 17 (n=4, 16)	-0.93 ± 3.782	-4.44 ± 3.005
Week 33 (n=3, 17)	-3.95 ± 2.147	-4.30 ± 3.331
Week 53 (n=1, 11)	-2.69	-6.33 ± 4.417
Week 69 (n=0, 12)		-5.44 ± 7.864

Percentage change from baseline in left caudate volume excluding patients with subdural hematoma

Description	Three-dimensional magnetic resonance imaging (MRI) data was acquired and used to measure brain volume at each time point and changes in brain volume longitudinally. Brain MRI scans were performed at each time point without gadolinium contrast. Changes in volumetric MRI

	were measured in regions of interests: ventricular, caudate (left and right) and total brain volume. The baseline MRI scan was obtained within 6 days prior to the first dose of study treatment.
Time Frame	Baseline, Week 17, Week 33, Week 53, Week 69
Analysis Population Description	Participants in the Safety Analysis Set (SAF) who had an available value for the outcome measure at baseline and the corresponding study visit, and who did not have subdural hematoma. SAF included all participants who received at least one dose of study drug.

	Placebo	**Branaplam 56 mg**
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	4	15
Percentage change from baseline in left caudate volume excluding patients with subdural hematoma (units: % change in left caudate volume)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Week 17 (n=4, 14)	-0.93 ± 3.782	-4.14 ± 2.300
Week 33 (n=3, 15)	-3.95 ± 2.147	-3.58 ± 2.692
Week 53 (n=1, 9)	-2.69	-6.24 ± 4.788
Week 69 (n=0, 10)		-4.81 ± 8.351

Percentage change from baseline in right caudate volume

Description	Three-dimensional magnetic resonance imaging (MRI) data was acquired and used to measure brain volume at each time point and changes in brain volume longitudinally. Brain MRI scans were performed at each time point without gadolinium contrast. Changes in volumetric MRI were measured in regions of interests: ventricular, caudate (left and right) and total brain volume. The baseline MRI scan was obtained within 6 days prior to the first dose of study treatment.
Time Frame	Baseline, Week 17, Week 33, Week 53, Week 69
Analysis Population Description	Participants in the Safety Analysis Set (SAF) who had an available value for the outcome measure at baseline and the corresponding study visit. SAF included all participants who received at least one dose of study drug.

	Placebo	Branaplam 56 mg
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	3	17
Percentage change from baseline in right caudate volume (units: % change in right caudate volume)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Week 17 (n=3, 17)	-3.28 ± 3.496	-2.79 ± 4.604
Week 33 (n=3, 17)	-6.91 ± 1.895	-4.11 ± 4.146
Week 53 (n=1, 11)	-5.34	-6.81 ± 4.251
Week 69 (n=0, 12)		-6.34 ± 6.934

Percentage change from baseline in right caudate volume excluding patients with subdural hematoma

Description	Three-dimensional magnetic resonance imaging (MRI) data was acquired and used to measure brain volume at each time point and changes in brain volume longitudinally. Brain MRI scans were performed at each time point without gadolinium contrast. Changes in volumetric MRI were measured in regions of interests: ventricular, caudate (left and right) and total brain volume. The baseline MRI scan was obtained within 6 days prior to the first dose of study treatment.
Time Frame	Baseline, Week 17, Week 33, Week 53, Week 69
Analysis Population Description	Participants in the Safety Analysis Set (SAF) who had an available value for the outcome measure at baseline and the corresponding study visit, and who did not have subdural hematoma. SAF included all participants who received at least one dose of study drug.

	Placebo	Branaplam 56 mg
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	3	15
Percentage change from baseline in right caudate volume excluding patients with subdural hematoma (units: % change in right caudate volume)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**

Week 17 (n=3, 15)	-3.28 ± 3.496	-2.67 ± 4.850
Week 33 (n=3, 15)	-6.91 ± 1.895	-3.23 ± 3.437
Week 53 (n=1, 9)	-5.34	-6.57 ± 4.418
Week 69 (n=0, 10)		-5.60 ± 7.249

Change from baseline in the Unified Huntington's Disease Rating Scales (UHDRS) Total Functional Capacity (TFC)

Description	The TFC focuses on the investigator's assessment of the participant's capacity to perform a range of activities of daily living. The responses are derived from interview with the participant and/or companion, if applicable. TFC score range from 0 to 13, with higher scores representing better functioning.
Time Frame	Baseline, Week 17, Week 33 and Week 69
Analysis Population Description	Participants in the Safety Analysis Set (SAF) who had an available value for the outcome measure at baseline and the corresponding study visit. SAF included all participants who received at least one dose of study drug.

	Placebo	**Branaplam 56 mg**
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	5	19
Change from baseline in the Unified Huntington's Disease Rating Scales (UHDRS) Total Functional Capacity (TFC) (units: score on scale)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Week 17 (n=5, 19)	-1.0 ± 2.35	-0.8 ± 2.39
Week 33 n=4, 17)	-0.5 ± 2.52	-1.3 ± 2.31
Week 69 n=0, 13)		-1.2 ± 2.94

Change from baseline in the Unified Huntington's Disease Rating Scales (UHDRS) Total Motor Scale (TMS)

Description	The TMS is the cumulative sum of the individual motor ratings obtained during the administration of the motor assessment portion of the UHDRS. TMS score range from 0 to 124 with higher scores representing more significant impairment.
Time Frame	Baseline, Week 17, Week 33 and Week 69
Analysis Population Description	Participants in the Safety Analysis Set (SAF) who had an available value for the outcome measure at baseline and the corresponding study visit. SAF included all participants who received at least one dose of study drug.

	Placebo	**Branaplam 56 mg**
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	5	19
Change from baseline in the Unified Huntington's Disease Rating Scales (UHDRS) Total Motor Scale (TMS) (units: score on scale)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Week 17 (n=5, 19)	6.0 ± 11.29	5.1 ± 9.14
Week 33 n=4, 17)	2.5 ± 10.34	2.6 ± 8.83
Week 69 n=0, 13)		3.6 ± 8.99

Change from baseline in the Unified Huntington's Disease Rating Scales (UHDRS) Independence Scale (IS)

Description	The IS represents the investigator's assessment of the participant's level of independence, including topics of employment, finances, self-care and feeding. The scale has 19 discrete scores, from 10 (tube fed, total bed care) to 100 (no special care needed) with 5-point increments in between.
Time Frame	Baseline, Week 17, Week 33 and Week 69
Analysis Population Description	Participants in the Safety Analysis Set (SAF) who had an available value for the outcome measure at baseline and the corresponding study visit. SAF included all participants who received at least one dose of study drug.

	Placebo	Branaplam 56 mg
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	5	19
Change from baseline in the Unified Huntington's Disease Rating Scales (UHDRS) Independence Scale (IS) (units: score on scale)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
Week 17 (n=5, 19)	-1.0 ± 11.40	-1.8 ± 9.16
Week 33 n=4, 17)	1.3 ± 16.52	-4.7 ± 8.19
Week 69 n=0, 13)		-6.5 ± 13.29

Concentrations of mHTT protein and total HTT in CSF

Description	Mutant Huntingtin (mHTT) protein and total HTT measured in cerebrospinal fluid (CSF) obtained via lumbar puncture. Baseline value is the last evaluable measurement prior to the first administration of study drug.
Time Frame	Baseline, Week 9, Week 17
Analysis Population Description	Participants in the Safety Analysis Set (SAF) who had an available value for the outcome measure at the corresponding study visit. SAF included all participants who received at least one dose of study drug.

	Placebo	Branaplam 56 mg
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	5	21
Concentrations of mHTT protein and total HTT in CSF (units: fmol)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
mHTT – Baseline (n=5, 21)	86.14 ± 35.590	102.03 ± 48.533

mHTT – Week 9 (n=5, 17)	86.31 ± 43.265	74.68 ± 37.111
mHTT – Week 17 (n=4, 9)	77.68 ± 33.077	65.58 ± 41.152
Total HTT – Baseline (n=0, 0)	NA ± NA[1]	NA ± NA[1]
Total HTT – Week 9 (n=0, 0)	NA ± NA[1]	NA ± NA[1]
Total HTT – Week 17 (n=0, 0)	NA ± NA[1]	NA ± NA[1]

[1] Assay issues did not allow a reliable quantification of total HTT in CSF.

Concentrations of mHTT protein and total HTT in plasma

Description	Mutant Huntingtin (mHTT) protein and total HTT measured in plasma. Baseline value is the last evaluable measurement prior to the first administration of study drug.
Time Frame	Baseline, Week 17
Analysis Population Description	Safety Analysis Set (SAF)

	Placebo	**Branaplam 56 mg**
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	5	21
Concentrations of mHTT protein and total HTT in plasma (units: fmol)	**Mean ± Standard Deviation**	**Mean ± Standard Deviation**
mHTT – Baseline (n=0, 0)	NA ± NA[1]	NA ± NA[1]
mHTT - Week 17 (n=0, 0)	NA ± NA[1]	NA ± NA[1]
Total HTT – Baseline (n=0, 0)	NA ± NA[2]	NA ± NA[2]
Total HTT – Week 17 (n=0, 0)	NA ± NA[2]	NA ± NA[2]

[1] Assay issues did not allow a reliable quantification of mHTT protein in plasma.
[2] Assay issues did not allow a reliable quantification of total HTT in plasma.

Maximum observed plasma concentration (Cmax) of branaplam and its metabolite UFB112

Description	Pharmacokinetic (PK) parameters were calculated based on branaplam and its metabolite UFB112 plasma concentrations by using non-compartmental methods. Cmax is defined as the maximum (peak) observed concentration following a dose.
Time Frame	pre-dose and 4, 7, 12, 22, 72 and 168 hours after branaplam dose at Week 1 and Week 17
Analysis Population Description	Patients in the PK analysis set with an available value for the outcome measure at each timepoint. The PK Analysis Set is only applicable to patients treated with branaplam and includes all participants with at least one evaluable concentration data sample.

	Branaplam 56 mg
Arm/Group Description	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	21
Maximum observed plasma concentration (Cmax) of branaplam and its metabolite UFB112 (units: ng/mL)	**Mean ± Standard Deviation**
Branaplam - Week 1 (n=21)	26.1 ± 7.99
Branaplam - Week 17 (n=4)	45.3 ± 7.96
UFB112 - Week 1 (n=21)	31.9 ± 12.6
UFB112 - Week 17 (n=4)	53.3 ± 20.4

Time to reach maximum plasma concentration (Tmax) of branaplam and its metabolite UFB112

Description	PK parameters were calculated based on branaplam and its metabolite UFB112 plasma concentrations by using non-compartmental methods. Tmax is defined as the time to reach maximum (peak) concentration following a dose. Actual recorded sampling times were considered for the calculations.
Time Frame	pre-dose and 4, 7, 12, 22, 72 and 168 hours after branaplam dose at Week 1 and Week 17
Analysis Population Description	Patients in the PK analysis set with an available value for the outcome measure at each timepoint. The PK Analysis Set is only applicable to patients treated with branaplam and includes all participants with at least one evaluable concentration data sample.

	Branaplam 56 mg
Arm/Group Description	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	21
Time to reach maximum plasma concentration (Tmax) of branaplam and its metabolite UFB112 (units: hours)	**Median (Full Range)**
Branaplam - Week 1 (n=21)	7.00 (3.77 to 23.0)
Branaplam - Week 17 (n=4)	4.18 (4.00 to 7.00)
UFB112 - Week 1 (n=21)	7.00 (4.00 to 72.00)
UFB112 - Week 17 (n=4)	14.5 (4.28 to 22.00)

Area under the plasma concentration-time curve from time zero to 168 hours (AUC0-168h) of branaplam and its metabolite UFB112

Description	PK parameters were calculated based on branaplam and its metabolite UFB112 plasma concentrations by using non-compartmental methods. The linear trapezoidal method was used for AUC0-168h calculation.
Time Frame	pre-dose and 4, 7, 12, 22, 72 and 168 hours after branaplam dose at Week 1 and Week 17
Analysis Population Description	Patients in the PK analysis set with an available value for the outcome measure at each timepoint. The PK Analysis Set is only applicable to patients treated with branaplam and includes all participants with at least one evaluable concentration data sample.

	Branaplam 56 mg
Arm/Group Description	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	21

Area under the plasma concentration-time curve from time zero to 168 hours (AUC0-168h) of branaplam and its metabolite UFB112 (units: hr*ng/mL)	**Mean** **± Standard Deviation**
Branaplam - Week 1 (n=20)	1880 ± 368
Branaplam - Week 17 (n=4)	3190 ± 455
UFB112 - Week 1 (n=21)	3670 ± 1560
UFB112 - Week 17 (n=4)	5640 ± 2750

Area under the plasma concentration-time curve from time zero to infinity (AUCinf) of branaplam and its metabolite UFB112

Description	PK parameters were calculated based on branaplam and its metabolite UFB112 plasma concentrations by using non-compartmental methods. The linear trapezoidal method and the regression analysis of the terminal elimination phase were used for AUCinf calculation.
Time Frame	pre-dose and 4, 7, 12, 22, 72 and 168 hours after branaplam dose at Week 1
Analysis Population Description	Patients in the PK analysis set with an available value for the outcome measure at each timepoint. The PK Analysis Set is only applicable to patients treated with branaplam and includes all participants with at least one evaluable concentration data sample.

	Branaplam 56 mg
Arm/Group Description	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	21
Area under the plasma concentration-time curve from time zero to infinity (AUCinf) of branaplam and its metabolite UFB112 (units: hr*ng/mL)	**Mean** **± Standard Deviation**
Branaplam - Week 1 (n=13)	2270 ± 467
UFB112 - Week 1 (n=1)	3530

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Trough concentration (Ctrough) of branaplam and its metabolite UFB112 in plasma

Description	Branaplam and its metabolite UFB112 concentrations were determined in plasma. Ctrough is defined as the concentration reached immediately before the next dose is administered. All drug concentrations below the lower limit of quantification were treated as zero for the calculation of PK parameters.
Time Frame	pre-dose at Weeks 2, 3, 5, 9, 13 and 17
Analysis Population Description	Patients in the PK analysis set with an available value for the outcome measure at each timepoint. The PK Analysis Set is only applicable to patients treated with branaplam and included all participants with at least one evaluable concentration data sample.

	Branaplam 56 mg
Arm/Group Description	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	20
Trough concentration (Ctrough) of branaplam and its metabolite UFB112 in plasma (units: ng/mL)	**Mean ± Standard Deviation**
Branaplam - Week 2 (n=20)	4.10 ± 1.29
Branaplam - Week 3 (n=20)	6.54 ± 1.78
Branaplam - Week 5 (n=20)	8.50 ± 3.20
Branaplam - Week 9 (n=15)	7.85 ± 2.12
Branaplam - Week 13 (n=9)	8.54 ± 2.27
Branaplam - Week 17 (n=6)	7.88 ± 2.11
UFB112 - Week 2 (n=20)	12.1 ± 6.22
UFB112 - Week 3 (n=20)	18.0 ± 8.25
UFB112 - Week 5 (n=20)	21.9 ± 11.5
UFB112 - Week 9 (n=15)	21.2 ± 11.5
UFB112 - Week 13 (n=9)	18.5 ± 8.71
UFB112 - Week 17 (n=6)	16.1 ± 5.33

Trough concentration (Ctrough) of branaplam and its metabolite UFB112 in CSF

Description	Branaplam and its metabolite UFB112 concentrations were determined in cerebrospinal fluid (CSF) obtained via lumbar puncture. Ctrough is defined as the concentration reached immediately before the next dose is administered. All drug concentrations below the lower limit of quantification were treated as zero for the calculation of PK parameters.
Time Frame	pre-dose at Weeks 9 and 17
Analysis Population Description	Patients in the PK analysis set with an available value for the outcome measure at each timepoint. The PK Analysis Set is only applicable to patients treated with branaplam and included all participants with at least one evaluable concentration data sample.

	Branaplam 56 mg
Arm/Group Description	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	12
Trough concentration (Ctrough) of branaplam and its metabolite UFB112 in CSF (units: ng/mL)	**Mean ± Standard Deviation**
Branaplam - Week 9 (n=12)	0.870 ± 0.311
Branaplam - Week 17 (n=5)	0.602 ± 0.355
UFB112 - Week 9 (n=12)	0.269 ± 0.184
UFB112 - Week 17 (n=5)	0.230 ± 0.154

Concentration ratio CSF/plasma of branaplam and its metabolite UFB112

Description	Branaplam and its metabolite UFB112 concentrations were determined plasma and in cerebrospinal fluid (CSF) obtained via lumbar puncture. Concentration ratios CSF/plasma were calculated for subjects for whom CSF and plasma concentrations were available at the respective time point.
Time Frame	pre-dose at Weeks 9 and 17
Analysis Population Description	Patients in the PK analysis set with an available value for the outcome measure at each timepoint. The PK Analysis Set is only applicable to patients treated with branaplam and included all participants with at least one evaluable concentration data sample.

	Branaplam 56 mg
Arm/Group Description	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	11
Concentration ratio CSF/plasma of branaplam and its metabolite UFB112 (units: concentration ratio)	**Mean ± Standard Deviation**
Branaplam - Week 9 (n=11)	0.115 ± NA[1]
Branaplam - Week 17 (n=4)	0.0864 ± NA[1]
UFB112 - Week 9 (n=11)	0.0141 ± NA[1]
UFB112 - Week 17 (n=4)	0.0161 ± NA[1]

[1] Standard deviation was not planned to be calculated for the concentration ratio CSF/plasma.

Other Pre-Specified Outcome Result(s)

Number of participants with NfL increase and recovery

Description	Neurofilament light chain (NfL) is a neuronal cytoplasmic protein highly expressed in large calibre myelinated axons. Its levels increase in cerebrospinal fluid (CSF) and serum in case of axonal damage in a variety of neurological disorders. The levels of NfL were determined in serum and CSF and the following 3 categories were defined: • Serum NfL (sNfL) increase: > 100 pg/mL or > 2 x baseline (BL) sNfL • sNfL recovery: Worsening criteria are no longer met (sNfL <= 100 pg/mL or sNfL <= 2 x BL sNfL) for visits after last visit with increase • CSF NfL increase: > 10000 pg/mL or > 2 x BL CSF NfL or > 2 x CSF NfL of the previous assessment
Time Frame	From baseline (before first dose of study treatment) up to Week 17 (CSF) and Week 69 (serum)
Analysis Population Description	Safety Analysis Set including all participants who received at least one dose of study drug. sNfL recovery was assessed in participants meeting the criterion for sNfL increase.

	Placebo	Branaplam 56 mg

Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly
Number of Participants Analyzed [units: participants]	5	21
Number of participants with NfL increase and recovery (units: participants)	**Count of Participants (Not Applicable)**	**Count of Participants (Not Applicable)**
sNfL increase (n=5, 21)	0 (%)	16 (76.19%)
sNfL recovery (n=0, 16)	0 (NaN%)	14 (87.5%)
CSF NfL increase (n=5, 21)	0 (%)	13 (61.9%)

Safety Results

Time Frame	From first dose of study treatment up to Week 69
Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Placebo N = 5	**Branaplam 56 mg N = 21**	**Overall N = 26**

Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly	All participants
Total Number Affected	0	0	0
Total Number At Risk	5	21	26

Serious Adverse Events

Time Frame	From first dose of study treatment up to Week 69
Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment

	Placebo N = 5	**Branaplam 56 mg N = 21**	**Overall N = 26**
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly	All participants
Total # Affected by any Serious Adverse Event	0	4	4
Total # at Risk by any Serious Adverse Event	5	21	26
Infections and infestations			
Vestibular neuronitis	0 (0.00%)	1 (4.76%)	1 (3.85%)
Injury, poisoning and procedural complications			

Subdural haematoma	0 (0.00%)	2 (9.52%)	2 (7.69%)
Reproductive system and breast disorders			
Uterine polyp	0 (0.00%)	1 (4.76%)	1 (3.85%)

Other (Not Including Serious) Adverse Events

Time Frame	From first dose of study treatment up to Week 69
Source Vocabulary for Table Default	MedDRA (26.1)
Collection Approach for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 5%

	Placebo N = 5	**Branaplam 56 mg N = 21**	**Overall N = 26**
Arm/Group Description	Treatment Arm A: matching placebo oral solution once weekly	Treatment Arm A: branaplam 56 mg oral solution once weekly	All participants
Total # Affected by any Other Adverse Event	2	15	17
Total # at Risk by any Other Adverse Event	5	21	26

Blood and lymphatic system disorders			
Anaemia	1 (20.00%)	4 (19.05%)	5 (19.23%)
Thrombocytosis	0 (0.00%)	2 (9.52%)	2 (7.69%)
Gastrointestinal disorders			
Diarrhoea	0 (0.00%)	2 (9.52%)	2 (7.69%)
General disorders and administration site conditions			
Puncture site pain	0 (0.00%)	3 (14.29%)	3 (11.54%)
Infections and infestations			
COVID-19	1 (20.00%)	2 (9.52%)	3 (11.54%)
Cystitis	0 (0.00%)	3 (14.29%)	3 (11.54%)
Urinary tract infection	0 (0.00%)	3 (14.29%)	3 (11.54%)
Injury, poisoning and procedural complications			
Head injury	0 (0.00%)	2 (9.52%)	2 (7.69%)
Musculoskeletal and connective tissue disorders			
Back pain	0 (0.00%)	2 (9.52%)	2 (7.69%)
Muscular weakness	0 (0.00%)	2 (9.52%)	2 (7.69%)
Nervous system disorders			
Balance disorder	0 (0.00%)	2 (9.52%)	2 (7.69%)
Headache	1 (20.00%)	2 (9.52%)	3 (11.54%)
Neuropathy peripheral	0 (0.00%)	2 (9.52%)	2 (7.69%)
Paraesthesia	1 (20.00%)	2 (9.52%)	3 (11.54%)
Polyneuropathy	0 (0.00%)	3 (14.29%)	3 (11.54%)

Psychiatric disorders			
Delusional disorder, persecutory type	1 (20.00%)	0 (0.00%)	1 (3.85%)
Reproductive system and breast disorders			
Benign prostatic hyperplasia	0 (0.00%)	2 (9.52%)	2 (7.69%)
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain	1 (20.00%)	0 (0.00%)	1 (3.85%)

Conclusion:

Development of LMI070 in HD was stopped due to signs/symptoms potentially indicative of peripheral neuropathy noticed in the branaplam 56 mg cohort. However, branaplam 56 mg did lower mHTT protein levels in the CSF as expected, demonstrating for the first time that an oral HTT lowering drug is able to reduce mHTT levels in the brain. In serum, NfL was used as an exploratory safety measure in the study, and the results demonstrate that it was effective as an early indicator of potential peripheral neuropathy. The participants who developed new symptoms and/or neurophysiological findings indicative of peripheral neuropathy who remained in the study after stopping treatment were noted to have improvement in most of their initial symptoms with an accompanied recovery observed in some participant's neurophysiological assessments. While an increase in lateral ventricle volume was evident in most participants receiving LMI070 56 mg, this was not associated with an adverse effect on cognitive or functional HD measures, and demonstrated reversal after treatment was stopped. The underlying cause of the increase in lateral ventricle volume is uncertain, but it is likely either due to an impact on CSF flow dynamics following the reduction in normal HTT protein, or a transient neurotoxic effect, or a combination of both.

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Date of Clinical Trial Report

18-Apr-2024