



## Clinical trial results:

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

#### Summary

EudraCT number	2020-000105-92
Trial protocol	DE HU ES FR IT BE LT
Global end of trial date	23 October 2023

#### Results information

Result version number	v1 (current)
This version publication date	12 September 2024
First version publication date	12 September 2024

#### Trial information

##### Trial identification

Sponsor protocol code	CLMI070C12203
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05111249
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis campus, Basel, Switzerland, CH-4056
Public contact	Clinical Disclosure Office, Novartis Pharma AS, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 October 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	23 October 2023
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

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)

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 December 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 6
Country: Number of subjects enrolled	Hungary: 5
Country: Number of subjects enrolled	Spain: 9
Worldwide total number of subjects	26
EEA total number of subjects	23

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0

Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	24
From 65 to 84 years	2
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Participants took part in 12 investigative sites in 5 countries.

### Pre-assignment

Screening details:

Screening period lasted up to 6 weeks. For eligible participants, baseline measurements were performed within 6 days prior to first dose of study treatment. In the Core period participants were randomized (4:1) to receive either branaplam or placebo.

The last study visit was performed at Week 69. The open label extension (OLE) period was not opened

### Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Placebo

Arm description:

Treatment Arm A: matching placebo oral solution once weekly

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Placebo oral solution administered once weekly.

<b>Arm title</b>	Branaplam 56 mg
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Arm description:

Treatment Arm A: branaplam 56 mg oral solution once weekly

Arm type	Experimental
Investigational medicinal product name	Branaplam
Investigational medicinal product code	LMI070
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Branaplam 56 mg oral solution administered once weekly. Branaplam was administered up to maximum 22 weeks.

<b>Number of subjects in period 1</b>	Placebo	Branaplam 56 mg
Started	5	21
Completed	4	13
Not completed	1	8
Physician decision	-	1
Participant decision	1	5
Lost to follow-up	-	2

## Baseline characteristics

### Reporting groups

Reporting group title	Placebo
Reporting group description:	
Treatment Arm A: matching placebo oral solution once weekly	
Reporting group title	Branaplam 56 mg
Reporting group description:	
Treatment Arm A: branaplam 56 mg oral solution once weekly	

Reporting group values	Placebo	Branaplam 56 mg	Total
Number of subjects	5	21	26
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	19	24
From 65-84 years	0	2	2
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	52.8	49.6	
standard deviation	± 15.30	± 10.06	-
Sex: Female, Male			
Units: participants			
Female	1	10	11
Male	4	11	15
Race/Ethnicity, Customized			
Units: Subjects			
White	5	18	23
Unknown	0	3	3

## End points

### End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Treatment Arm A: matching placebo oral solution once weekly	
Reporting group title	Branaplam 56 mg
Reporting group description:	
Treatment Arm A: branaplam 56 mg oral solution once weekly	

### Primary: Percentage change from baseline to Week 17 in mHTT protein in CSF

End point title	Percentage change from baseline to Week 17 in mHTT protein in CSF <sup>[1]</sup>
End point 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.	
End point type	Primary
End point timeframe:	
Baseline, Week 17	
Notes:	
[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.	
Justification: No statistical analysis were planned for this endpoint.	

End point values	Placebo	Branaplam 56 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	9		
Units: % change in mHTT protein				
arithmetic mean (standard deviation)	-1.38 (± 20.517)	-26.61 (± 22.354)		

### Statistical analyses

No statistical analyses for this end point

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

End point title	Number of participants with adverse events (AEs) and serious adverse events (SAEs) <sup>[2]</sup>
End point 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).	
End point type	Primary

End point timeframe:

From first dose of study treatment up to Week 69

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical analysis were planned for this endpoint.

End point values	Placebo	Branaplam 56 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	21		
Units: participants				
AEs	2	18		
Study drug-related AEs	1	14		
SAEs	0	4		
Study drug-related SAEs	0	3		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage change from baseline in total brain volume

End point title	Percentage change from baseline in total brain volume
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End point 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.

Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary
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End point timeframe:

Baseline, Week 17, Week 33, Week 53, Week 69

End point values	Placebo	Branaplam 56 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	17		
Units: % change in total brain volume				
arithmetic 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 (± 999)	-1.34 (± 0.848)		
Week 69 (n=0, 12)	999 (± 999)	-1.63 (± 0.877)		



## Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage change from baseline in total brain volume excluding patients with subdural hematoma
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End point 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.

Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary
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End point timeframe:

Baseline, Week 17, Week 33, Week 53, Week 69

End point values	Placebo	Branaplam 56 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	15		
Units: % change in total brain volume arithmetic 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 (± 999)	-1.30 (± 0.748)		
Week 69 (n=0, 10)	999 (± 999)	-1.68 (± 0.751)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage change from baseline in lateral ventricles volume

End point title	Percentage change from baseline in lateral ventricles volume
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End point 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.

Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary
End point timeframe:	
Baseline, Week 17, Week 33, Week 53, Week 69	

End point values	Placebo	Branaplam 56 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	17		
Units: % change in lateral ventricles volume				
arithmetic 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 (± 999)	15.77 (± 10.842)		
Week 69 (n=0, 12)	999 (± 999)	17.40 (± 10.182)		

## Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage change from baseline in lateral ventricles volume excluding patients with subdural hematoma
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End point 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.

Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary
End point timeframe:	
Baseline, Week 17, Week 33, Week 53, Week 69	

End point values	Placebo	Branaplam 56 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	15		
Units: % change in lateral ventricles volume				
arithmetic 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 (± 999)	12.38 (± 6.193)		
Week 69 (n=0, 10)	999 (± 999)	14.45 (± 6.040)		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage change from baseline in left caudate volume

End point title	Percentage change from baseline in left caudate volume
End point description:	
<p>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.</p> <p>Changes in volumetric MRI were measured in regions of interests: ventricular, caudate (left and right) and total brain volume.</p> <p>The baseline MRI scan was obtained within 6 days prior to the first dose of study treatment.</p> <p>Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.</p>	
End point type	Secondary
End point timeframe:	
Baseline, Week 17, Week 33, Week 53, Week 69	

End point values	Placebo	Branaplam 56 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	17		
Units: % change in left caudate volume				
arithmetic 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 (± 999)	-6.33 (± 4.417)		
Week 69 (n=0, 12)	999 (± 999)	-5.44 (± 7.864)		

## Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage change from baseline in left caudate volume excluding patients with subdural hematoma
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End point 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.

Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary
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End point timeframe:

Baseline, Week 17, Week 33, Week 53, Week 69

End point values	Placebo	Branaplam 56 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4	15		
Units: % change in left caudate volume				
arithmetic 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 (± 999)	-6.24 (± 4.788)		
Week 69 (n=0, 10)	999 (± 999)	-4.81 (± 8.351)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Percentage change from baseline in right caudate volume

End point title	Percentage change from baseline in right caudate volume
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End point 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.

Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary
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End point timeframe:

Baseline, Week 17, Week 33, Week 53, Week 69

End point values	Placebo	Branaplam 56 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	17		
Units: % change in right caudate volume				
arithmetic 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 (± 999)	-6.81 (± 4.251)		
Week 69 (n=0, 12)	999 (± 999)	-6.34 (± 6.934)		

## Statistical analyses

No statistical analyses for this end point

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

End point title	Percentage change from baseline in right caudate volume excluding patients with subdural hematoma
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End point 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.

Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary
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End point timeframe:

Baseline, Week 17, Week 33, Week 53, Week 69

End point values	Placebo	Branaplam 56 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3	15		
Units: % change in right caudate volume				
arithmetic mean (standard deviation)				
Week 17 (n=3, 15)	-3.28 (± 3.496)	-2.67 (± 4.850)		

Week 33 (n=3, 15)	-6.91 ( $\pm$ 1.895)	-3.23 ( $\pm$ 3.437)		
Week 53 (n=1, 9)	-5.34 ( $\pm$ 999)	-6.57 ( $\pm$ 4.418)		
Week 69 (n=0, 10)	999 ( $\pm$ 999)	-5.60 ( $\pm$ 7.249)		

## Statistical analyses

No statistical analyses for this end point

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

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

Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary
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End point timeframe:

Baseline, Week 17, Week 33 and Week 69

End point values	Placebo	Branaplam 56 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	19		
Units: score on scale				
arithmetic mean (standard deviation)				
Week 17 (n=5, 19)	-1.0 ( $\pm$ 2.35)	-0.8 ( $\pm$ 2.39)		
Week 33 (n=4, 17)	-0.5 ( $\pm$ 2.52)	-1.3 ( $\pm$ 2.31)		
Week 69 (n=0, 13)	999 ( $\pm$ 999)	-1.2 ( $\pm$ 2.94)		

## Statistical analyses

No statistical analyses for this end point

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

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

Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary
End point timeframe:	
Baseline, Week 17, Week 33 and Week 69	

End point values	Placebo	Branaplam 56 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	19		
Units: score on scale				
arithmetic 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)	999 (± 999)	3.6 (± 8.99)		

## Statistical analyses

No statistical analyses for this end point

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

End point title	Change from baseline in the Unified Huntington's Disease Rating Scales (UHDRS) Independence Scale (IS)
End point description:	
<p>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.</p> <p>Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.</p>	
End point type	Secondary
End point timeframe:	
Baseline, Week 17, Week 33 and Week 69	

End point values	Placebo	Branaplam 56 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	19		
Units: score on scale				
arithmetic 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)	999 (± 999)	-6.5 (± 13.29)		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Concentrations of mHTT protein and total HTT in plasma

End point title	Concentrations of mHTT protein and total HTT in plasma
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End point 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.

End point type	Secondary
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End point timeframe:

Baseline, Week 17

End point values	Placebo	Branaplam 56 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 <sup>[3]</sup>	0 <sup>[4]</sup>		
Units: fmol				
arithmetic mean (standard deviation)				
mHTT - Baseline	()	()		
mHTT - Week 17	()	()		
Total HTT - Baseline	()	()		
Total HTT - Week 17	()	()		

Notes:

[3] - Assay issues did not allow a reliable quantification of mHTT protein and total HTT in plasma.

[4] - Assay issues did not allow a reliable quantification of mHTT protein and total HTT in plasma.

## Statistical analyses

No statistical analyses for this end point

### Secondary: Concentrations of mHTT protein and total HTT in CSF

End point title	Concentrations of mHTT protein and total HTT in CSF
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End point 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.

Assay issues did not allow a reliable quantification of total HTT in CSF. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not available'). Therefore, not available values are indicated as '999'.

End point type	Secondary
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End point timeframe:

Baseline, Week 9, Week 17



End point values	Placebo	Branaplam 56 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	21		
Units: fmol				
arithmetic 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)	999 (± 999)	999 (± 999)		
Total HTT - Week 9 (n=0, 0)	999 (± 999)	999 (± 999)		
Total HTT - Week 17 (n=0, 0)	999 (± 999)	999 (± 999)		

### Statistical analyses

No statistical analyses for this end point

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

End point title	Maximum observed plasma concentration (Cmax) of branaplam and its metabolite UFB112 <sup>[5]</sup>
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End point 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.

End point type	Secondary
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End point timeframe:

pre-dose and 4, 7, 12, 22, 72 and 168 hours after branaplam dose at Week 1 and Week 17

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is applicable to branaplam arm only.

End point values	Branaplam 56 mg			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: ng/mL				
arithmetic 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)			

## Statistical analyses

No statistical analyses for this end point

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

End point title	Time to reach maximum plasma concentration (Tmax) of branaplam and its metabolite UFB112 <sup>[6]</sup>
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End point 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.

End point type	Secondary
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End point timeframe:

pre-dose and 4, 7, 12, 22, 72 and 168 hours after branaplam dose at Week 1 and Week 17

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint is applicable to branaplam arm only.

<b>End point values</b>	Branaplam 56 mg			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: hours				
median (full range (min-max))				
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)			

## Statistical analyses

No statistical analyses for this end point

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

End point title	Area under the plasma concentration-time curve from time zero to 168 hours (AUC0-168h) of branaplam and its metabolite UFB112 <sup>[7]</sup>
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End point 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.

End point type	Secondary
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End point timeframe:

pre-dose and 4, 7, 12, 22, 72 and 168 hours after branaplam dose at Week 1 and Week 17

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is applicable to branaplam arm only.

<b>End point values</b>	Branaplam 56 mg			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: hr*ng/mL				
arithmetic 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)			

## Statistical analyses

No statistical analyses for this end point

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

End point title	Area under the plasma concentration-time curve from time zero to infinity (AUCinf) of branaplam and its metabolite UFB112 <sup>[8]</sup>
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End point 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.

Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary
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End point timeframe:

pre-dose and 4, 7, 12, 22, 72 and 168 hours after branaplam dose at Week 1

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is applicable to branaplam arm only.

<b>End point values</b>	Branaplam 56 mg			
Subject group type	Reporting group			
Number of subjects analysed	21			
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
Branaplam - Week 1 (n=13)	2270 (± 467)			
UFB112 - Week 1 (n=1)	3530 (± 999)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Trough concentration (C<sub>trough</sub>) of branaplam and its metabolite UFB112 in plasma

End point title	Trough concentration (C <sub>trough</sub> ) of branaplam and its metabolite UFB112 in plasma <sup>[9]</sup>
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End point description:

Branaplam and its metabolite UFB112 concentrations were determined in plasma. C<sub>trough</sub> 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.

End point type	Secondary
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End point timeframe:

pre-dose at Weeks 2, 3, 5, 9, 13 and 17

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is applicable to branaplam arm only.

End point values	Branaplam 56 mg			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: ng/mL				
arithmetic 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)			

## Statistical analyses

No statistical analyses for this end point

### Secondary: Trough concentration (C<sub>trough</sub>) of branaplam and its metabolite UFB112

## in CSF

End point title	Trough concentration (C <sub>trough</sub> ) of branaplam and its metabolite UFB112 in CSF <sup>[10]</sup>
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### End point description:

Branaplam and its metabolite UFB112 concentrations were determined in cerebrospinal fluid (CSF) obtained via lumbar puncture. C<sub>trough</sub> 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.

End point type	Secondary
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### End point timeframe:

pre-dose at Weeks 9 and 17

### Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is applicable to branaplam arm only.

<b>End point values</b>	Branaplam 56 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: ng/mL				
arithmetic 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)			

## Statistical analyses

No statistical analyses for this end point

## Secondary: Concentration ratio CSF/plasma of branaplam and its metabolite UFB112

End point title	Concentration ratio CSF/plasma of branaplam and its metabolite UFB112 <sup>[11]</sup>
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### End point 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.

Standard deviation was not planned to be calculated for the concentration ratio CSF/plasma. Since data fields in the table cannot contain letters (eg. NA indicating 'not available') due to EudraCT system limitations, NA values are indicated as '999'.

End point type	Secondary
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### End point timeframe:

pre-dose at Weeks 9 and 17

### Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: This endpoint is applicable to branaplam arm only.

<b>End point values</b>	Branaplam 56 mg			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: concentration ratio				
arithmetic mean (standard deviation)				
Branaplam - Week 9	0.115 (± 999)			
Branaplam - Week 17	0.0864 (± 999)			
UFB112 - Week 9	0.0141 (± 999)			
UFB112 - Week 17	0.0161 (± 999)			

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Number of participants with NfL increase and recovery

End point title	Number of participants with NfL increase and recovery
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End point 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

End point type	Other pre-specified
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End point timeframe:

From baseline (before first dose of study treatment) up to Week 17 (CSF) and Week 69 (serum)

<b>End point values</b>	Placebo	Branaplam 56 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	21		
Units: participants				
sNfL increase (n=5, 21)	0	16		
sNfL recovery(n=0, 16)	0	14		
CSF NfL increase (n=5, 21)	0	13		

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From first dose of study treatment up to Week 69

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.1
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### Reporting groups

Reporting group title	Placebo
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Reporting group description:

Treatment Arm A: matching placebo oral solution once weekly

Reporting group title	Overall
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Reporting group description:

All participants

Reporting group title	Branaplam 56 mg
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Reporting group description:

Treatment Arm A: branaplam 56 mg oral solution once weekly

Serious adverse events	Placebo	Overall	Branaplam 56 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	4 / 26 (15.38%)	4 / 21 (19.05%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 5 (0.00%)	2 / 26 (7.69%)	2 / 21 (9.52%)
occurrences causally related to treatment / all	0 / 0	2 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Uterine polyp			
subjects affected / exposed	0 / 5 (0.00%)	1 / 26 (3.85%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Vestibular neuronitis			

subjects affected / exposed	0 / 5 (0.00%)	1 / 26 (3.85%)	1 / 21 (4.76%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

<b>Non-serious adverse events</b>	Placebo	Overall	Branaplam 56 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 5 (40.00%)	17 / 26 (65.38%)	15 / 21 (71.43%)
Injury, poisoning and procedural complications			
Head injury			
subjects affected / exposed	0 / 5 (0.00%)	2 / 26 (7.69%)	2 / 21 (9.52%)
occurrences (all)	0	2	2
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 5 (20.00%)	3 / 26 (11.54%)	2 / 21 (9.52%)
occurrences (all)	1	3	2
Balance disorder			
subjects affected / exposed	0 / 5 (0.00%)	2 / 26 (7.69%)	2 / 21 (9.52%)
occurrences (all)	0	2	2
Polyneuropathy			
subjects affected / exposed	0 / 5 (0.00%)	3 / 26 (11.54%)	3 / 21 (14.29%)
occurrences (all)	0	3	3
Paraesthesia			
subjects affected / exposed	1 / 5 (20.00%)	3 / 26 (11.54%)	2 / 21 (9.52%)
occurrences (all)	1	4	3
Neuropathy peripheral			
subjects affected / exposed	0 / 5 (0.00%)	2 / 26 (7.69%)	2 / 21 (9.52%)
occurrences (all)	0	2	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 5 (20.00%)	5 / 26 (19.23%)	4 / 21 (19.05%)
occurrences (all)	1	7	6
Thrombocytosis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 26 (7.69%)	2 / 21 (9.52%)
occurrences (all)	0	2	2



General disorders and administration site conditions Puncture site pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	3 / 26 (11.54%) 3	3 / 21 (14.29%) 3
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 26 (7.69%) 3	2 / 21 (9.52%) 3
Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0	2 / 26 (7.69%) 2	2 / 21 (9.52%) 2
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 26 (3.85%) 1	0 / 21 (0.00%) 0
Psychiatric disorders Delusional disorder, persecutory type subjects affected / exposed occurrences (all)	1 / 5 (20.00%) 1	1 / 26 (3.85%) 1	0 / 21 (0.00%) 0
Musculoskeletal and connective tissue disorders Muscular weakness subjects affected / exposed occurrences (all)  Back pain subjects affected / exposed occurrences (all)	0 / 5 (0.00%) 0  0 / 5 (0.00%) 0	2 / 26 (7.69%) 2  2 / 26 (7.69%) 3	2 / 21 (9.52%) 2  2 / 21 (9.52%) 3
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)  Cystitis subjects affected / exposed occurrences (all)  Urinary tract infection	1 / 5 (20.00%) 1  0 / 5 (0.00%) 0	3 / 26 (11.54%) 3  3 / 26 (11.54%) 4	2 / 21 (9.52%) 2  3 / 21 (14.29%) 4

subjects affected / exposed	0 / 5 (0.00%)	3 / 26 (11.54%)	3 / 21 (14.29%)
occurrences (all)	0	3	3

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 May 2022	• Revisions to the exploratory objectives; • Clarification of language in several protocol sections
30 January 2023	This amendment documented the changes regarding follow-up of participants after the Urgent Safety Measure (USM) Investigator Notifications (IN) distributed on 05-Aug-2022 and 06-Dec-2022, addressing temporary and then permanent study treatment discontinuation, respectively.

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 August 2022	The Urgent Safety Measure (USM) Investigator Notification (IN) (05-Aug-2022) was issued by Novartis to immediately and temporarily suspend study treatment for all participants in the study. With the USM Follow-up IN (06-Dec-2022), study drug was permanently discontinued in the VIBRANT-HD study and no further cohorts were initiated. Participants randomized to placebo did not require additional safety assessments and could be discontinued from the study at their upcoming Week 33 visit or immediately if this visit had already been completed. Participants randomized to branaplam were requested to continue assessments for approximately one year from last dose.	-

Notes:

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/#/>

Notes: