Clinical trial results:
A multicenter, single-arm, open-label trial to evaluate efficacy and safety of oral, twice daily iptacopan in adult PNH patients who are naive to complement inhibitor therapy

Summary

EudraCT number	2020-003172-41
Trial protocol	FR CZ IT
Global end of trial date	18 April 2023

Results information

Result version number	v1 (current)
This version publication date	25 April 2024
First version publication date	25 April 2024

Trial information

Trial identification

Sponsor protocol code	CLNP023C12301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04820530
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 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	18 April 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Increase from baseline Hb levels ≥ 2 g/dL (assessed between Day 126 and Day 168) in the absence of RBC transfusion between Day 14 and Day 168.

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	19 July 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	Korea, Republic of: 2
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	China: 20
Country: Number of subjects enrolled	France: 4
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Italy: 2
Worldwide total number of subjects	40
EEA total number of subjects	10

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	37
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 12 investigative sites in 8 countries: France(1), United Kingdom(1), Italy(1), Korea, Republic of(1), Singapore(1), China(3), Malaysia(2), Germany(2)

Pre-assignment

Screening details:

All patients provided written informed consent prior to the start of any study-related activities. Vaccination against Neisseria meningitidis, Streptococcus pneumoniae and Haemophilus influenzae infections was required prior to the start of treatment.

Period 1

Period 1 title	Core treatment period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	LNP023

Arm description:

Participants receive LNP023 at a dose of 200 mg b.i.d. orally

Arm type	Experimental
Investigational medicinal product name	Iptacopan
Investigational medicinal product code	LNP023
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

LNP023 200mg b.i.d.

Number of subjects in period 1	LNP023
Started	40
Completed	40

Period 2

Period 2 title	Extension treatment period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	LNP023

Arm description:

Participants receive LNP023 at a dose of 200 mg b.i.d. orally

Arm type	Experimental
Investigational medicinal product name	Iptacopan
Investigational medicinal product code	LNP023
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

LNP023 200mg b.i.d.

Number of subjects in period 2	LNP023
Started	40
Completed	40

Baseline characteristics

Reporting groups	
Reporting group title	LNP023
Reporting group description:	
Participants receive LNP023 at a dose of 200 mg b.i.d. orally	

Reporting group values	LNP023	Total	
Number of subjects	40	40	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	37	37	
From 65-84 years	3	3	
85 years and over	0	0	
Age Continuous Units: years			
arithmetic mean	42.1		
standard deviation	± 15.85	-	
Sex: Female, Male Units: participants			
Female	17	17	
Male	23	23	
Race/Ethnicity, Customized Units: Subjects			
White	12	12	
Black or African American	1	1	
Asian	27	27	

End points

End points reporting groups

Reporting group title	LNP023
Reporting group description:	
Participants receive LNP023 at a dose of 200 mg b.i.d. orally	
Reporting group title	LNP023
Reporting group description:	
Participants receive LNP023 at a dose of 200 mg b.i.d. orally	

Primary: Marginal Proportion (expressed as percentage) of participants with sustained increase in hemoglobin levels from baseline of ≥ 2 g/dL in the absence of red blood cell transfusions

End point title	Marginal Proportion (expressed as percentage) of participants with sustained increase in hemoglobin levels from baseline of ≥ 2 g/dL in the absence of red blood cell transfusions[1]

End point description:

Sustained increase in hemoglobin levels (responder) is defined as an increase from baseline in hemoglobin levels of ≥ 2 g/dL on three out of four measurements between Day 126 and 168 of the core treatment period, without requiring red blood cell (RBC) transfusions between Day 14 and Day 168. Requiring RBC transfusions refers to any patient receiving transfusions or meeting protocol defined criteria (Hemoglobin level of ≤9 g/dL (≤8 g/dL for Chinese population) with signs and or symptoms of sufficient severity to warrant a transfusion or Hemoglobin of ≤7 g/dL (≤6 g/dL for Chinese population), regardless of presence of clinical signs and/or symptoms).
The term 'marginal proportion' can be interpreted as the population average probability of being a responder. Results incorporated a method to handle missing data using multiple imputation. Hence, all 40 patients enrolled contributed to the primary analysis.

End point type	Primary

End point timeframe:

Baseline, hemoglobin between Day 126 and Day 168 and absence of transfusions between Day 14 and Day 168

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 was planned for this primary outcome

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Percentage of responders				
number (confidence interval 95%)	92.2 (82.5 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Marginal proportion (expressed as percentage) of participants who remain free from transfusions

End point title	Marginal proportion (expressed as percentage) of participants

	who remain free from transfusions

End point description:

Marginal proportion (expressed as percentage) of participants who did not require transfusions between Day 14 and Day 168.
Requiring RBC transfusions refers to any patient receiving transfusions or meeting protocol defined criteria (Hemoglobin level of ≤9 g/dL (≤8 g/dL for Chinese population) with signs and or symptoms of sufficient severity to warrant a transfusion or Hemoglobin of ≤7 g/dL (≤6 g/dL for Chinese population), regardless of presence of clinical signs and/or symptoms). The term 'marginal proportion' can be interpreted as the population average probability of being a responder.
The 95% CI was obtained using the bootstrap method

End point type	Secondary

End point timeframe:

Between Day 14 and Day 168

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Percentage of participants				
number (confidence interval 95%)	97.6 (92.5 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Marginal proportion (expressed as percentage) with sustained hemoglobin levels of ≥ 12 g/dL in the absence of red blood cell transfusions

End point title	Marginal proportion (expressed as percentage) with sustained hemoglobin levels of ≥ 12 g/dL in the absence of red blood cell transfusions

End point description:

Sustained hemoglobin levels (responder) is defined as hemoglobin levels ≥ 12 g/dL on three out of four measurements between Day 126 and 168 of the core treatment period, without requiring red blood cell (RBC) transfusions between Day 14 and Day 168. Requiring RBC transfusions refers to any patient receiving transfusions or meeting protocol defined criteria (Hemoglobin level of ≤9 g/dL (≤8 g/dL for Chinese population) with signs and or symptoms of sufficient severity to warrant a transfusion or Hemoglobin of ≤7 g/dL (≤6 g/dL for Chinese population), regardless of presence of clinical signs and/or symptoms).
The term 'marginal proportion' can be interpreted as the population average probability of being a responder. Results incorporated a method to handle missing data using multiple imputation. Hence, all 40 patients enrolled contributed to the analysis.

End point type	Secondary

End point timeframe:

Hemoglobin between Day 126 and Day 168 and absence of transfusions between Day 14 and Day 168

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Percentage of responders				
number (confidence interval 95%)	62.8 (47.5 to 77.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in hemoglobin levels in the core treatment period

End point title	Change from baseline in hemoglobin levels in the core treatment period

End point description:

Change from baseline in hemoglobin levels as mean of visits between Day 126 and Day 168.
In order to factor out the effect of transfusions in this analysis, if a patient had a transfusion during the core treatment period, the hemoglobin (Hb) values during 30 days following the transfusion were excluded and Hb data were imputed.
Change from baseline was analyzed using a mixed model of repeated measures which included age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, and baseline hemoglobin as fixed effects and the interaction between visit and baseline hemoglobin levels.

End point type	Secondary

End point timeframe:

Baseline, Day 126 to 168

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: g/dL				
arithmetic mean (confidence interval 95%)	4.28 (3.87 to 4.70)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change from baseline in LDH

End point title	Percent change from baseline in LDH

End point description:

Percent change from baseline in lactate dehydrogenase (LDH) levels as mean of visits between Day 126 and Day 168.
Percentage change from baseline was analyzed using a mixed model for repeated measures (MMRM) which includes age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, baseline LDH as fixed effects and visit*baseline LDH as interaction.
Results incorporated a method to handle missing data using multiple imputation. Hence, all 40 patients enrolled contributed to the analysis.

End point type	Secondary

End point timeframe:

Baseline, Day 126 to 168

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Percent change from baseline in LDH				
arithmetic mean (confidence interval 95%)	-83.55 (-84.90 to -82.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted annualized Major Adverse Vascular Events rate in the core treatment period

End point title	Adjusted annualized Major Adverse Vascular Events rate in the core treatment period

End point description:

Adjusted annual rate is carried out using the Wilson method. A MAVE is defined as: acute peripheral vascular occlusion, amputation (non-traumatic; nondiabetic), cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, dermal thrombosis, gangrene (non-traumatic; nondiabetic), hepatic/portal vein thrombosis (Budd-Chiari syndrome), mesenteric/visceral arterial, thrombosis or infarction, mesenteric/visceral vein thrombosis or infarction, myocardial infarction, pulmonary embolus, renal arterial thrombosis, renal vein thrombosis, thrombophlebitis / deep vein thrombosis, transient ischemic attack, unstable angina or other.

End point type	Secondary

End point timeframe:

Between Day 1 and Day 168

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: MAVE events/year				
number (confidence interval 95%)	0.00 (0.00 to 0.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in absolute reticulocyte count

End point title	Change from baseline in absolute reticulocyte count

End point description:

Change from baseline in absolute reticulocyte counts as mean of visits between Day 126 and Day 168. Change from baseline was analyzed using a MMRM which includes age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, baseline reticulocyte counts as fixed effects and visit*baseline reticulocyte counts as interaction.

End point type	Secondary

End point timeframe:

Baseline and mean of visits between Day 126 and 168

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: x10^9 cells/L				
arithmetic mean (confidence interval 95%)	-82.48 (-89.33 to -75.62)			

Statistical analyses

No statistical analyses for this end point

Secondary: Adjusted annualized clinical BTH rate in the core treatment period

End point title	Adjusted annualized clinical BTH rate in the core treatment period

End point description:

Adjusted annualized rate of clinical breakthrough hemolysis (BTH) events is carried out using the Wilson method. The breakthrough is defined clinical if either there is a decrease in hemoglobin levels equal to or more than 2 g/dL (compared to the latest assessment, or within 15 days) or if patients present signs or symptoms of gross hemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs & symptoms, in presence of laboratory evidence of intravascular hemolysis.

End point type	Secondary

End point timeframe:

Between Day 1 and Day 168

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: BTH events/year				
number (confidence interval 95%)	0.00 (0.00 to 0.17)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in FACIT-Fatigue score between Day 126 and Day 168

End point title	Change from baseline in FACIT-Fatigue score between Day 126 and Day 168

End point description:

Change from baseline in FACIT-Fatigue scores as mean of visits between Day 126 and Day 168. The FACIT-Fatigue is a 13-item questionnaire with support for its validity and reliability in PNH that assesses patient self-reported fatigue and its impact on daily activities and function. All FACIT scales are scored so that a high score is better. As each of the 13 items of the FACIT-F Scale ranges from 0-4, the range of possible scores is 0-52, with 0 being the worst possible score and 52 the best.
Change from baseline was analyzed using a Mixed Model of Repeated Measures (MMRM) which includes age (indicator variable of age ≥ 45 years), sex, history of transfusion (yes/no) prior to study treatment, visit, baseline FACIT-Fatigue score as fixed effects and visit*baseline FACIT-Fatigue score as interaction.

End point type	Secondary

End point timeframe:

Baseline and mean of visits between Day 126 and Day 168

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: score on a scale				
arithmetic mean (confidence interval 95%)	10.75 (8.66 to 12.84)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Marginal Proportion (expressed as percentage) of patients not receiving and not requiring RBC transfusions

End point title	Marginal Proportion (expressed as percentage) of patients not receiving and not requiring RBC transfusions

End point description:

Requiring Red Blood Cells (RBC) transfusions refers to any patient receiving transfusions or meeting protocol defined criteria (Hemoglobin level of ≤9 g/dL (≤8 g/dL for Chinese population) with signs and or symptoms of sufficient severity to warrant a transfusion or Hemoglobin of ≤7 g/dL (≤6 g/dL for Chinese population), regardless of presence of clinical signs and/or symptoms).

End point type	Other pre-specified

End point timeframe:

Between Day 14 and Day 336

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: Percentage of participants				
number (confidence interval 95%)	97.5 (92.5 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Percentage of patients meeting hematological response criteria irrespective of RBC transfusions

End point title	Percentage of patients meeting hematological response criteria irrespective of RBC transfusions

End point description:

Patients with hematological response are those with an increase in Hb from baseline ≥ 2g/dL irrespective of red blood cell (RBC) transfusions and patients achieving Hb ≥ 12g/dL irrespective of RBC transfusions.

End point type	Other pre-specified

End point timeframe:

Baseline, Day 336

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: Percentage of participants				
number (not applicable)				
≥2 g/dL increase in Hb from baseline Hb ≥ 12g/dL	97.4 79.5			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline in Hemoglobin levels

End point title	Change from baseline in Hemoglobin levels

End point description:

Change from baseline in Hemoglobin at Visit Day 336

End point type	Other pre-specified

End point timeframe:

Baseline, Day 336

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: g/dL				
arithmetic mean (standard deviation)	5.09 (± 2.010)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline in LDH at Visit Day 336

End point title	Change from baseline in LDH at Visit Day 336

End point description:

Change from baseline in Lactate dehydrogenase (LDH) at Visit Day 336

End point type	Other pre-specified

End point timeframe:

Baseline, Day 336

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: U/L				
arithmetic mean (standard deviation)	-1393.3 (± 652.15)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Adjusted annualized clinical BTH rate after the start of LNP023 treatment

End point title	Adjusted annualized clinical BTH rate after the start of LNP023 treatment

End point description:

Adjusted annualized rate of clinical breakthrough hemolysis (BTH) events is carried out using the Wilson method. The breakthrough is defined clinical if either there is a decrease in hemoglobin levels equal to or more than 2 g/dL (compared to the latest assessment, or within 15 days) or if patients present signs or symptoms of gross hemoglobinuria, painful crisis, dysphagia or any other significant clinical PNH-related signs & symptoms, in presence of laboratory evidence of intravascular hemolysis.

End point type	Other pre-specified

End point timeframe:

Between Day 1 and Day 336

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: BTH events/year				
number (confidence interval 95%)	0.05 (0.01 to 0.17)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Adjusted annualized Major Adverse Vascular Events rate after the start of LNP023 treatment

End point title	Adjusted annualized Major Adverse Vascular Events rate after the start of LNP023 treatment

End point description:

Adjusted annual rate is carried out using the Wilson method. A Major Adverse Vascular Events (MAVE) is defined as: acute peripheral vascular occlusion, amputation (non-traumatic; nondiabetic), cerebral arterial occlusion/cerebrovascular accident, cerebral venous occlusion, dermal thrombosis, gangrene (non-traumatic; nondiabetic), hepatic/portal vein thrombosis (Budd-Chiari syndrome), mesenteric/visceral arterial, thrombosis or infarction, mesenteric/visceral vein thrombosis or infarction, myocardial infarction, pulmonary embolus, renal arterial thrombosis, renal vein thrombosis, thrombophlebitis / deep vein thrombosis, transient ischemic attack, unstable angina or other

End point type	Other pre-specified

End point timeframe:

Between Day 1 and Day 336

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	40			
Units: MAVE events/year				
number (confidence interval 95%)	0.00 (0.00 to 0.09)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline in absolute reticulocyte count at Day 336

End point title	Change from baseline in absolute reticulocyte count at Day 336

End point description:

Change from baseline in absolute reticulocyte count at visit Day 336.

End point type	Other pre-specified

End point timeframe:

Baseline, Day 336

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: x10^9 cells/L				
arithmetic mean (standard deviation)	-76.55 (± 50.149)			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline in FACIT-Fatigue score at Day 336

End point title	Change from baseline in FACIT-Fatigue score at Day 336

End point description:

The FACIT-Fatigue is a 13-item questionnaire with support for its validity and reliability in PNH that assesses patient self-reported fatigue and its impact on daily activities and function. All FACIT scales are scored so that a high score is better. As each of the 13 items of the FACIT-F Scale ranges from 0-4, the range of possible scores is 0-52, with 0 being the worst possible score and 52 the best.

End point type	Other pre-specified

End point timeframe:

Baseline, Day 336

End point values	LNP023			
Subject group type	Reporting group			
Number of subjects analysed	39			
Units: score on a scale				
arithmetic mean (standard deviation)	10.4 (± 10.14)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events of LNP023 group were reported from first dose of study treatment until the end of study treatment plus up to 30 days, up to a maximum duration of 48 weeks	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups	
Reporting group title	LNP023 200mg b.i.d.
Reporting group description:	
LNP023 200mg b.i.d.	

Serious adverse events	LNP023 200mg b.i.d.		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 40 (20.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant melanoma			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Breakthrough haemolysis			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Cataract			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
COVID-19			

subjects affected / exposed	2 / 40 (5.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 40 (2.50%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	LNP023 200mg b.i.d.		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 40 (60.00%)		
Nervous system disorders			
Headache			
subjects affected / exposed	12 / 40 (30.00%)		
occurrences (all)	14		
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	3 / 40 (7.50%)		
occurrences (all)	3		

Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all)	 3 / 40 (7.50%) 3 6 / 40 (15.00%) 7 3 / 40 (7.50%) 3 3 / 40 (7.50%) 3		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) COVID-19 subjects affected / exposed occurrences (all)	 7 / 40 (17.50%) 10 7 / 40 (17.50%) 7		
Metabolism and nutrition disorders Iron deficiency subjects affected / exposed occurrences (all)	 3 / 40 (7.50%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 August 2021	This amendment was implemented to address several requests from Health Authorities. The amendment provided more flexibility on timing of vaccination against encapsulated bacteria at study entry, and the associated need for prophylactic antibiotic. Additionally, this amendment was also implemented to further assess the hematological response of iptacopan in the study by adding both a threshold for response rate as well as a Hb stabilization assessment, and to specifically address new requirements regarding SAE reporting in Germany. Furthermore, due to the use of (high dose) steroids as first line therapy in some countries, reduction of the maximum allowed dose at study entry reduces the risk of tapering down during the Core treatment period. Further updates have been made to certain exclusion criteria, provide new juvenile toxicity animal data, add the possibility for interim safety analyses when study is still ongoing, and add a supplementary estimand that considers use of rescue medication as a treatment failure.
23 November 2021	This amendment was implemented to provide a more comprehensive evaluation of patients' hematological parameters by the central laboratory, by replacing the abbreviated hematology assessments with full hematology assessments. The amendment was also implemented to add the possibility to use PK-PD data for modeling at the time of an interim safety analysis. In addition, simplification of the analyses of the PRO have been introduced. A comprehensive analysis of a separate PRO report are documented in a separate statistical analysis plan. Changes have also been made to provide additional clarity on AE/SAE reporting post-treatment discontinuation and to address new requirements regarding SAE reporting.
28 March 2022	This amendment was implemented to address the request from the Chinese Health Authority (Center for Drug Evaluation) to collect additional historical data in Chinese trial patients. The retrospective data collection of laboratory values for Hb, LDH and absolute reticulocyte count over 6 months before screening for patients from China was intended to support the regulatory filing in China.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported