Clinical trial results:
An open-label, multi-center, phase 2 basket study to assess efficacy, safety and pharmacokinetics of iptacopan (LNP023) in participants with autoimmune benign hematological disorders

Summary

EudraCT number	2021-002039-40
Trial protocol	DE IT ES
Global end of trial date	17 May 2024

Results information

Result version number	v1 (current)
This version publication date	20 March 2025
First version publication date	20 March 2025

Trial information

Trial identification

Sponsor protocol code	CLNP023L12201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05086744
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	17 May 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 May 2024
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objectives of the trial were:
• Cohort 1 (ITP): To assess the ability of iptacopan to induce a clinically meaningful increase in platelet count in participants with primary ITP
• Cohort 2 (CAD): To assess the ability of iptacopan to induce a clinically meaningful increase in hemoglobin levels in participants with primary CAD

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	21 December 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Korea, Republic of: 3
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 1
Worldwide total number of subjects	19
EEA total number of subjects	11

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)	12
From 65 to 84 years	7
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 8 investigative sites in 6 countries.

Pre-assignment

Screening details:

The screening period began once patients had signed the study informed consent. Screening evaluations had to be completed within 8 weeks prior to the first dose of study treatment. The treatment period started on Day 1 of Part A.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (ITP)

Arm description:

Iptacopan 200 mg twice daily (b.i.d.) in participants with primary immune thrombocytopenia (ITP)

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

Dosage and administration details:

Iptacopan 200 mg given orally twice daily (b.i.d.)

Arm title	Cohort 2 (CAD)

Arm description:

Iptacopan 200 mg twice daily (b.i.d.) in participants with primary cold agglutinin disease (CAD)

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

Dosage and administration details:

Iptacopan 200 mg given orally twice daily (b.i.d.)

Number of subjects in period 1	Cohort 1 (ITP)	Cohort 2 (CAD)
Started	9	10
PD analysis set	8	10
ITP - sC5b-9 low	5	0 [1]
ITP - sC5b-9 high	4	0 [2]
Completed	4	9
Not completed	5	1
Adverse Event	-	1
Subject decision	1	-
Protocol deviation	1	-
Lack of efficacy	3	-

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The stratification groups "ITP - sC5b-9 low" and "ITP - sC5b-9 low" are only applicable to Cohort 1.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The stratification groups "ITP - sC5b-9 low" and "ITP - sC5b-9 low" are only applicable to Cohort 1.

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cohort 1 (ITP)

Arm description:

Iptacopan 200 mg twice daily (b.i.d.) in participants with primary immune thrombocytopenia (ITP)

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

Dosage and administration details:

Iptacopan 200 mg given orally twice daily (b.i.d.)

Arm title	Cohort 2 (CAD)

Arm description:

Iptacopan 200 mg twice daily (b.i.d.) in participants with primary cold agglutinin disease (CAD)

Arm type	Experimental

Investigational medicinal product name	Iptacopan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Iptacopan 200 mg given orally twice daily (b.i.d.)

Number of subjects in period 2[3]	Cohort 1 (ITP)	Cohort 2 (CAD)
Started	1	8
ITP - sC5b-9 high	1	0
ITP - sC5b-9 low	0	0
Completed	0	0
Not completed	1	8
Adverse event, non-fatal	-	1
Study terminated by sponsor	1	6
Lack of efficacy	-	1

Notes:

[3] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Only responders and non-responders who had signs of clinical benefit according to the investigator’s assessment could continue treatment with iptacopan in Part B.

Baseline characteristics

Reporting groups	
Reporting group title	Cohort 1 (ITP)
Reporting group description:	
Iptacopan 200 mg twice daily (b.i.d.) in participants with primary immune thrombocytopenia (ITP)	
Reporting group title	Cohort 2 (CAD)
Reporting group description:	
Iptacopan 200 mg twice daily (b.i.d.) in participants with primary cold agglutinin disease (CAD)	

Reporting group values	Cohort 1 (ITP)	Cohort 2 (CAD)	Total
Number of subjects	9	10	19
Age Categorical Units: Participants			
18 - <65 years	7	5	12
65 - <85 years	2	5	7
Age Continuous Units: years			
arithmetic mean	44.2	66.7	
standard deviation	± 20.77	± 10.01	-
Sex: Female, Male Units: Participants			
Female	5	10	15
Male	4	0	4
Race/Ethnicity, Customized Units: Subjects			
Asian	3	0	3
White	6	10	16
Platelets			
Platelet count in blood at baseline for participants in Cohort 1. This is not applicable to Cohort 2. Due to EudraCT system limitations, data fields in the table cannot be empty or contain letters (e.g. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.			
Units: platelets*10^9/liter			
arithmetic mean	14.6	999	
standard deviation	± 10.53	± 999	-
Hemoglobin			
Hemoglobin in blood at baseline for participants in Cohort 2. This is not applicable to Cohort 1. Due to EudraCT system limitations, data fields in the table cannot be empty or contain letters (e.g. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.			
Units: gram/liter			
arithmetic mean	999	86.7	
standard deviation	± 999	± 9.06	-

End points

End points reporting groups

Reporting group title	Cohort 1 (ITP)
Reporting group description:	
Iptacopan 200 mg twice daily (b.i.d.) in participants with primary immune thrombocytopenia (ITP)	
Reporting group title	Cohort 2 (CAD)
Reporting group description:	
Iptacopan 200 mg twice daily (b.i.d.) in participants with primary cold agglutinin disease (CAD)	
Reporting group title	Cohort 1 (ITP)
Reporting group description:	
Iptacopan 200 mg twice daily (b.i.d.) in participants with primary immune thrombocytopenia (ITP)	
Reporting group title	Cohort 2 (CAD)
Reporting group description:	
Iptacopan 200 mg twice daily (b.i.d.) in participants with primary cold agglutinin disease (CAD)	
Subject analysis set title	Cohort 1 (ITP) - sC5b-9 high
Subject analysis set type	Full analysis
Subject analysis set description:	
Iptacopan 200 mg b.i.d. in participants with primary ITP and high complement activation (i.e., high sC5b-9 levels)	
Subject analysis set title	Cohort 1 (ITP) - sC5b-9 low
Subject analysis set type	Full analysis
Subject analysis set description:	
Iptacopan 200 mg b.i.d. in participants with primary ITP and low complement activation (i.e., low sC5b-9 levels)	

Primary: Cohort 1 (ITP): Number of participants with a clinically meaningful response

End point title	Cohort 1 (ITP): Number of participants with a clinically meaningful response[1][2]
End point description:	
A study participant with ITP was considered a responder if all the below criteria were met: 1. Platelet count of ≥50 k/µL sustained for at least 2 consecutive weeks during the main, 12-week treatment part 2. Absence of rescue therapy or prohibited medications to treat ITP 3. Lack of treatment discontinuation	
End point type	Primary
End point timeframe:	
Up to 12 weeks (Part A)	

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 analyses were planned for this endpoint.

[2] - 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 Cohort 1 only.

End point values	Cohort 1 (ITP)	Cohort 1 (ITP) - sC5b-9 high	Cohort 1 (ITP) - sC5b-9 low	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	3	5	
Units: participants	0	0	0	

Statistical analyses

No statistical analyses for this end point

Primary: Cohort 2 (CAD): Number of participants with a clinically meaningful response

End point title	Cohort 2 (CAD): Number of participants with a clinically meaningful response[3][4]

End point description:

A study participant with CAD was considered a responder if all the below criteria were met:
1. Hemoglobin level increase of ≥1.5 g/dL above baseline sustained for at least 2 consecutive weeks during the main, 12-week treatment part
2. Absence of rescue therapy or prohibited medications to treat CAD
3. Lack of treatment discontinuation

End point type	Primary

End point timeframe:

Baseline, up to 12 weeks (Part A)

Notes:

[3] - 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 analyses were planned for this endpoint.

[4] - 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 Cohort 2 only.

End point values	Cohort 2 (CAD)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: participants	5			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1 (ITP): Time to first platelet count ≥50 k/µL

End point title	Cohort 1 (ITP): Time to first platelet count ≥50 k/µL[5]

End point description:

The first time that a participant had a platelet count ≥50 k/µL after first dose of study treatment. Time to the first response was assessed for responders only.

End point type	Secondary

End point timeframe:

Up to 12 weeks (Part A)

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 Cohort 1 only.

End point values	Cohort 1 (ITP)	Cohort 1 (ITP) - sC5b-9 high	Cohort 1 (ITP) - sC5b-9 low	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[6]	0[7]	0[8]	
Units: days				
median (full range (min-max))	(to)	(to)	(to)	

Notes:

[6] - There were no responders

[7] - There were no responders

[8] - There were no responders

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 2 (CAD): Time to first hemoglobin level ≥1.5 g/dL above baseline

End point title	Cohort 2 (CAD): Time to first hemoglobin level ≥1.5 g/dL above baseline[9]

End point description:

The first time that a participant had a hemoglobin level ≥1.5 g/dL above baseline after first dose of study treatment. Time to the first response was assessed for responders only.

End point type	Secondary

End point timeframe:

Baseline, up to 12 weeks (Part A)

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 Cohort 2 only.

End point values	Cohort 2 (CAD)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: days				
median (full range (min-max))	29.0 (23 to 63)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1 (ITP): Duration of time during which platelet count remains ≥50 k/µL without the use of rescue therapy

End point title	Cohort 1 (ITP): Duration of time during which platelet count remains ≥50 k/µL without the use of rescue therapy[10]

End point description:

The duration of response corresponds to the duration of time during which a participant's platelet count remains ≥50 k/µL without the use of rescue therapy. The duration of response was considered as cumulative if there were non-continuous periods of response. Duration of response was analyzed for

responders only.

End point type	Secondary

End point timeframe:

Up to 12 weeks (Part A)

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 Cohort 1 only.

End point values	Cohort 1 (ITP)	Cohort 1 (ITP) - sC5b-9 high	Cohort 1 (ITP) - sC5b-9 low	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	0[11]	0[12]	0[13]	
Units: days				
median (full range (min-max))	(to)	(to)	(to)	

Notes:

[11] - There were no responders

[12] - There were no responders

[13] - There were no responders

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 2 (CAD): Duration of time during which hemoglobin level remains ≥1.5 g/dL above baseline without the use of rescue therapy

End point title	Cohort 2 (CAD): Duration of time during which hemoglobin level remains ≥1.5 g/dL above baseline without the use of rescue therapy[14]

End point description:

The duration of response corresponds to the duration of time during which a participant's hemoglobin level remained ≥1.5 g/dL above baseline without the use of rescue therapy. The duration of response was considered as cumulative if there were non-continuous periods of response. Duration of response was analyzed for responders only.

End point type	Secondary

End point timeframe:

Baseline, up to 12 weeks (Part A)

Notes:

[14] - 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 Cohort 2 only.

End point values	Cohort 2 (CAD)			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: days				
median (full range (min-max))	56.0 (28 to 63)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1 (ITP): Magnitude of platelet count increase from baseline

End point title	Cohort 1 (ITP): Magnitude of platelet count increase from baseline[15]

End point description:

The magnitude of increase in platelet count compared to baseline was derived for each participant at each visit and time point. Best response across all visits is presented (highest value).
The following categories were used: absolute platelet counts increase <50, ≥50 and <100, ≥100 and <150, and ≥150 k/uL.
This endpoint is only applicable to participants without rescue therapy in the treatment period.

End point type	Secondary

End point timeframe:

Baseline, up to 12 weeks (Part A)

Notes:

[15] - 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 Cohort 1 only.

End point values	Cohort 1 (ITP)	Cohort 1 (ITP) - sC5b-9 high	Cohort 1 (ITP) - sC5b-9 low	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	3	1	2	
Units: participants				
Absolute platelet count increase <50 k/uL	3	1	2	
Absolute platelet count increase >=50 & <100 k/uL	0	0	0	
Absolute platelet count increase >=100 & <150 k/uL	0	0	0	
Absolute platelet count increase >=150 k/uL	0	0	0	

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 2 (CAD): Magnitude of hemoglobin increase from baseline

End point title	Cohort 2 (CAD): Magnitude of hemoglobin increase from baseline[16]

End point description:

The magnitude of increase in hemoglobin level compared to baseline was derived for each participant at each visit and time point. Best response across all visits is presented (highest value).
The following categories were used: Hb increase from baseline by <1, ≥1 and <1.5, ≥1.5 and <2, and ≥2 g/dL.
This endpoint is only applicable to participants without rescue therapy in the treatment period.

End point type	Secondary

End point timeframe:

Baseline, up to 12 weeks (Part A)

Notes:

[16] - 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 Cohort 2 only.

End point values	Cohort 2 (CAD)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: participants				
Hb increase by <1.0 g/dL	2			
Hb increase by >=1.0 g/dL and <1.5 g/dL	1			
Hb increase by =>1.5 g/dL and <2 g/dL	2			
Hb increase by =>2 g/dL	4			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1 (ITP): Need for rescue therapy during Part A

End point title	Cohort 1 (ITP): Need for rescue therapy during Part A[17]

End point description:

Rescue therapy was defined as any therapy with ITP indication that started on or after Day 1.
Rescue therapy, if indicated, could be initiated at the Investigator's discretion. From Day 1 onwards, if rescue therapy was needed before response criteria were met, the participant was treated as a non-responder. Conversely, use of rescue therapy after the primary endpoint was met, would not impact the response status with respect to that endpoint.
For ITP, rescue therapy generally consisted of corticosteroids, intravenous immunoglobulins or anti-Rho(D) immunoglobulin and may had been indicated in case of worsening thrombocytopenia and/or signs or symptoms of bleeding.

End point type	Secondary

End point timeframe:

Up to 12 weeks (Part A)

Notes:

[17] - 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 Cohort 1 only.

End point values	Cohort 1 (ITP)	Cohort 1 (ITP) - sC5b-9 high	Cohort 1 (ITP) - sC5b-9 low	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	8	3	5	
Units: participants				
No	3	1	2	
Yes	5	2	3	

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 2 (CAD): Need for rescue therapy during Part A

End point title	Cohort 2 (CAD): Need for rescue therapy during Part A[18]

End point description:

Rescue therapy was defined as any therapy with CAD indication that started on or after Day 1.
Rescue therapy, if indicated, could be initiated at the Investigator's discretion. From Day 1 onwards, if rescue therapy was needed before response criteria were met, the participant was treated as a non-responder. Conversely, use of rescue therapy after the primary endpoint was met, would not impact the response status with respect to that endpoint.
For CAD, rescue therapy generally consisted of plasmapheresis, intravenous immunoglobulins (IVIG) and/or red blood cell transfusions and may had been indicated in case of worsening anemia and/or critical hemolysis.

End point type	Secondary

End point timeframe:

Up to 12 weeks (Part A)

Notes:

[18] - 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 Cohort 2 only.

End point values	Cohort 2 (CAD)			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: participants				
No	9			
Yes	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 2 (CAD): Change from baseline in lactate dehydrogenase (LDH)

End point title	Cohort 2 (CAD): Change from baseline in lactate dehydrogenase (LDH)[19]

End point description:

LDH was measured in serum samples to assess the effect of treatment with iptacopan on relevant disease biomarkers.

End point type	Secondary

End point timeframe:

Baseline, up to 12 weeks (Part A)

Notes:

[19] - 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 Cohort 2 only.

End point values	Cohort 2 (CAD)			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: Units/liter (U/L)				
arithmetic mean (standard deviation)	-277.83 (± 88.966)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 2 (CAD): Change from baseline in total bilirubin

End point title	Cohort 2 (CAD): Change from baseline in total bilirubin[20]

End point description:

Total bilirubin was measured in serum samples to assess the effect of treatment with iptacopan on relevant disease biomarkers.

End point type	Secondary

End point timeframe:

Baseline, up to 12 weeks (Part A)

Notes:

[20] - 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 Cohort 2 only.

End point values	Cohort 2 (CAD)			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: micromole/liter (µmol/L)				
arithmetic mean (standard deviation)	-15.63 (± 12.979)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 2 (CAD): Change from baseline in reticulocyte count

End point title	Cohort 2 (CAD): Change from baseline in reticulocyte count[21]

End point description:

Reticulocyte count was measured in blood samples to assess the effect of treatment with iptacopan on relevant disease biomarkers.

End point type	Secondary

End point timeframe:

Baseline, up to 12 weeks (Part A)

Notes:

[21] - 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 Cohort 2 only.

End point values	Cohort 2 (CAD)			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: reticulocytes * 10^9/liter				
arithmetic mean (standard deviation)	-37.45 (± 17.205)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 2 (CAD): Change from baseline in haptoglobin

End point title	Cohort 2 (CAD): Change from baseline in haptoglobin[22]

End point description:

Haptoglobin was measured in serum or plasma samples to assess the effect of treatment with iptacopan on relevant disease biomarkers.

End point type	Secondary

End point timeframe:

Baseline, up to 12 weeks (Part A)

Notes:

[22] - 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 Cohort 2 only.

End point values	Cohort 2 (CAD)			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: gram/liter (g/L)				
arithmetic mean (standard deviation)	0.12 (± 0.236)			

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1 and 2: Number of participants with AEs and SAEs during the on-treatment period in Part A and B

End point title	Cohort 1 and 2: Number of participants with AEs and SAEs during the on-treatment period in Part A and B

End point description:

Number of participants with AEs (any adverse events regardless of seriousness) and serious adverse events (SAEs), including changes from baseline in vital signs, electrocardiograms and laboratory results qualifying and reported as AEs.
AE grades to characterize the severity of the AEs were based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For CTCAE v5.0, Grade 1 = mild; Grade 2 = moderate; Grade 3 = severe; Grade 4 = life-threatening; Grade 5 = death related to AE.
The on-treatment period is defined from the day of first administration of study drug up to 7 days after the last administration of study drug.

End point type	Secondary

End point timeframe:

From first dose of study treatment to 7 days after last dose, up to approximately 43 weeks (Cohort 1) and 103 weeks (Cohort 2)

End point values	Cohort 1 (ITP)	Cohort 2 (CAD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	10		
Units: participants				
AEs	7	9		
Treatment-related AEs	2	3		
Severe AEs	1	0		
Treatment-related severe AEs	1	0		
SAEs	0	1		
Treatment-related SAEs	0	0		
Fatal SAEs	0	0		
Treatment-related fatal SAEs	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1 and 2: Maximum observed plasma concentration (Cmax) of iptacopan

End point title	Cohort 1 and 2: Maximum observed plasma concentration (Cmax) of iptacopan

End point description:

Pharmacokinetic (PK) parameters were calculated based on iptacopan plasma concentrations by using non-compartmental methods. Cmax is defined as the maximum (peak) observed concentration following a dose.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 2, 4 and 6 hours after iptacopan administration on Day 15 and Day 57 of Part A

End point values	Cohort 1 (ITP)	Cohort 2 (CAD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	9		
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 15 (n=7,8)	3190.0 (± 465.00)	4800.0 (± 838.00)		
Day 57 (n=3,9)	2940.0 (± 1020.00)	4420.0 (± 1300.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1 and 2: Time to maximum observed plasma concentration (Tmax) of iptacopan

End point title	Cohort 1 and 2: Time to maximum observed plasma concentration (Tmax) of iptacopan

End point description:

PK parameters were calculated based on iptacopan plasma concentrations by using non-compartmental methods. Tmax is defined as the time to reach maximum (peak) observed concentration following a dose. Actual sampling times were considered for the calculation of PK parameters.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 2, 4 and 6 hours after iptacopan administration on Day 15 and Day 57 of Part A

End point values	Cohort 1 (ITP)	Cohort 2 (CAD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	9		
Units: hours				
median (full range (min-max))				
Day 15 (n=7,8)	2 (0.75 to 5.15)	1 (1 to 2)		
Day 57 (n=2,9)	2 (2 to 2)	1.97 (1 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1 and 2: Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of iptacopan

End point title	Cohort 1 and 2: Area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration (AUClast) of iptacopan

End point description:

PK parameters were calculated based on iptacopan plasma concentrations by using non-compartmental methods. The linear trapezoidal method was used for area under the curve (AUC) calculation.

End point type	Secondary

End point timeframe:

Pre-dose, 0.5, 2, 4 and 6 hours after iptacopan administration on Day 15 and Day 57 of Part A

End point values	Cohort 1 (ITP)	Cohort 2 (CAD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	7	9		
Units: hr*ng/mL				
arithmetic mean (standard deviation)				
Day 15 (n=7,8)	24200.0 (± 6110.00)	31100.0 (± 5830.00)		
Day 57 (n=3,9)	21300.0 (± 5280.00)	28200.0 (± 6880.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cohort 1 and 2: Trough plasma concentration (Ctrough) of iptacopan

End point title	Cohort 1 and 2: Trough plasma concentration (Ctrough) of iptacopan

End point description:

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.

End point type	Secondary

End point timeframe:

Pre-dose on Day 15, 29 and 57 of Part A

End point values	Cohort 1 (ITP)	Cohort 2 (CAD)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	8	9		
Units: ng/mL				
arithmetic mean (standard deviation)				
Day 15 (n=8,9)	1670.0 (± 1320.00)	1980.0 (± 1720.00)		
Day 29 (n=6,7)	1670.0 (± 927.00)	1330.0 (± 337.00)		
Day 57 (n=5,9)	1680.0 (± 758.00)	1410.0 (± 320.00)		

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 to 30 days after last dose, up to approximately 46 weeks (Cohort 1) and 106 weeks (Cohort 2)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups	
Reporting group title	Cohort 1 (ITP)
Reporting group description:	
Iptacopan 200 mg twice daily (b.i.d.) in participants with primary immune thrombocytopenia (ITP)	
Reporting group title	All Patients
Reporting group description:	
All patients in the study	
Reporting group title	Cohort 2 (CAD)
Reporting group description:	
Iptacopan 200 mg twice daily (b.i.d.) in participants with primary cold agglutinin disease (CAD)	

Serious adverse events	Cohort 1 (ITP)	All Patients	Cohort 2 (CAD)
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 9 (11.11%)	2 / 19 (10.53%)	1 / 10 (10.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Blood creatinine increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Cohort 1 (ITP)	All Patients	Cohort 2 (CAD)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 9 (77.78%)	16 / 19 (84.21%)	9 / 10 (90.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer recurrent			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 9 (0.00%)	3 / 19 (15.79%)	3 / 10 (30.00%)
occurrences (all)	0	3	3
Pyrexia			
subjects affected / exposed	0 / 9 (0.00%)	2 / 19 (10.53%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Reproductive system and breast disorders			
Heavy menstrual bleeding			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	2 / 9 (22.22%)	2 / 19 (10.53%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Cough			
subjects affected / exposed	1 / 9 (11.11%)	3 / 19 (15.79%)	2 / 10 (20.00%)
occurrences (all)	1	3	2
Psychiatric disorders			

Depressed mood			
subjects affected / exposed	0 / 9 (0.00%)	2 / 19 (10.53%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Blood creatinine increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Blood iron increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Reverse tri-iodothyronine increased			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Immunisation reaction			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Congenital, familial and genetic disorders			
Thyroglossal cyst			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	2	2
Head discomfort			

subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Headache			
subjects affected / exposed	2 / 9 (22.22%)	5 / 19 (26.32%)	3 / 10 (30.00%)
occurrences (all)	3	7	4
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Neutrophilia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Ear and labyrinth disorders			
Tinnitus			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Vertigo positional			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	2	2
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Constipation			
subjects affected / exposed	0 / 9 (0.00%)	2 / 19 (10.53%)	2 / 10 (20.00%)
occurrences (all)	0	3	3
Gingival bleeding			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Haematochezia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Haemorrhoids			

subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Nausea			
subjects affected / exposed	1 / 9 (11.11%)	3 / 19 (15.79%)	2 / 10 (20.00%)
occurrences (all)	1	4	3
Vomiting			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Eczema			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	2	2	0
Hair texture abnormal			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Petechiae			
subjects affected / exposed	3 / 9 (33.33%)	3 / 19 (15.79%)	0 / 10 (0.00%)
occurrences (all)	4	4	0
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Back pain			
subjects affected / exposed	0 / 9 (0.00%)	2 / 19 (10.53%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Myalgia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Muscle spasms			

subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Joint swelling			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Pain in extremity			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
COVID-19			
subjects affected / exposed	1 / 9 (11.11%)	2 / 19 (10.53%)	1 / 10 (10.00%)
occurrences (all)	1	2	1
Diverticulitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Ear infection			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Fungal foot infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Gastroenteritis			
subjects affected / exposed	1 / 9 (11.11%)	1 / 19 (5.26%)	0 / 10 (0.00%)
occurrences (all)	1	1	0
Nasopharyngitis			
subjects affected / exposed	0 / 9 (0.00%)	2 / 19 (10.53%)	2 / 10 (20.00%)
occurrences (all)	0	3	3
Oral herpes			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)	2 / 19 (10.53%)	1 / 10 (10.00%)
occurrences (all)	2	3	1

Tooth abscess			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	2 / 19 (10.53%)	2 / 10 (20.00%)
occurrences (all)	0	2	2
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 9 (0.00%)	1 / 19 (5.26%)	1 / 10 (10.00%)
occurrences (all)	0	1	1
Hypokalaemia			
subjects affected / exposed	1 / 9 (11.11%)	2 / 19 (10.53%)	1 / 10 (10.00%)
occurrences (all)	1	2	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 October 2021	The purpose of this amendment was to address questions raised by the BfArM. Inclusion criteria were revised to clarify that ITP should be persistent or chronic and diagnosed at least 3 months prior to baseline. Exclusion criteria were revised to exclude participants with any severe concurrent co-morbidities. The protocol was also amended to implement analysis of hematology samples from CAD participants at local clinical diagnostic laboratories, due to the high risk of spontaneous red blood cell agglutination in the blood samples from these participants at room temperature.
01 December 2021	The purpose of this amendment was to address a comment received from the South Korean HA, to add South Korea-specific instruction for the ITP inclusion criteria.
26 April 2022	The purpose of this amendment was to update the eligibility criteria related to liver disease or injury. For CAD participants, the acceptable levels for AST were increased to account for potential increases due to hemolysis only. For all participants, the acceptable limit for the liver enzymes were also increased to account for the patient populations of interest, particularly for participants with cold agglutinin disease, who may be expected to have mildly elevated liver enzymes.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported