Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Study With an Open-Label Extension to Evaluate the Efficacy and Safety of Avatrombopag for the Treatment of Chemotherapy-Induced Thrombocytopenia in Subjects With Active Non-Hematological Cancers

Summary

EudraCT number	2018-000023-13
Trial protocol	HU PL
Global end of trial date	24 January 2023

Results information

Result version number	v1 (current)
This version publication date	21 October 2023
First version publication date	21 October 2023

Trial information

Trial identification

Sponsor protocol code	AVA-CIT-330

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03471078
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Sobi Inc.
Sponsor organisation address	240 Leigh Farm Rd, Durham, United States, 27707
Public contact	Clinical Development, Sobi Inc, +1 7817867370, naclinical@sobi.com
Scientific contact	Clinical Development, Sobi Inc., +1 7817867370, naclinical@sobi.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	28 August 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	24 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of avatrombopag in increasing platelet counts and therefore preventing the need for a platelet transfusion or chemotherapy dose reduction or delay in subjects with CIT.

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) and 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	25 June 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Regulatory reason
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Hungary: 15
Country: Number of subjects enrolled	China: 8
Country: Number of subjects enrolled	Russian Federation: 30
Country: Number of subjects enrolled	Serbia: 16
Country: Number of subjects enrolled	Ukraine: 32
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	122
EEA total number of subjects	22

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)	72
From 65 to 84 years	50
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

To be eligible for the study, subjects must have experienced thrombocytopenia during their current chemotherapy regimen. Subjects must have been screened ≤28 days prior to the Baseline Visit, unless the Screening and Baseline Visits were performed on the same day, and the subject began treatment during cycle.

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, Monitor, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Avatrombopag

Arm description: -

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

Dosage and administration details:

60 mg avatrombopag or matching placebo administered orally once daily for 5 days prior to Chemotherapy Day and for 5 days immediately following Chemotherapy Day

Arm title	Placebo

Arm description: -

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

Dosage and administration details:

60 mg avatrombopag or matching placebo administered orally once daily for 5 days prior to Chemotherapy Day and for 5 days immediately following Chemotherapy Day

Number of subjects in period 1	Avatrombopag	Placebo
Started	82	40
Completed	61	34
Not completed	21	6
Adverse event, serious fatal	2	-
Consent withdrawn by subject	9	1
Physician decision	3	2
Adverse event, non-fatal	4	1
Undetermined	3	2

Baseline characteristics

Reporting groups	
Reporting group title	Avatrombopag
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Avatrombopag	Placebo	Total
Number of subjects	82	40	122
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	61.0	60.8	
standard deviation	± 10.08	± 10.41	-
Gender categorical Units: Subjects			
Female	43	22	65
Male	39	18	57
ECOG Performance Status			
The Eastern Cooperative Oncology Group (ECOG) performance status score describes a patient's level of functioning in terms of their ability to care for themself, daily activity, and physical ability (walking, working, etc.). 0=Fully active, able to carry on all pre-disease performance without restriction 1=Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work 2=Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours			
Units: Subjects			
ECOG Score 0	21	8	29
ECOG Score 1	60	31	91
ECOG Score 2	1	1	2
Number of Eligible Chemotherapy Agents Currently Receiving per IWRS Units: Subjects			
Receiving 1 Agent	40	20	60
Receiving ≥ 2 Agents	42	20	62

End points

End points reporting groups

Reporting group title	Avatrombopag
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Percentage of Subjects Who do Not Require Platelet Transfusion, Dose Reduction in Chemotherapy by 15%, or Chemotherapy Delay by >=4 Days

End point title	Percentage of Subjects Who do Not Require Platelet Transfusion, Dose Reduction in Chemotherapy by 15%, or Chemotherapy Delay by >=4 Days
End point description:	
End point type	Primary
End point timeframe:	
Randomization up to 33 days	

End point values	Avatrombopag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	40		
Units: Count of Participants	57	29		

Statistical analyses

Statistical analysis title	Primary Efficacy Responder Criteria
Statistical analysis description:	
Primary efficacy responders are subjects who meet all of the following criteria during the period after post-chemotherapy study drug treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2: not requiring a platelet transfusion; not requiring a chemotherapy dose reduction by ≥15% due to thrombocytopenia; not requiring a chemotherapy delay by ≥4 days in Cycle X+2	
Comparison groups	Avatrombopag v Placebo
Number of subjects included in analysis	122
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.7186
Method	Cochran-Mantel-Haenszel
Parameter estimate	Mean difference (final values)
Point estimate	-3

Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.7
upper limit	15.6
Variability estimate	Standard deviation

Secondary: Duration of severe thrombocytopenia defined as a platelet count <50 x 10^9/L

End point title	Duration of severe thrombocytopenia defined as a platelet count <50 x 10^9/L

End point description:

The duration of severe thrombocytopenia is defined as the total number of days with a platelet count <50×10^9/L during the period after post-chemotherapy study drug treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2.

End point type	Secondary

End point timeframe:

Randomization up to 33 days

End point values	Avatrombopag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	40		
Units: Days				
arithmetic mean (standard deviation)	4.6 (± 5.53)	4.7 (± 6.56)		

Statistical analyses

Statistical analysis title	Duration of Severe Thrombocytopenia
Comparison groups	Avatrombopag v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8372
Method	Van Elteren Test

Secondary: Change in platelet count from baseline (nadir)

End point title	Change in platelet count from baseline (nadir)

End point description:

Comparison of avatrombopag 60 mg vs. placebo, adjusted for the number of chemotherapy agents currently receiving per IWRS (1, ≥2).
Cycle X nadir is defined as the lowest platelet count value prior to the first dose of study drug; Cycle X+1 nadir is defined as the lowest platelet count value during the period after post-chemotherapy study drug treatment in Cycle X+1 through Chemotherapy Day in Cycle X+2.

End point type	Secondary

End point timeframe:

Randomization up to 33 days

End point values	Avatrombopag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	40		
Units: Platelets x 10^9/L				
arithmetic mean (standard deviation)	51.5 (± 61.85)	29.1 (± 39.48)		

Attachments (see zip file)	Mean Platelet Counts Over Time/MicrosoftTeams-image (1).png

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects who did not have major or non-major clinically relevant bleeding during the period after post-chemotherapy study drug treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2.

End point title	Percentage of subjects who did not have major or non-major clinically relevant bleeding during the period after post-chemotherapy study drug treatment in Cycle X+1 through Chemotherapy Day of Cycle X+2.

End point description:

End point type	Secondary

End point timeframe:

Randomization up to 33 days

End point values	Avatrombopag	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	40		
Units: Count of Participants	82	40		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected during the Double-Blind Treatment Phase and included two 21- or 28-day chemotherapy cycles

Adverse event reporting additional description:

Adverse events were assessed by Investigators at each study visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Avatrombopag

Reporting group description: -

Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Avatrombopag	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 82 (19.51%)	8 / 40 (20.00%)	
number of deaths (all causes)	2	0	
number of deaths resulting from adverse events			
Investigations			
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 82 (1.22%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Capillary leak syndrome			
subjects affected / exposed	1 / 82 (1.22%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic cerebral infarction			
subjects affected / exposed	1 / 82 (1.22%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Lacunar infarction			
subjects affected / exposed	1 / 82 (1.22%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia			
subjects affected / exposed	0 / 82 (0.00%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	4 / 82 (4.88%)	4 / 40 (10.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	3 / 82 (3.66%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 82 (1.22%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 82 (1.22%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Leukopenia			
subjects affected / exposed	1 / 82 (1.22%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	0 / 82 (0.00%)	2 / 40 (5.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Stomatitis			
subjects affected / exposed	1 / 82 (1.22%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
non-small cell lun			
subjects affected / exposed	1 / 82 (1.22%)	0 / 40 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 82 (1.22%)	1 / 40 (2.50%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Avatrombopag	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	71 / 82 (86.59%)	36 / 40 (90.00%)	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	32 / 82 (39.02%)	21 / 40 (52.50%)	
occurrences (all)	53	53	
Leukopenia			
subjects affected / exposed	24 / 82 (29.27%)	15 / 40 (37.50%)	
occurrences (all)	39	39	
Neutropenia			
subjects affected / exposed	24 / 82 (29.27%)	17 / 40 (42.50%)	
occurrences (all)	41	41	
Thrombocytopenia			

subjects affected / exposed	15 / 82 (18.29%)	13 / 40 (32.50%)	
occurrences (all)	28	28	
Thrombocytosis			
subjects affected / exposed	9 / 82 (10.98%)	2 / 40 (5.00%)	
occurrences (all)	11	11	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 82 (6.10%)	4 / 40 (10.00%)	
occurrences (all)	9	9	
Fatigue			
subjects affected / exposed	3 / 82 (3.66%)	3 / 40 (7.50%)	
occurrences (all)	6	6	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	6 / 82 (7.32%)	6 / 40 (15.00%)	
occurrences (all)	12	12	
Vomiting			
subjects affected / exposed	5 / 82 (6.10%)	0 / 40 (0.00%)	
occurrences (all)	5	5	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	4 / 82 (4.88%)	2 / 40 (5.00%)	
occurrences (all)	6	6	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 April 2019	This protocol amendment was introduced to include an additional tumor type (small cell lung cancer), clarify the time period for the assessment of the efficacy endpoints, and clarify certain inclusion and exclusion criteria. Additionally, the amendment allowed the Screening and Baseline Visits to be combined and performed on the same day and increased the window for a separate Screening Visit to 28 days.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/35240074