



Clinical trial results:

A Multicenter, Open-label, Non-randomized Phase 3 Study to Assess the Safety, Efficacy and Pharmacokinetics of Subcutaneous Administration of Icatibant (TAK-667) in Japanese Children and Adolescents with Acute Attacks of Hereditary Angioedema

Summary

EudraCT number	2022-002627-35
Trial protocol	Outside EU/EEA
Global end of trial date	27 July 2021

Results information

Result version number	v1 (current)
This version publication date	11 August 2022
First version publication date	11 August 2022

Trial information

Trial identification

Sponsor protocol code	TAK-667-3001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04654351
WHO universal trial number (UTN)	U1111-1260-2627

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421A
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.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 July 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 July 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the safety, efficacy and PK of icatibant for the treatment of acute attacks in Japanese children and adolescents with type I or type II hereditary angioedema (HAE).

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 January 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	Japan: 2
Worldwide total number of subjects	2
EEA total number of subjects	0

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)	1
Adolescents (12-17 years)	1
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 2 investigative sites in Japan from 15 January 2021 to 27 July 2021.

Pre-assignment

Screening details:

Participants with diagnosis of hereditary angioedema (HAE) type I or II were enrolled in single arm to receive TAK-667 single-dose per attack. Up to two additional injections were permitted per attack. Participants who subsequently experienced an acute attack continued to receive TAK-667 for up to total of 3 eligible icatibant-treated attacks.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	TAK-667 10-30 mg
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Arm description:

TAK-667 five-weight-band dosing of up to maximum of 10-30 mg injection, subcutaneously (SC), once on Day 1, and if necessary (there was insufficient relief or worsening of symptoms), up to two additional doses with a time interval of at least 6 hours between doses within 48 hours of initial injection per attack for up to 3 HAE attacks till the end of study (approximately 6 months). The dose of TAK-667 depended upon the participant's body weight (10 mg for 12 kg to 25 kg, 15 mg for 26 kg to 40 kg, 20 mg for 41 kg to 50kg, 25 mg for 51 kg to 65 kg, 30 mg for >65 kg).

Arm type	Experimental
Investigational medicinal product name	TAK-667
Investigational medicinal product code	
Other name	Icatibant
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TAK-667 single SC administration

Number of subjects in period 1	TAK-667 10-30 mg
Started	2
Completed	2

Baseline characteristics

Reporting groups

Reporting group title	Overall Study
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Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	2	2	
Age categorical			
Units: Subjects			
In Utero	0	0	
Preterm newborn infants (gestional age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days - 23 months)	0	0	
Children (2 - 11 years)	1	1	
12 - 17 years	1	1	
Adults (18 - 64 years)	0	0	
From 65 - 84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Not specified due to risk of identification	2	2	

End points

End points reporting groups

Reporting group title	TAK-667 10-30 mg
Reporting group description: TAK-667 five-weight-band dosing of up to maximum of 10-30 mg injection, subcutaneously (SC), once on Day 1, and if necessary (there was insufficient relief or worsening of symptoms), up to two additional doses with a time interval of at least 6 hours between doses within 48 hours of initial injection per attack for up to 3 HAE attacks till the end of study (approximately 6 months). The dose of TAK-667 depended upon the participant's body weight (10 mg for 12 kg to 25 kg, 15 mg for 26 kg to 40 kg, 20 mg for 41 kg to 50kg, 25 mg for 51 kg to 65 kg, 30 mg for >65 kg).	

Primary: Number of Participants Who Experienced at Least One Treatment-Emergent Adverse Events (TEAE)

End point title	Number of Participants Who Experienced at Least One Treatment-Emergent Adverse Events (TEAE) ^[1]
End point description: An adverse event (AE) means any untoward medical occurrence in a participant administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. A treatment-emergent adverse event (TEAE) was defined as any adverse event occurring after the start of Icatibant administration of the treatment period. Safety analysis set included all participants who received at least 1 dose of study drug.	
End point type	Primary
End point timeframe: Up to approximately 6 months	

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 have been specified for this primary end point.

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants With Injection Site Reactions

End point title	Number of Participants With Injection Site Reactions ^[2]
End point description: Injection sites were examined for erythema, swelling, cutaneous pain, burning sensation, itching/pruritus, and warm sensation. Data for injection site reactions were collected separately from general reports of AEs. As pre-defined in the protocol, an injection site reaction not meeting SAE criteria was not required to be reported additionally as an AE. Safety analysis set included all participants who received at least 1 dose of study drug.	

End point type	Primary
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End point timeframe:

Postdose, up to Day 8

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 analyses have been specified for this primary end point.

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: percentage of participants				
number (not applicable)	2			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced at Least One TEAE Related to Resting 12-lead Electrocardiogram

End point title	Number of Participants Who Experienced at Least One TEAE Related to Resting 12-lead Electrocardiogram
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End point description:

An AE means any untoward medical occurrence in a participant administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. A TEAE was defined as any AE occurring after the start of Icatibant administration of the Treatment Period. A resting 12-lead ECG was recorded and reported for participants shifts from within normal limits at baseline to abnormal, but not clinically significant, or abnormal and clinically significant after study drug administration. Safety analysis set included all participants who received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

Up to approximately 6 months

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced at Least One TEAE Related to Clinical Laboratory Parameters

End point title	Number of Participants Who Experienced at Least One TEAE Related to Clinical Laboratory Parameters
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End point description:

An AE means any untoward medical occurrence in a participant administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. A TEAE was defined as any AE occurring after the start of Icatibant administration of the Treatment Period. The laboratory parameters included hematology, serum chemistries, and urinalysis. Safety analysis set included all participants who received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

Up to approximately 6 months

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experienced at Least One TEAE Related to Vital Sign

End point title	Number of Participants Who Experienced at Least One TEAE Related to Vital Sign
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End point description:

An AE means any untoward medical occurrence in a participant administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. A TEAE was defined as any AE occurring after the start of Icatibant administration of the Treatment Period. Vital signs included body temperature (oral), sitting blood pressure (after 5 minutes resting), respiration rate and pulse (beats per minute [bpm]). Safety analysis set included all participants who received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

Up to approximately 6 months

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Symptom Relief With Investigator-Rated Symptom Scores Assessed by Investigator

End point title	Time to Onset of Symptom Relief With Investigator-Rated Symptom Scores Assessed by Investigator
End point description:	
<p>The time to onset of symptom relief, defined as the duration of time in hours from the time of icatibant administration to the earliest time at which at least a 20% improvement is observed in the average post-treatment score with no worsening of any single component score. Investigator-rated symptom score was used for assessment and scoring of cutaneous, abdominal, and laryngeal symptoms of acute HAE attacks related to daily activities. The score ranged from 0 to 4 and each number of scores meant the following: 0 = none; absence of symptoms, 1 = mild (no to mild interference with daily activities), 2 = moderate (moderate interference with daily activities), 3 = severe (severe interference with daily activities), 4 = very severe (very severe interference with daily activities). Full analysis set included all participants who received at least 1 dose of study drug. 0.99999=Data was not estimated due to low number of participants (as there were less than 3 participants).</p>	
End point type	Secondary
End point timeframe:	
Baseline, and post dose on Day 1	

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: hours				
median (full range (min-max))	0.99999 (0.9 to 1.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Reported Presence of Anti-icatibant Antibodies

End point title	Number of Participants Who Reported Presence of Anti-icatibant Antibodies
End point description:	
<p>Serum samples for immunogenicity testing were collected for determination of anti-icatibant antibodies. If hypersensitivity was observed, it was reported as an AEs of special interest. An AE means any untoward medical occurrence in a participant administered a pharmaceutical product; the untoward</p>	

medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. Safety analysis set was defined as all participants who received at least 1 dose of study drug.

End point type	Secondary
End point timeframe:	
Up to approximately 6 months	

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Experience at Least One TEAE Related to Clinically Significant Changes in Reproductive Hormones

End point title	Number of Participants Who Experience at Least One TEAE Related to Clinically Significant Changes in Reproductive Hormones
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End point description:

An AE means any untoward medical occurrence in a participant administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. A TEAE was defined as any AE occurring after the start of Icatibant administration of the Treatment Period. Blood samples were collected to assess follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol, and progesterone in females, and FSH, LH, and testosterone in males. Safety analysis set included all participants who received at least 1 dose of study drug.

End point type	Secondary
End point timeframe:	
Up to approximately 6 months	

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: participants	0			

Statistical analyses

Secondary: Time to Onset of Symptom Relief With Faces Pain Scale-Revised (FPS-R) Scores for Participants of 4 Years Age and Older

End point title	Time to Onset of Symptom Relief With Faces Pain Scale-Revised (FPS-R) Scores for Participants of 4 Years Age and Older
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End point description:

The time to onset of symptom relief, defined as the duration of time in hours from the time of icatibant administration to the earliest time at which the post-treatment score improved by at least 1 level. Participants of 4 years age and older self-assessed their HAE-related pain using the FPS-R instrument. FPS-R is a self-reported measure used to assess the intensity of children's pain and it is scored using a 0 to 10 scale (0=no pain to 10=very much pain). Full analysis set included all participants who received at least 1 dose of study drug. 0.99999=Data was not estimated due to low number of participants (as there were less than 3 participants).

End point type	Secondary
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End point timeframe:

Baseline, and post dose on Day 1

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: hours				
median (full range (min-max))	0.99999 (0.9 to 1.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Onset of Symptom Relief by Faces, Legs, Activity, Cry, and Consolability (FLACC) Scale Assessed by Investigator for Participants of Younger Than 4 Years Age

End point title	Time to Onset of Symptom Relief by Faces, Legs, Activity, Cry, and Consolability (FLACC) Scale Assessed by Investigator for Participants of Younger Than 4 Years Age
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End point description:

The time to onset of symptom relief, defined as the earliest time at which a 20% improvement is observed in the total post-treatment score. Participants of younger than 4 years age underwent investigator assessment of HAE-related pain (cutaneous, abdominal, and laryngeal) using the FLACC compartmental pain scale. Each of the 5 categories were scored from 0 to 2. Face(F): 0 (no particular expression/smile) - 2 (frequent to constant frown clenched jaw quivering chin); Legs(L): 0 (normal position/relaxed) - 2 (kicking/legs drawn up); Activity(A): 0 (lying quietly, normal position, moves easily) - 2 (arched rigid/jerking); Cry(C): 0 (No cry [awake/asleep]) - 2 (crying steadily/screams/sobs or frequent complaints); Consolability(C): 0 (content/relaxed) - 2 (difficult to console/comfort), resulting in a total score between 0 and 10.

End point type	Secondary
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End point timeframe:

Baseline, and post dose on Day 1

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	0 ^[3]			
Units: hours				
number (not applicable)				

Notes:

[3] - No participants between 2 to <4 years in this study, data was not collected for this endpoint.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Worsened Intensity of Clinical HAE Symptoms Between 2 and 4 Hours After Treatment With SC Icatibant Using Investigator-Rated Symptom Scores

End point title	Number of Participants With Worsened Intensity of Clinical HAE Symptoms Between 2 and 4 Hours After Treatment With SC Icatibant Using Investigator-Rated Symptom Scores
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End point description:

Investigator-rated symptom score was used for assessment and scoring of cutaneous, abdominal, and laryngeal symptoms of acute HAE attacks related to daily activities. The score ranged from 0 to 4 and each number of scores means following; 0 = none; absence of symptoms, 1 = mild (no to mild interference with daily activities), 2 = moderate (moderate interference with daily activities), 3 = severe (severe interference with daily activities), 4 = very severe (very severe interference with daily activities). Full analysis set was defined as all participants who had received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

From 2 hours post-dose to 4 hours post-dose

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Initial Symptom Improvement Reported by Investigator

End point title	Time to Initial Symptom Improvement Reported by Investigator
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End point description:

Time to initial symptom improvement reported by investigator, was defined as the duration of time in

hours from icatibant administration until the time when overall participant improvement was first noted by investigator. Full analysis set was defined as all participants who had received at least 1 dose of study drug. 0.99999=Data was not estimated due to low number of participants (as there were less than 3 participants).

End point type	Secondary
End point timeframe:	
Up to 8 hours post dose (or till the onset of HAE attacks were resolved)	

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: hours				
median (full range (min-max))	0.99999 (0.3 to 1.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Were Treated With Rescue Medication During Study

End point title	Number of Participants Who Were Treated With Rescue Medication During Study
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End point description:

Rescue medication included therapies for HAE used for HAE attack and symptomatic treatment used in order to improve symptoms of angioedema (e.g., pain and nausea). Safety analysis set was defined as all participants who received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

Up to approximately 6 months

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Initial Symptom Improvement Reported by Participant

End point title	Time to Initial Symptom Improvement Reported by Participant
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End point description:

Time to initial symptom improvement reported by participant, defined as the duration of time in hours from icatibant administration until the time when overall participant improvement was first noted by participant, participant's parent or participant's legal guardian. Full analysis set was defined as all participants who had received at least 1 dose of study drug. 0.99999=Data was not estimated due to low number of participants (as there were less than 3 participants).

End point type	Secondary
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End point timeframe:

Up to 8 hours post dose (or till the onset of HAE attacks were resolved)

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: hours				
median (full range (min-max))	0.99999 (0.3 to 1.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration for TAK-667

End point title	Plasma Concentration for TAK-667
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End point description:

Safety analysis set was defined as all participants who received at least 1 dose of study drug.

End point type	Secondary
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End point timeframe:

Day 1 pre-dose and at multiple timepoints post-dose

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: ug/l				
arithmetic mean (standard deviation)				
Baseline (pre-dose)	0 (± 0)			
0.5 hours postdose	970 (± 11.313)			
1 hour postdose	869 (± 18.385)			
2 hours postdose	405.5 (± 6.364)			
4 hours postdose	53.85 (± 21.284)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration for TAK-667 Metabolite M-I

End point title	Plasma Concentration for TAK-667 Metabolite M-I
End point description: Safety analysis set was defined as all participants who received at least 1 dose of study drug.	
End point type	Secondary
End point timeframe: Day 1 pre-dose and at multiple timepoints post-dose	

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: ug/l				
arithmetic mean (standard deviation)				
Baseline (pre-dose)	0 (± 0)			
0.5 hours postdose	104.5 (± 2.121)			
1 hour postdose	205 (± 25.456)			
2 hour postdose	233.5 (± 19.092)			
4 hour postdose	130.5 (± 9.192)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration for TAK-667 Metabolite M-II

End point title	Plasma Concentration for TAK-667 Metabolite M-II
End point description: Safety analysis set was defined as all participants who received at least 1 dose of study drug.	
End point type	Secondary
End point timeframe: Day 1 pre-dose and at multiple timepoints post-dose	

End point values	TAK-667 10-30 mg			
Subject group type	Reporting group			
Number of subjects analysed	2			
Units: ug/l				
arithmetic mean (standard deviation)				
Baseline (pre-dose)	0 (\pm 0)			
0.5 hours postdose	109.5 (\pm 9.192)			
1 hour postdose	200 (\pm 22.627)			
2 hours postdose	251.5 (\pm 34.648)			
4 hours postdose	149 (\pm 2.828)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Up to approximately 6 months

Adverse event reporting additional description:

Any event reported by participant or observed by investigator was recorded, irrespective of relation to study treatment. Data for injection site reactions were collected separately from general reports of AEs. Per protocol, an injection site reaction not meeting SAE criteria was not required to be reported additionally as an AE.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	TAK-667 10-30 mg
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Reporting group description:

TAK-667 five-weight-band dosing of up to maximum of 10-30 mg injection, subcutaneously (SC), once on Day 1, and if necessary (there was insufficient relief or worsening of symptoms), up to two additional doses with a time interval of at least 6 hours between doses within 48 hours of initial injection per attack for up to 3 HAE attacks till the end of study (approximately 6 months). The dose of TAK-667 depended upon the participant's body weight (10 mg for 12 kg to 25 kg, 15 mg for 26 kg to 40 kg, 20 mg for 41 kg to 50 kg, 25 mg for 51 kg to 65 kg, 30 mg for >65 kg).

Serious adverse events	TAK-667 10-30 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	TAK-667 10-30 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)		

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: There were very low number of participants and due to risk of identification the data for non-serious adverse events was not reported.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2020	The changes implemented based on Amendment 1 were: -Information of genetic mutation was added as an additional example for the basis of medical judgement on the diagnosis of HAE. -Presence of previous icatibant administration and any clinically significant conditions or diseases relevant to treatment were added so that the information planned to be obtained was clear. -Clarification of representation in the original protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported