



Clinical trial results:

A Pilot Study of the Efficacy, Safety, and Tolerability of AX-8 for the Treatment of Refractory Chronic Cough

Summary

EudraCT number	2017-003108-27
Trial protocol	GB
Global end of trial date	11 June 2018

Results information

Result version number	v1 (current)
This version publication date	27 June 2019
First version publication date	27 June 2019

Trial information

Trial identification

Sponsor protocol code	AX8-001
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Axalbion SA
Sponsor organisation address	EPFL-Innovation Park, Bâtiment C, Lausanne, Switzerland, CH-1015
Public contact	Olivier Poirot, Axalbion SA, +41 76 341 81 38, opoirot@axalbion.com
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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	11 June 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effectiveness of AX-8 for the treatment of refractory chronic cough (RCC) and associated upper airway symptoms after one dose of treatment in reducing awake cough frequency compared to baseline, for the purpose of planning a future randomised controlled trial.

Protection of trial subjects:

The study was performed in accordance with the current version of the declaration of Helsinki (52nd WMA General Assembly, Edinburgh, Scotland, October 2000). The study was conducted in agreement with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP). All subjects provided written informed consent to participate in the study prior to being screened.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 December 2017
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	United Kingdom: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

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)	7
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

12 subjects were enrolled in the United Kingdom.

Pre-assignment

Screening details:

16 subjects were screened for the study and 12 received study drug.

Period 1

Period 1 title	Screening (Visit 1)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	AX-8 orally disintegrating tablet (ODT) 5 mg
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Arm description:

Subjects did not receive treatment during the screening period.

Arm type	Experimental
Investigational medicinal product name	AX-8 orally disintegrating tablet (ODT) 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects did not receive treatment during the screening period.

Number of subjects in period 1	AX-8 orally disintegrating tablet (ODT) 5 mg
Started	12
Completed	12

Period 2

Period 2 title	Baseline (Visit 2)
Is this the baseline period?	Yes ^[1]
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	AX-8 orally disintegrating tablet (ODT) 5 mg
Arm description: Subjects did not receive treatment during the baseline period.	
Arm type	Experimental
Investigational medicinal product name	AX-8 orally disintegrating tablet (ODT) 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Subjects did not receive treatment during the baseline period.	
Notes: [1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period. Justification: Period 1 was the screening period.	

Number of subjects in period 2	AX-8 orally disintegrating tablet (ODT) 5 mg
Started	12
Completed	12

Period 3	
Period 3 title	Treatment (Visits 3 and 4)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Arm title	AX-8 orally disintegrating tablet (ODT) 5 mg
Arm description: Subjects received a single dose of AX-8 orally disintegrating tablet (ODT) 5 mg by mouth.	
Arm type	Experimental
Investigational medicinal product name	AX-8 orally disintegrating tablet (ODT) 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: Subjects received a single dose of AX-8 orally disintegrating tablet (ODT) 5 mg by mouth.	

Number of subjects in period 3	AX-8 orally disintegrating tablet (ODT) 5 mg
Started	12
Completed	12

Period 4

Period 4 title	Follow-up (Visit 5/Withdraw/Study End)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	AX-8 orally disintegrating tablet (ODT) 5 mg
Arm description: Subjects did not receive treatment during the follow-up period.	
Arm type	Experimental
Investigational medicinal product name	AX-8 orally disintegrating tablet (ODT) 5 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects did not receive treatment during the follow-up period.

Number of subjects in period 4	AX-8 orally disintegrating tablet (ODT) 5 mg
Started	12
Completed	11
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups

Reporting group title	Baseline (Visit 2)
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Reporting group description: -

Reporting group values	Baseline (Visit 2)	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	63.9 ± 10.9	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	3	3	

End points

End points reporting groups

Reporting group title	AX-8 orally disintegrating tablet (ODT) 5 mg
Reporting group description: Subjects did not receive treatment during the screening period.	
Reporting group title	AX-8 orally disintegrating tablet (ODT) 5 mg
Reporting group description: Subjects did not receive treatment during the baseline period.	
Reporting group title	AX-8 orally disintegrating tablet (ODT) 5 mg
Reporting group description: Subjects received a single dose of AX-8 orally disintegrating tablet (ODT) 5 mg by mouth.	
Reporting group title	AX-8 orally disintegrating tablet (ODT) 5 mg
Reporting group description: Subjects did not receive treatment during the follow-up period.	

Primary: Change from Baseline in Objective Awake Cough Frequency Over 24 hours after 1 Dose of Treatment

End point title	Change from Baseline in Objective Awake Cough Frequency Over 24 hours after 1 Dose of Treatment ^[1]
End point description: The change in awake and asleep cough rates was estimated from audio recordings and calculated by taking the total number of cough events during the monitoring period while the subject was awake and dividing by the total duration (in hours) for the monitoring period the subject was awake. Any session with a recording duration < 4 hours was considered as missing. The full analysis set included all enrolled subjects who took at least one dose of study medication and provided at least one baseline and at least one post-baseline primary endpoint observation during the treatment period.	
End point type	Primary
End point timeframe: Baseline and 24 hours post-dose	

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: Descriptive statistics are presented for this single-arm analysis.

End point values	AX-8 orally disintegrating tablet (ODT) 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: cough per hour				
median (inter-quartile range (Q1-Q3))				
Baseline	64.1 (27.4 to 94.4)			
Post-treatment	54.8 (16.4 to 79.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Hourly Objective Cough Frequency Over 24 Hours After 1 Dose of Treatment

End point title	Change from Baseline in Hourly Objective Cough Frequency Over 24 Hours After 1 Dose of Treatment
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End point description:

The change in hourly cough rates was estimated from audio recordings and calculated by taking the total number of cough events during the monitoring period (24 hours) and dividing by the total duration (in hours) for the monitoring period (24). Any session with a recording duration < 4 hours was considered as missing. The full analysis set included all enrolled subjects who took at least one dose of study medication and provided at least one baseline and at least one post-baseline primary endpoint observation during the treatment period.

End point type	Secondary
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End point timeframe:

Comparison of periods of 4, 8, and 24 hours after the installation of the cough monitor (baseline visit) with periods of 4, 8, and 24 hours after dosing (treatment visit)

End point values	AX-8 orally disintegrating tablet (ODT) 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percent change				
number (not applicable)				
Changes over 4 hours post-dose	-42.0			
Changes over 8 hours post-dose	-36.9			
Changes over 24 hours post-dose	-15.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with $\geq 30\%$ Reduction in Awake Cough Frequency per Hour

End point title	Percentage of Subjects with $\geq 30\%$ Reduction in Awake Cough Frequency per Hour
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End point description:

The percentage of subjects with $\geq 30\%$ of reduction from baseline in awake cough frequency is the number of subjects with $\leq -30\%$ change in awake cough frequency divided by the total number of subjects with available data. The full analysis set included all enrolled subjects who took at least one dose of study medication and provided at least one baseline and at least one post-baseline primary endpoint observation during the treatment period.

End point type	Secondary
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End point timeframe:

24 hours post-dose

End point values	AX-8 orally disintegrating tablet (ODT) 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of subjects				
number (not applicable)	33.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with $\geq 30\%$ Reduction in Cough Frequency per Hour

End point title	Percentage of Subjects with $\geq 30\%$ Reduction in Cough Frequency per Hour
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End point description:

The percentage of subjects with $\geq 30\%$ reduction from baseline in 24-cough frequency is the number of subjects with $\leq -30\%$ change in cough frequency divided by the total number of subjects with available data. The full analysis set included all enrolled subjects who took at least one dose of study medication and provided at least one baseline and at least one post-baseline primary endpoint observation during the treatment period.

End point type	Secondary
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End point timeframe:

Periods of 4, 8, and 24 hours post-dose

End point values	AX-8 orally disintegrating tablet (ODT) 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of subjects				
number (not applicable)				
Changes over 4 hours post-dose	41.7			
Changes over 8 hours post-dose	58.3			
Changes over 24 hours post-dose	33.3			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Cough Severity Visual Analogue Scale (VAS)

End point title	Change from Baseline in Cough Severity Visual Analogue Scale (VAS)
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End point description:

Subjects rated cough severity 30 mins before cough monitor installation or dosing, on baseline and treatment days, respectively, and then hourly for 6 hours using a 100-mm visual analogue scale (VAS). The VAS for the first 4 hours were recorded in the clinic and the last 2 hours were recorded at home using a patient diary. The subject's impression at a time point during the baseline visit was compared to the overall impression during more than a 24-hour period. Therefore, the value >24h is an overall impression at a specific time point. The full analysis set included all enrolled subjects who took at least one dose of study medication and provided at least one baseline and at least one post-baseline primary endpoint observation during the treatment period.

End point type	Secondary
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End point timeframe:

Baseline (Day 0) and up to ≥24 hours post-dose (Day 1)

End point values	AX-8 orally disintegrating tablet (ODT) 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: mm				
median (full range (min-max))				
30 min before cough monitor installation (n=12)	65.0 (53 to 95)			
1 hr after cough monitor installation (n=12)	65.5 (14 to 86)			
2 hr after cough monitor installation (n=12)	65.0 (8 to 91)			
3 hr after cough monitor installation (n=12)	64.0 (5 to 85)			
4 hr after cough monitor installation (n=12)	62.0 (2 to 82)			
5 hr after cough monitor installation (n=12)	59.5 (13 to 88)			
6 hr after cough monitor installation (n=12)	60.0 (11 to 92)			
30 min pre-dose (n=12)	66.0 (18 to 87)			
1 hr post-dose (n=12)	48.0 (2 to 81)			
2 hr post-dose (n=12)	49.0 (2 to 86)			
3 hr post-dose (n=12)	44.5 (2 to 85)			
4 hr post-dose (n=12)	42.5 (2 to 91)			
5 hr post-dose (n=11)	47.0 (2 to 88)			
6 hr post-dose (n=11)	47.0 (1 to 86)			
Overall period ≥24 hr post-dose (n=12)	47.0 (6 to 96)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Urge-to-Cough VAS

End point title	Change from Baseline in Urge-to-Cough VAS
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End point description:

Subjects rated urge-to-cough 30 mins before cough monitor installation or dosing, on baseline and treatment days, respectively, and then hourly for 6 hours using a 100-mm visual analogue scale (VAS). The VAS for the first 4 hours were recorded in the clinic and the last 2 hours were recorded at home using a patient diary. The subject's impression at a time point during the baseline visit was compared to the overall impression during more than a 24-hour period. Therefore, the value >24h is an overall impression at a specific time point. The full analysis set included all enrolled subjects who took at least one dose of study medication and provided at least one baseline and at least one post-baseline primary endpoint observation during the treatment period.

End point type	Secondary
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End point timeframe:

Baseline (Day 0) and up to ≥ 24 hours post-dose (Day 1)

End point values	AX-8 orally disintegrating tablet (ODT) 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: mm				
median (full range (min-max))				
30 min before cough monitor installation (n=12)	62.0 (14 to 93)			
1 hr after cough monitor installation (n=12)	57.0 (11 to 88)			
2 hr after cough monitor installation (n=12)	51.0 (3 to 92)			
3 hr after cough monitor installation (n=12)	49.0 (4 to 86)			
4 hr after cough monitor installation (n=12)	52.5 (2 to 90)			
5 hr after cough monitor installation (n=12)	49.0 (2 to 83)			
6 hr after cough monitor installation (n=12)	55.5 (4 to 90)			
30 min pre-dose (n=12)	62.5 (7 to 90)			
1 hr post-dose (n=12)	48.0 (1 to 92)			
2 hr post-dose (n=12)	43.0 (2 to 87)			
3 hr post-dose (n=12)	26.0 (2 to 85)			
4 hr post-dose (n=12)	34.0 (1 to 92)			
5 hr post-dose (n=11)	36.0 (1 to 83)			
6 hr post-dose (n=11)	41.0 (1 to 84)			
Overall period ≥ 24 hr post-dose (n=12)	46.0 (3 to 95)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Throat Irritation VAS

End point title	Change from Baseline in Throat Irritation VAS
End point description:	
Subjects rated cough severity 30 mins before cough monitor installation or dosing, on baseline and treatment days, respectively, and then hourly for 6 hours using a 100-mm visual analogue scale (VAS). The VAS for the first 4 hours were recorded in the clinic and the last 2 hours were recorded at home using a patient diary. The subject's impression at a time point during the baseline visit was compared to the overall impression during more than a 24-hour period. Therefore, the value >24h is an overall impression at a specific time point. The full analysis set included all enrolled subjects who took at least one dose of study medication and provided at least one baseline and at least one post-baseline primary endpoint observation during the treatment period.	
End point type	Secondary
End point timeframe:	
Baseline (Day 0) and up to ≥24 hours post-dose (Day 1)	

End point values	AX-8 orally disintegrating tablet (ODT) 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: mm				
median (full range (min-max))				
30 min before cough monitor installation (n=12)	56.5 (1 to 92)			
1 hr after cough monitor installation (n=12)	42.0 (1 to 86)			
2 hr after cough monitor installation (n=12)	39.0 (0 to 91)			
3 hr after cough monitor installation (n=12)	32.5 (0 to 90)			
4 hr after cough monitor installation (n=12)	36.0 (0 to 89)			
5 hr after cough monitor installation (n=12)	30.0 (0 to 90)			
6 hr after cough monitor installation (n=12)	35.0 (0 to 91)			
30 min pre-dose (n=12)	40.5 (0 to 83)			
1 hr post-dose (n=12)	22.5 (1 to 86)			
2 hr post-dose (n=12)	7.5 (0 to 71)			
3 hr post-dose (n=12)	5.0 (0 to 78)			
4 hr post-dose (n=12)	5.5 (0 to 77)			
5 hr post-dose (n=11)	7.0 (2 to 76)			
6 hr post-dose (n=11)	6.0 (1 to 79)			
Overall period ≥24 hr post-dose (n=12)	9.0 (1 to 97)			

Statistical analyses

No statistical analyses for this end point

Secondary: Throat Cooling VAS

End point title	Throat Cooling VAS
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End point description:

Subjects rated cough severity 30 mins before cough monitor installation or dosing, on baseline and treatment days, respectively, and then hourly for 6 hours using a 100-mm visual analogue scale (VAS). The VAS for the first 4 hours were recorded in the clinic and the last 2 hours were recorded at home using a patient diary. The subject's impression at a time point during the baseline visit was compared to the overall impression during more than a 24-hour period. Therefore, the value >24h is an overall impression at a specific time point. The full analysis set included all enrolled subjects who took at least one dose of study medication and provided at least one baseline and at least one post-baseline primary endpoint observation during the treatment period.

End point type	Secondary
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End point timeframe:

Up to ≥24 hours post-dose (Day 1)

End point values	AX-8 orally disintegrating tablet (ODT) 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: mm				
median (full range (min-max))				
30 min pre-dose (n=10)	1.5 (0 to 20)			
30 min post-dose (n=12)	19.0 (2 to 80)			
1 hr post-dose (n=12)	3.5 (1 to 67)			
1.5 hr post-dose (n=12)	2.0 (0 to 63)			
2 hr post-dose (n=12)	2.0 (0 to 56)			
2.5 hr post-dose (n=12)	3.5 (0 to 65)			
3 hr post-dose (n=12)	2.0 (0 to 42)			
4 hr post-dose (n=12)	1.5 (0 to 14)			
5 hr post-dose (n=11)	2.0 (0 to 45)			
6 hr post-dose (n=11)	2.0 (0 to 48)			
Overall period ≥24 hr post-dose (n=12)	3.0 (0 to 20)			

Statistical analyses

No statistical analyses for this end point

Secondary: Global Rating of Change Scale (GRCS) - Cough Frequency

End point title	Global Rating of Change Scale (GRCS) - Cough Frequency
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End point description:

Subjects assessed overall status of cough frequency since dosing using the GRCS instrument, with 3 categories and a 14-point scale range: better (1-7), about the same, and worse (8-14). GRCS were measured 4h post-dose on Treatment Day 1 and 24h post-dose on Treatment Day 2. The full analysis set included all enrolled subjects who took at least one dose of study medication and provided at least one baseline and at least one post-baseline primary endpoint observation during the treatment period. pd=post-dose.

End point type	Secondary
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End point timeframe:

4h post-dose on Treatment Day 1 and 24h post-dose on Treatment Day 2

End point values	AX-8 orally disintegrating tablet (ODT) 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects				
4h pd: better (n=12)	4			
4h pd: about the same (n=12)	7			
4h pd: worse (n=12)	1			
24h pd: better (n=11)	4			
24h pd: about the same (n=11)	6			
24h pd: worse (n=11)	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Global Rating of Change Scale (GRCS) - Cough Severity

End point title	Global Rating of Change Scale (GRCS) - Cough Severity
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End point description:

Subjects assessed overall status of cough severity since dosing using the GRCS instrument, with 3 categories and a 14-point scale range: better (1-7), about the same, and worse (8-14). GRCS were measured 4h post-dose on Treatment Day 1 and 24h post-dose on Treatment Day 2. The full analysis set included all enrolled subjects who took at least one dose of study medication and provided at least one baseline and at least one post-baseline primary endpoint observation during the treatment period. pd=post-dose.

End point type	Secondary
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End point timeframe:

4h post-dose on Treatment Day 1 and 24h post-dose on Treatment Day 2

End point values	AX-8 orally disintegrating tablet (ODT) 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: Subjects				
4h pd: better (n=12)	5			
4h pd: about the same (n=12)	6			
4h pd: worse (n=12)	1			
24h pd: better (n=11)	4			
24h pd: about the same (n=11)	6			
24h pd: worse (n=11)	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Treatment-Emergent Adverse Events (TEAEs)

End point title	Percentage of Subjects with Treatment-Emergent Adverse Events (TEAEs)
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End point description:

TEAEs were defined as AEs with a date of onset on or after first study medication intake. The incidence of TEAEs was classified by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA). For incidence reporting, if a subject reported more than one AE that was coded to the same system organ class or preferred term, the subject was counted only once for that specific system organ class or preferred term. The safety analysis set consisted of all enrolled subjects who received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

Approximately 30 days

End point values	AX-8 orally disintegrating tablet (ODT) 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of subjects				
number (not applicable)	58.33			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Serious Adverse Events (SAEs)

End point title	Percentage of Subjects with Serious Adverse Events (SAEs)
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End point description:

SAEs were defined as AEs that resulted in death, threat to life, hospitalization, persistent or significant incapacity, congenital anomaly/birth defect, or important medical event that was considered serious by the investigator or Sponsor or would require medical/surgical intervention to prevent any of the prior outcomes. The safety analysis set consisted of all enrolled subjects who received at least one dose of study medication.

End point type	Secondary
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End point timeframe:

Approximately 30 days

End point values	AX-8 orally disintegrating tablet (ODT) 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of subjects				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Approximately 30 days

Adverse event reporting additional description:

The safety analysis set consisted of all enrolled subjects who received at least one dose of study medication.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.0
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Reporting groups

Reporting group title	AX-8
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Reporting group description:

Subjects received a single dose of AX-8 orally disintegrating tablet (ODT) 5 mg by mouth.

Serious adverse events	AX-8		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	AX-8		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)		
Injury, poisoning and procedural complications			
Bruising			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		
Twitching eyelid			

subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Tiredness subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Gastrointestinal disorders Worsening acid reflux subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Paraesthesia oral subjects affected / exposed occurrences (all) Taste disturbance subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1 1 / 12 (8.33%) 1		
Respiratory, thoracic and mediastinal disorders Sore throat subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Musculoskeletal and connective tissue disorders Chronic back pain subjects affected / exposed occurrences (all)	1 / 12 (8.33%) 1		
Infections and infestations Lower respiratory tract infection subjects affected / exposed occurrences (all) Upper respiratory tract infection	1 / 12 (8.33%) 1		

subjects affected / exposed	2 / 12 (16.67%)		
occurrences (all)	2		
Aches and fever			
subjects affected / exposed	1 / 12 (8.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 January 2018	<p>The following substantial changes have been made to the protocol: Blood sampling for pharmacokinetic (PK) analysis was added (+15, +30 mins, +1, +1.25, +1.5, +1.75, +2, +2.5, +3, +3.5 hours).</p> <p>PK sample will be taken anytime pre-dose on Day 1, post-dose + 15, +30, +45 minutes, +1, +1.25, +1.5, +1.75, +2, +2.5, +3, +3.5, +4 hours (i.e., 1hr, 1hr15 mins, 1hr30mins, 1hr45mins, 2hr, 2hr30mins, 3hr, 3hr30mins, 4hr).</p> <p>PK analysis changed from being a secondary endpoint to being an exploratory endpoint. Synopsys updated: Study Objectives completed and section "Exploratory Endpoint" added. Section 2 – Study Objectives. New paragraph "Exploratory Objectives" added.</p> <p>New section 3.3.4 – Exploratory Endpoint. The patient information sheet (PIS) has been updated in line with these protocol changes.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported