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

6 X P P D U \

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

5 H V X O W V L Q I R U P D W L R Q

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

7 U L D O L Q I R U P D W L R Q

7 U L D O L G H Q W L I L F D W L R Q

Sponsor protocol code	AX8-001

$ G G L W L R Q D O V W X G \ L G H Q W L I L H U V

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

Notes:

6 S R Q V R U V

Sponsor organisation name	Axalbion SA
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Notes:

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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:

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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:

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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:

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Country: Number of subjects enrolled	United Kingdom: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

Notes:

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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

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Recruitment details:

12 subjects were enrolled in the United Kingdom.

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Screening details:

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

3HULRG

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

$UPV

$UP WLWOH	AX-8 orally disintegrating tablet (ODT) 5 mg

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.

1XPEHU RI VXEMHFWV LQ SHULRG	AX-8 orally disintegrating tablet (ODT) 5 mg
Started	12
Completed	12

3HULRG

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

$UPV

$UP WLWOH	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.

1XPEHU RI VXEMHFWV LQ SHULRG	AX-8 orally disintegrating tablet (ODT) 5 mg
Started	12
Completed	12

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

$UPV	
$UP WLWOH	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.

1XPEHU RI VXEMHFWV LQ SHULRG	AX-8 orally disintegrating tablet (ODT) 5 mg
Started	12
Completed	12

3HULRG	
Period 4 title	Follow-up (Visit 5/Withdraw/Study End)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded
$UPV	
$UP WLWOH	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.

1XPEHU RI VXEMHFWV LQ SHULRG	AX-8 orally disintegrating tablet (ODT) 5 mg
Started	12
Completed	11
Not completed	1
Adverse event, non-fatal	1

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Reporting group title	Baseline (Visit 2)

Reporting group description: -

5HSRUWLQJ JURXS YDOXHV	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	

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(QG SRLQWV UHSRUWLQJ JURXSV	
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.	

3ULPDU\ &KDQJH IURP %DVHOLQH LQ 2EMHFWLYH $ZDNH &RXJK)UHTXH DIWHU 'RVH RI 7UHDWPHQW	
End point title	Change from Baseline in Objective Awake Cough Frequency Over 24 hours after 1 Dose of Treatment[1]

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 m

No statistical analyses for this end point

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

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

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)

(QG SRLQW YDOXHV	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			

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No statistical analyses for this end point

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End point title	Percentage of Subjects with ≥ 30% Reduction in Awake Cough Frequency per Hour

End point description:

The percentage of subjects with ≥ 30% of reduction from baseline in awake cough frequency is the number of subjects with ≤ -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

End point timeframe:

24 hours post-dose

(QG SRLQW YDOXHV	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			

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No statistical analyses for this end point

6HFRQGDU\ 3HUFHQWDJH RI 6XEMHFWV ZLWK • 5HGXFWLRQ LQ &RXJ +RXU

End point title	Percentage of Subjects with ≥ 30% Reduction in Cough Frequency per Hour

End point description:

The percentage of subjects with ≥ 30% reduction from baseline in 24-cough frequency is the number of subjects with ≤ -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

End point timeframe:

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

(QG SRLQW YDOXHV	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			

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No statistical analyses for this end point

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

(QG SRLQW YDOXHV	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)			

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No statistical analyses for this end point

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

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

End point timeframe:

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

(QG SRLQW YDOXHV	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)			

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No statistical analyses for this end point

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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)

(QG SRLQW YDOXHV	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)			

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No statistical analyses for this end point

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End point title	Throat Cooling 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:

Up to ≥24 hours post-dose (Day 1)

(QG SRLQW YDOXHV	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)			

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No statistical analyses for this end point

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

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

End point timeframe:

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

(QG SRLQW YDOXHV	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			

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No statistical analyses for this end point

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

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

End point timeframe:

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

(QG SRLQW YDOXHV	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			

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No statistical analyses for this end point

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

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

End point timeframe:

Approximately 30 days

(QG SRLQW YDOXHV	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			

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No statistical analyses for this end point

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

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

End point timeframe:

Approximately 30 days

(QG SRLQW YDOXHV	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			

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No statistical analyses for this end point

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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 name	MedDRA
Dictionary version	20.0

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Reporting group title	AX-8

Reporting group description:

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

6HULRXV DGYHUVH HYHQWV	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 %

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

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

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