Clinical trial results:
A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Pharmacokinetics, Safety, and Antiviral Activity of JNJ-63623872 in Combination With Oseltamivir in Adult and Elderly Hospitalized Patients With Influenza A Infection

Summary

EudraCT number	2015-003002-17
Trial protocol	SE BE DE NL ES
Global end of trial date	15 March 2017

Results information

Result version number	v1 (current)
This version publication date	31 March 2018
First version publication date	31 March 2018

Trial information

Trial identification

Sponsor protocol code	63623872FLZ2002

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Janssen-Cilag International, NV
Sponsor organisation address	Turnhoutseweg 30, Beerse, Belgium, 2340
Public contact	Janssen-Cilag International, NV, Clinical Registry group, ClinicalTrialsEU@its.jnj.com
Scientific contact	Janssen-Cilag International, NV, Clinical Registry group, ClinicalTrialsEU@its.jnj.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	15 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the pharmacokinetic (PK) parameters of pimodivir in combination with oseltamivir (OST) in elderly subjects (aged 65 to less than or equal to [<=] 85 years) compared to adults (aged 18 to <= 64 years) with influenza A infection.

Protection of trial subjects:

Safety evaluations included monitoring of adverse events (AEs), clinical laboratory tests (hematology, serum chemistry, and urinalysis), vital signs measurements, physical examinations, electrocardiography (ECGs), pregnancy testing and specific toxicities.

Background therapy:

All subjects received OST

Evidence for comparator: -

Actual start date of recruitment	19 January 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	Spain: 23
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Malaysia: 7
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Sweden: 12
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	United States: 29
Worldwide total number of subjects	99
EEA total number of subjects	52

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)	60
From 65 to 84 years	38
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Total 194 subjects were screened, 102 were randomized out of which 99 treated.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Pimodivir 600 mg bid + Oseltamivir 75 mg bid

Arm description:

Subjects received Pimodivir 600 milligram (mg) tablets and oseltamivir 75 mg capsules orally twice daily (bid) for 7 days. Dose of oseltamivir was adjusted from 75 mg to 30 mg and vice versa during the course of treatment based on the estimated glomerular filtration rate (eGFR) value.

Arm type	Experimental
Investigational medicinal product name	Pimodivir 600 milligram (mg)
Investigational medicinal product code	JNJ-63623872
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received Pimodivir 600 mg (2*300 mg tablets) orally twice daily for 7 days.

Investigational medicinal product name	Oseltamivir 75 mg bid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects received oseltamivir 75 mg capsules orally twice daily for 7 days.

Arm title	Pimodivir placebo bid + Oseltamivir 75 mg bid

Arm description:

Subjects received placebo matched to pimodivir tablets and oseltamivir 75 mg capsules orally twice daily for 7 days. Dose of oseltamivir was adjusted from 75 mg to 30 mg and vice versa during the course of treatment based on the eGFR value.

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

Dosage and administration details:

Subjects received placebo matched to Pimodivir tablets orally twice daily for 7 days

Investigational medicinal product name	Oseltamivir 75 mg bid
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received oseltamivir 75 mg capsules orally twice daily for 7 days.

Number of subjects in period 1	Pimodivir 600 mg bid + Oseltamivir 75 mg bid	Pimodivir placebo bid + Oseltamivir 75 mg bid
Started	64	35
Completed	55	30
Not completed	9	5
Adverse event, serious fatal	1	-
Consent withdrawn by subject	8	3
Adverse event, non-fatal	-	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Pimodivir 600 mg bid + Oseltamivir 75 mg bid
Reporting group description:	
Subjects received Pimodivir 600 milligram (mg) tablets and oseltamivir 75 mg capsules orally twice daily (bid) for 7 days. Dose of oseltamivir was adjusted from 75 mg to 30 mg and vice versa during the course of treatment based on the estimated glomerular filtration rate (eGFR) value.	
Reporting group title	Pimodivir placebo bid + Oseltamivir 75 mg bid
Reporting group description:	
Subjects received placebo matched to pimodivir tablets and oseltamivir 75 mg capsules orally twice daily for 7 days. Dose of oseltamivir was adjusted from 75 mg to 30 mg and vice versa during the course of treatment based on the eGFR value.	

Reporting group values	Pimodivir 600 mg bid + Oseltamivir 75 mg bid	Pimodivir placebo bid + Oseltamivir 75 mg bid	Total
Number of subjects	64	35	99
Title for AgeCategorical Units: subjects			
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	39	21	60
From 65 to 84 years	24	14	38
85 years and over	1	0	1
Title for AgeContinuous Units: years			
arithmetic mean	58.1	57.2	
standard deviation	± 16.06	± 13.71	-
Title for Gender Units: subjects			
Female	27	18	45
Male	37	17	54

End points

End points reporting groups

Reporting group title	Pimodivir 600 mg bid + Oseltamivir 75 mg bid

Reporting group description:

Subjects received Pimodivir 600 milligram (mg) tablets and oseltamivir 75 mg capsules orally twice daily (bid) for 7 days. Dose of oseltamivir was adjusted from 75 mg to 30 mg and vice versa during the course of treatment based on the estimated glomerular filtration rate (eGFR) value.

Reporting group title	Pimodivir placebo bid + Oseltamivir 75 mg bid

Reporting group description:

Subjects received placebo matched to pimodivir tablets and oseltamivir 75 mg capsules orally twice daily for 7 days. Dose of oseltamivir was adjusted from 75 mg to 30 mg and vice versa during the course of treatment based on the eGFR value.

Subject analysis set title	Elderly Adults
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received Pimodivir 600 milligram (mg) or matching placebo to Pimodivir tablets and oseltamivir 75 mg capsules orally twice daily for 7 days. Dose of oseltamivir was adjusted from 75 to 30 and vice versa during the course of treatment based on the estimated glomerular filtration rate (eGFR) value.

Subject analysis set title	Non-elderly Adults
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received Pimodivir 600 milligram (mg) or matching placebo to Pimodivir tablets and oseltamivir 75 mg capsules orally twice daily for 7 days. Dose of oseltamivir was adjusted from 75 mg to 30 mg and vice versa during the course of treatment based on the eGFR value.

Primary: Maximum Observed Plasma Concentration (Cmax) of Pimodivir

End point title	Maximum Observed Plasma Concentration (Cmax) of Pimodivir

End point description:

Cmax is the maximum observed plasma concentration. Pharmacokinetic (PK) population included all randomized participants who received at least 1 dose of the study drug and with 1 PK blood sample.Here 'n' signifies number of subjects analyzed for under specific age groups for whom Cmax could be determined.

End point type	Primary

End point timeframe:

Pre-dose, 1, 2, 4, 6, 8, 10 and 12 hours post-dose on Day 3

End point values	Elderly Adults	Non-elderly Adults		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	20		
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)	5933 (± 4427)	5378 (± 3888)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Elderly Adults v Non-elderly Adults

Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio
Point estimate	111.71
Confidence interval	
level	90 %
sides	2-sided
lower limit	70.7
upper limit	176.52

Primary: Minimum Observed Plasma Concentration (Cmin) of Pimodivir

End point title	Minimum Observed Plasma Concentration (Cmin) of Pimodivir

End point description:

Cmin is the minimum observed plasma concentration. PK population included all randomized participants who received at least 1 dose of the study drug and with 1 PK blood sample. Here 'N' signifies number of subjects who were evaluable for this endpoint. Here 'n' signifies number of subjects analyzed for specific arm under specific age groups for whom Cmin could be determined.

End point type	Primary

End point timeframe:

Pre-dose, 1, 2, 4, 6, 8, 10 and 12 hours post-dose on Day 3

End point values	Elderly Adults	Non-elderly Adults		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	21		
Units: ng/mL				
arithmetic mean (standard deviation)	738 (± 892)	507 (± 414)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Elderly Adults v Non-elderly Adults
Number of subjects included in analysis	36
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio
Point estimate	104.97
Confidence interval	
level	90 %
sides	2-sided
lower limit	62.14
upper limit	177.33

Primary: Area Under the Plasma Concentration-Time Curve From Time of Administration to 12 hours After Dosing (AUC [0-12])

End point title	Area Under the Plasma Concentration-Time Curve From Time of Administration to 12 hours After Dosing (AUC [0-12])

End point description:

The AUC(0-12) was the area under the plasma concentration-time curve from time zero to 12 hours. PK population included all randomized participants who received at least 1 dose of the study drug and with 1 PK blood sample. Here 'n' signifies number of subjects analyzed under specific age groups for whom AUC[0-12] could be determined.

End point type	Primary

End point timeframe:

Pre-dose, 1, 2, 4, 6, 8, 10 and 12 hours post-dose on Day 3

End point values	Elderly Adults	Non-elderly Adults		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	20		
Units: nanogram*hour per milliliter (ng*h/mL)				
arithmetic mean (standard deviation)	27386 (± 25191)	20101 (± 11063)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Elderly Adults v Non-elderly Adults
Number of subjects included in analysis	35
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Geometric Mean Ratio
Point estimate	116.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	76.49
upper limit	176.22

Secondary: Median Time to Influenza Viral Negativity

End point title	Median Time to Influenza Viral Negativity

End point description:

Time to influenza viral negativity was measured based on quantitative reverse transcription polymerase chain reaction (qRT-PCR) and/or viral culture from nasal mid-turbinate (MT) swabs and, if applicable, based on PCR-based rapid molecular testing from nasal MT swabs. Full Analysis set was defined as all

randomly assigned subjects who received at least 1 dose of study drug and who have a confirmed infection with influenza A.

End point type	Secondary

End point timeframe:

Up to Day 14

End point values	Pimodivir 600 mg bid + Oseltamivir 75 mg bid	Pimodivir placebo bid + Oseltamivir 75 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	32		
Units: days				
median (confidence interval 95%)	9.53 (8.55 to 12.68)	9.74 (6.67 to 12.99)		

Statistical analyses

No statistical analyses for this end point

Secondary: Influenza Viral Load Over Time

End point title	Influenza Viral Load Over Time

End point description:

Viral load over time was measured by qRT-PCR and/or viral culture. Full analysis set was defined as all randomly assigned subjects who received at least 1 dose of study drug and who have a confirmed infection with influenza A. Here 'n' signifies number of subjects analyzed for specific time point. 99999 indicates that the data was not estimable due no subject was evaluable.

End point type	Secondary

End point timeframe:

Up to Day 14

End point values	Pimodivir 600 mg bid + Oseltamivir 75 mg bid	Pimodivir placebo bid + Oseltamivir 75 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	32		
Units: Log10 viral particles/milliliter (vp/mL)				
median (full range (min-max))				
Baseline (n=58, n=30)	5.64 (0.0 to 8.4)	5.83 (3.1 to 9.1)		
Day 1 (n=4, n=1)	6.57 (5.4 to 7.0)	4.43 (4.43 to 4.43)		
Day 2 (n=57, n=28)	4.87 (2.1 to 7.1)	4.67 (0.0 to 7.3)		
Day 3 (n=45, n=24)	3.93 (0.0 to 6.8)	4.10 (0.0 to 6.9)		

Day 4 (n=34, n=15)	3.31 (0.0 to 5.1)	3.15 (0.0 to 5.6)		
Day 5 (n=55, n=28)	2.67 (0.0 to 7.5)	2.78 (0.0 to 6.5)		
Day 6 (n=14, n=6)	2.63 (0.0 to 4.0)	1.66 (0.0 to 5.2)		
Day 7 (n=14, n=5)	2.12 (0.0 to 4.7)	3.34 (0.0 to 4.4)		
Day 8 (n=55, n=20)	2.12 (0.0 to 5.9)	1.06 (0.0 to 5.1)		
Day 9 (n=7, n=1)	2.12 (0.0 to 2.12)	0.0 (0.0 to 0.0)		
Day 10 (n=54, n=23)	0.0 (0.0 to 5.7)	0.0 (0.0 to 3.3)		
Day 11 (n=6, n=1)	0.0 (0.0 to 2.5)	0.0 (0.0 to 0.0)		
Day 12 (n=2, n=0)	1.06 (0.0 to 2.1)	99999 (-99999 to 99999)		
Day 13 (n=2, n=0)	1.06 (-99999 to 2.1)	99999 (-99999 to 99999)		
Day 14 (n=51, n=22)	0.0 (0.0 to 5.3)	0.0 (0.0 to 2.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of Change in Viral Load

End point title	Rate of Change in Viral Load

End point description:

Rate of change in viral load during treatment as measured by qRT-PCR and/or viral culture. Full analysis set was defined as all randomly assigned subjects who received at least 1 dose of study drug and who have a confirmed infection with influenza A. Here 'N' signifies number of subjects who were evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Up to Day 14

End point values	Pimodivir 600 mg bid + Oseltamivir 75 mg bid	Pimodivir placebo bid + Oseltamivir 75 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	32		
Units: Log10 vp/mL/day				
median (confidence interval 95%)	-0.35 (-0.39 to -0.30)	-0.42 (-0.49 to -0.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Plasma Concentration-Time Curve (AUC) of Viral Load

End point title	Area Under the Plasma Concentration-Time Curve (AUC) of Viral Load

End point description:

The AUC of viral load as measured by quantitative polymerase chain reaction (qRT-PCR) and/or viral culture. Full analysis set was defined as all randomly assigned subjects who received at least 1 dose of study drug and who have a confirmed infection with influenza A.

End point type	Secondary

End point timeframe:

Up to Day 8

End point values	Pimodivir 600 mg bid + Oseltamivir 75 mg bid	Pimodivir placebo bid + Oseltamivir 75 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	32		
Units: days*vp/mL				
arithmetic mean (confidence interval 95%)	22.8 (20.4 to 25.1)	22.1 (19.0 to 25.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Influenza Complications

End point title	Percentage of Subjects with Influenza Complications

End point description:

Disease status and incidence of complications associated with influenza were: bacterial pneumonia (culture confirmed where possible), other bacterial superinfections, respiratory failure, pulmonary disease (example, asthma, chronic obstructive pulmonary disease [COPD]), cardiovascular and cerebrovascular disease (example, myocardial infarction, congestive heart failure [CHF], arrhythmia, stroke). Full analysis set was defined as all randomly assigned subjects who received at least 1 dose of study drug and who have a confirmed infection with influenza A.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Pimodivir 600 mg bid + Oseltamivir 75 mg bid	Pimodivir placebo bid + Oseltamivir 75 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	32		
Units: Percentage of subjects				
number (not applicable)				
All Complications	7.9	15.6		

Bacterial Pneumonia	0	0		
Bacterial Superinfections	1.6	3.1		
Respiratory Failure	1.6	0		
Pulmonary Disease	3.2	6.3		
Cardiovascular and Cerebrovascular Disease	1.6	0		
Post-baseline ICU Admission	1.6	0		
All-cause Mortality	1.6	0		
Other	3.2	6.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Duration and Severity of Clinical Symptoms as Measured by the FLU-PRO through Day 33

End point title	Change in Duration and Severity of Clinical Symptoms as Measured by the FLU-PRO through Day 33

End point description:

Change in duration and severity of clinical symptoms as measured by the influenza patient-reported outcome questionnaire (FLU-PRO). The FLU-PRO total score is computed as a mean score across 32 items contained by the instrument. The total score ranges from 0 (symptom free) to 4 (very severe symptoms). Analysis set is defined as all randomly assigned subjects who received at least 1 dose of study drug and who have a confirmed infection with influenza A. Here 'n' signifies number of subjects analyzed for specific arm. 99999 indicates that the data was not estimable due to less number of events.

End point type	Secondary

End point timeframe:

Baseline up to Day 33

End point values	Pimodivir 600 mg bid + Oseltamivir 75 mg bid	Pimodivir placebo bid + Oseltamivir 75 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	32		
Units: units on a scale				
arithmetic mean (standard deviation)				
Day 1 (n=20, n=16)	-0.08 (± 0.247)	-0.11 (± 0.349)		
Day 2 (n=35, n=20)	-0.48 (± 0.644)	-0.33 (± 0.798)		
Day 3 (n=38, n=22)	-0.60 (± 0.624)	-0.52 (± 0.641)		
Day 4 (n=35, n=19)	-0.71 (± 0.702)	-0.56 (± 0.625)		
Day 5 (n=33, n=17)	-0.76 (± 0.689)	-0.67 (± 0.643)		
Day 6 (n=33, n=17)	-0.85 (± 0.692)	-0.75 (± 0.659)		
Day 7 (n=33, n=17)	-0.87 (± 0.738)	-0.69 (± 0.623)		

Day 8 (n=33, n=18)	-0.89 (± 0.729)	-0.80 (± 0.764)		
Day 9 (n=31, n=20)	-0.93 (± 0.764)	-0.84 (± 0.732)		
Day 10 (n=32, n=20)	-0.91 (± 0.723)	-0.81 (± 0.743)		
Day 11 (n=28, n=18)	-0.87 (± 0.756)	-0.76 (± 0.534)		
Day 12 (n=29, n=18)	-0.87 (± 0.725)	-0.89 (± 0.695)		
Day 13 (n=28, n=20)	-0.93 (± 0.702)	-0.94 (± 0.650)		
Day 14 (n=29, n=19)	-0.85 (± 0.613)	-0.92 (± 0.670)		
Day 15 (n=25, n=15)	-0.88 (± 0.630)	-0.90 (± 0.724)		
Day 16 (n=23, n=14)	-0.84 (± 0.588)	-0.90 (± 0.762)		
Day 17 (n=22, n=15)	-0.98 (± 0.690)	-0.97 (± 0.774)		
Day 18 (n=19, n=15)	-1.06 (± 0.753)	-1.00 (± 0.868)		
Day 19 (n=21, n=13)	-1.06 (± 0.749)	-1.05 (± 0.880)		
Day 20 (n=21, n=15)	-1.03 (± 0.710)	-1.03 (± 0.847)		
Day 21 (n=22, n=16)	-1.00 (± 0.701)	-0.98 (± 0.849)		
Day 22 (n=18, n=15)	-1.02 (± 0.789)	-0.92 (± 0.690)		
Day 23 (n=21, n=14)	-1.11 (± 0.858)	-0.96 (± 0.731)		
Day 24 (n=19, n=11)	-0.87 (± 0.534)	-0.91 (± 0.580)		
Day 25 (n=17, n=11)	-0.94 (± 0.659)	-0.85 (± 0.661)		
Day 26 (n=18, n=11)	-0.86 (± 0.755)	-0.87 (± 0.742)		
Day 27 (n=15, n=8)	-1.02 (± 0.745)	-0.74 (± 0.734)		
Day 28 (n=12, n=7)	-0.60 (± 0.505)	-0.82 (± 0.675)		
Day 29 (n=2, n=2)	-1.13 (± 0.354)	-1.63 (± 0.398)		
Day 30 (n=2, n=0)	-0.61 (± 0.552)	99999 (± 99999)		
Day 31 (n=1, n=0)	-0.75 (± 99999)	99999 (± 99999)		
Day 32 (n=2, n=0)	-0.61 (± 0.420)	99999 (± 99999)		
Day 33 (n=1, n=0)	-0.94 (± 99999)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Improvement of Vital Signs

End point title	Time to Improvement of Vital Signs

End point description:

The time to improvement of vital signs is defined as the time from first study treatment to when at least 4 of 5 symptoms (temperature, blood oxygen saturation, heart rate, SBP, respiration rate) are recovered, including normalization of temperature and blood oxygen saturation. Full analysis set was defined as all randomly assigned subjects who received at least 1 dose of study drug and who have a confirmed infection with influenza A. Here 'N' signifies number of subjects who were evaluable for this endpoint. 99999 indicates that the upper limit of CI was not estimable due to less number of events.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Pimodivir 600 mg bid + Oseltamivir 75 mg bid	Pimodivir placebo bid + Oseltamivir 75 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	28		
Units: hour				
median (confidence interval 95%)	169.92 (46.63 to 99999)	69.90 (35.83 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Improvement of Respiratory Status

End point title	Time to Improvement of Respiratory Status

End point description:

Time to improvement of respiratory status is defined as normalization of blood oxygen saturation and respiration rate. Full analysis set was defined as all randomly assigned subjects who received at least 1 dose of study drug and who have a confirmed infection with influenza A. Here 'N' signifies number of subjects who were evaluable for this endpoint. 99999 indicates that the upper limit of CI was not estimable due to less number of events.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Pimodivir 600 mg bid + Oseltamivir 75 mg bid	Pimodivir placebo bid + Oseltamivir 75 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	28		
Units: hour				
median (confidence interval 95%)	33.53 (21.33 to 241.92)	40.57 (22.75 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects by Ordinal Scale Category

End point title	Percentage of Subjects by Ordinal Scale Category

End point description:

The ordinal scale will be used to assess participant's status and consists of 6 categories or clinical states that are exhaustive, mutually exclusive, and ordered, where 1- Death, 2- Admitted to Intensive Care Unit (ICU) or mechanically ventilated/ extracorporeal membrane oxygenation (ECMO), 3- Non-ICU plus supplemental oxygen, 4- Non-ICU plus no supplemental oxygen, 5- Not hospitalized (NH), but unable to continue activity, 6- Not hospitalized and continues activities.Full Analysis set was defined as all randomly assigned subjects who received at least 1 dose of study drug and who have a confirmed infection with influenza A. Here 'n' signifies number of subjects analyzed for specific category.

End point type	Secondary

End point timeframe:

Baseline and Day 8

End point values	Pimodivir 600 mg bid + Oseltamivir 75 mg bid	Pimodivir placebo bid + Oseltamivir 75 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	32		
Units: Percentage of subjects				
number (not applicable)				
Baseline (n=63,32) Non-ICU+No Supplemental Oxygen	49.2	59.4		
Baseline (n=63,32) Non-ICU+Supplemental Oxygen	50.8	40.6		
Day 8 (n=62,31) NH and Continues Activities	40.3	29.0		
Day 8 (n=62,31)NH, but Unable to Continue Activity	27.4	45.2		
Day 8 (n=62,31) Non-ICU+No Supplemental Oxygen	14.5	6.5		
Day 8 (n=62,31) Non-ICU+Supplemental Oxygen	8.1	3.2		
Day 8 (n=62,31) Death	1.6	0		
Day 8 (n=62,31) Missing	8.1	16.1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with the Emergence of Drug Resistance Mutations with Oseltamivir (OST) and Pimodivir

End point title	Number of Subjects with the Emergence of Drug Resistance Mutations with Oseltamivir (OST) and Pimodivir

End point description:

The number of subjects with the emergence (from Baseline) of drug resistance mutations was measured. Full Analysis set was defined as all randomly assigned subjects who received at least 1 dose of study drug and who have a confirmed infection with influenza A.

End point type	Secondary

End point timeframe:

Baseline up to Day 28

End point values	Pimodivir 600 mg bid + Oseltamivir 75 mg bid	Pimodivir placebo bid + Oseltamivir 75 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	32		
Units: subjects				
number (not applicable)				
Emergence of Pimodivir Mutation	0	0		
Emergence of OST Mutation	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Return to Premorbid Functional Status

End point title	Time to Return to Premorbid Functional Status

End point description:

Time to return to premorbid functional (time to return usual activities) status was evaluated. Full Analysis set was defined as all randomly assigned subjects who received at least 1 dose of study drug and who have a confirmed infection with influenza A. Here 'N' signifies number of subjects who were evaluable for this endpoint. 99999 indicates that the data was not estimable due to less number of events.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Pimodivir 600 mg bid + Oseltamivir 75 mg bid	Pimodivir placebo bid + Oseltamivir 75 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	32		
Units: hour				
median (confidence interval 95%)	142.85 (83.27	154.83 (74.97		

to 220.15)	to 386.52)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Hospital Discharge

End point title	Time to Hospital Discharge

End point description:

Time to hospital discharge in days will be analyzed using an accelerated failure time model (if the data provide an acceptable model fit) or alternatively a Cox proportional hazards model (in case the hazards are proportional). Full analysis set was defined as all randomly assigned subjects who received at least 1 dose of study drug and who have a confirmed infection with influenza A.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Pimodivir 600 mg bid + Oseltamivir 75 mg bid	Pimodivir placebo bid + Oseltamivir 75 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	63	32		
Units: days				
median (confidence interval 95%)	4.00 (3.00 to 5.00)	4.00 (3.00 to 4.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Reporting Treatment-Emergent Adverse Events (TEAEs)

End point title	Number of Subjects Reporting Treatment-Emergent Adverse Events (TEAEs)

End point description:

TEAEs are defined as adverse events with onset or worsening on or after date of first dose of study treatment. An adverse event is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. The Safety Analysis Set included all enrolled subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Up to Day 28

End point values	Pimodivir 600 mg bid + Oseltamivir 75 mg bid	Pimodivir placebo bid + Oseltamivir 75 mg bid		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	64	35		
Units: subjects	48	25		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Screening up to Follow-up (up to Day 28)	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Pimodivir 600 mg bid + oseltamivir 75 mg bid

Reporting group description:

Subjects received Pimodivir 600 milligram (mg) tablets and oseltamivir 75 mg capsules orally twice daily (bid) for 7 days. Dose of oseltamivir was adjusted from 75 mg to 30 mg and vice versa during the course of treatment based on the estimated glomerular filtration rate (eGFR) value.

Reporting group title	Pimodivir placebo bid + oseltamivir 75 mg bid

Reporting group description:

Subjects received matching placebo to Pimodivir tablets and oseltamivir 75 mg capsules orally twice daily for 7 days. Dose of oseltamivir was adjusted from 75 mg to 30 mg and vice versa during the course of treatment based on the eGFR value.

Serious adverse events	Pimodivir 600 mg bid + oseltamivir 75 mg bid	Pimodivir placebo bid + oseltamivir 75 mg bid	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 64 (17.19%)	4 / 35 (11.43%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic dissection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Circulatory collapse			

subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypotension			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Orthostatic hypotension			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
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			
Neutropenia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Bronchial hyperreactivity			

subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis exfoliative			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Bladder outlet obstruction			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (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			
Bacterial infection			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infective pulmonary exacerbation of cystic fibrosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oral candidiasis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Pimodivir 600 mg bid + oseltamivir 75 mg bid	Pimodivir placebo bid + oseltamivir 75 mg bid	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 64 (70.31%)	24 / 35 (68.57%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Phlebitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Chills			

subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Face oedema			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	4 / 64 (6.25%)	1 / 35 (2.86%)	
occurrences (all)	4	1	
Malaise			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Oedema peripheral			
subjects affected / exposed	2 / 64 (3.13%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Pyrexia			
subjects affected / exposed	4 / 64 (6.25%)	0 / 35 (0.00%)	
occurrences (all)	4	0	
Reproductive system and breast disorders			
Prostatomegaly			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 64 (1.56%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Bronchospasm			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Cough			
subjects affected / exposed	4 / 64 (6.25%)	4 / 35 (11.43%)	
occurrences (all)	4	4	
Dyspnoea			
subjects affected / exposed	2 / 64 (3.13%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Epistaxis			

subjects affected / exposed	2 / 64 (3.13%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Haemothorax			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Increased upper airway secretion			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal discomfort			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 64 (1.56%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Rhinorrhoea			
subjects affected / exposed	1 / 64 (1.56%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Sneezing			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Hallucination			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	3 / 64 (4.69%)	0 / 35 (0.00%)	
occurrences (all)	3	0	
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Blood bicarbonate decreased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	0 / 64 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Blood lactate dehydrogenase increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Blood triglycerides increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Hepatic enzyme increased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
International normalised ratio			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Liver function test increased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Lymphocyte count decreased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Neutrophil count increased			

subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Transaminases increased			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Troponin increased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Post-traumatic pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Procedural pneumothorax			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Sinus bradycardia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 64 (3.13%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Dizziness postural			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Dysgeusia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Headache			

subjects affected / exposed	7 / 64 (10.94%)	3 / 35 (8.57%)	
occurrences (all)	7	4	
Paraesthesia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Restless legs syndrome			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Somnolence			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Syncope			
subjects affected / exposed	1 / 64 (1.56%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Polycythaemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Splenomegaly			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Thrombocytosis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Vertigo			

subjects affected / exposed	1 / 64 (1.56%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Eye disorders			
Amaurosis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Eye pruritus			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Eyelid oedema			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Photopsia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 64 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Abdominal pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Cheilitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	2 / 64 (3.13%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			

subjects affected / exposed	13 / 64 (20.31%)	4 / 35 (11.43%)	
occurrences (all)	14	4	
Dry mouth			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	4 / 64 (6.25%)	1 / 35 (2.86%)	
occurrences (all)	4	1	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Gingival pain			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	9 / 64 (14.06%)	5 / 35 (14.29%)	
occurrences (all)	9	5	
Oral pain			
subjects affected / exposed	2 / 64 (3.13%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	6 / 64 (9.38%)	2 / 35 (5.71%)	
occurrences (all)	6	2	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Hepatic steatosis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Hyperbilirubinaemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	

Hypertransaminasaemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Dyshidrotic eczema			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Hyperhidrosis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Prurigo			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	1 / 64 (1.56%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Rash maculo-papular			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Nocturia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Proteinuria			

subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Urinary hesitation			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 64 (0.00%)	2 / 35 (5.71%)	
occurrences (all)	0	2	
Arthritis			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	2 / 64 (3.13%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Muscle spasms			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	1 / 64 (1.56%)	1 / 35 (2.86%)	
occurrences (all)	1	1	
Musculoskeletal pain			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	2 / 64 (3.13%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Neck pain			
subjects affected / exposed	2 / 64 (3.13%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Infections and infestations			
Hepatitis c			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Oral candidiasis			

subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Pulmonary tuberculosis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Sinusitis			
subjects affected / exposed	2 / 64 (3.13%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	2 / 64 (3.13%)	0 / 35 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 64 (3.13%)	1 / 35 (2.86%)	
occurrences (all)	2	1	
Gout			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	0 / 64 (0.00%)	1 / 35 (2.86%)	
occurrences (all)	0	1	
Hypertriglyceridaemia			
subjects affected / exposed	1 / 64 (1.56%)	0 / 35 (0.00%)	
occurrences (all)	1	0	
Hypokalaemia			
subjects affected / exposed	2 / 64 (3.13%)	1 / 35 (2.86%)	
occurrences (all)	2	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 October 2015	The overall reason for the amendment INT-1 to remove text regarding inclusion of the adolescent population and accordingly, the sample size justification was re-written based on FDA feedback.
09 December 2015	The overall reason for the amendment INT-2 add a urine pregnancy test (for females of childbearing potential) was added to Day 5 procedures and a hierarchal ordinal scale for clinical outcome was added as a secondary efficacy endpoint based on feedback by Food and Drug Administration (FDA).
19 September 2016	The overall reason for the amendment INT-3 was to correct exclusion criteria.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported