Clinical trial results:
A Phase 3, Randomized, Double Blind, Placebo-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Favipiravir in Adult Subjects with Uncomplicated Influenza

Summary

EudraCT number	2013-002149-13
Trial protocol	BE HU BG NL ES SE
Global end of trial date	16 March 2015

Results information

Result version number	v1 (current)
This version publication date	03 June 2016
First version publication date	03 June 2016

Trial information

Trial identification

Sponsor protocol code	T705aUS316

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	U1111-1147-8470

Notes:

Sponsors

Sponsor organisation name	MDVI, LLC
Sponsor organisation address	One Post Office Square, Boston , United States, 02109
Public contact	Robert Morgan, MDVI, LLC, +1 617-398-5978, rmorgan@medivector.com
Scientific contact	Carol R. Epstein, MD, MDVI, LLC, +1 617-398-5911, cepstein@medivector.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	14 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 March 2015
Global end of trial reached?	Yes
Global end of trial date	16 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the clinical efficacy of favipiravir compared with placebo in treating adult subjects with confirmed uncomplicated influenza.

Protection of trial subjects:

This study was conducted in accordance with GCP, as described in International Conference on Harmonisation (ICH) Guideline E6, Good Clinical Practice, Consolidated Guidance (April 1996). The ICH GCP guideline is consistent with the World Medical Assembly Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 January 2014
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	Poland: 43
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Bulgaria: 47
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Australia: 35
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	Ukraine: 9
Country: Number of subjects enrolled	United States: 527
Country: Number of subjects enrolled	New Zealand: 14
Country: Number of subjects enrolled	South Africa: 126
Worldwide total number of subjects	860
EEA total number of subjects	133

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)	799
From 65 to 84 years	61
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from local sites and their environs (from database, First Patient First Visit 21 January 2014, Last Patient Last Visit 16 Mart 2015).

Pre-assignment

Screening details:

Subjects were screened and randomized on the same day. ICF, pregnancy test, Inclusion Criteria/Exclusion Criteria, RAT test, demographics and medical history, height/weight measurements, physical examination, vital signs, body temperature (oral), assessment of influenza symptoms, 12-lead electrocardiogram (ECG), Randomization.

Pre-assignment period milestones

Number of subjects started	860
Number of subjects completed	855

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Randomized but not dosed: 5

Period 1

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

Blinding implementation details:

The study remained blinded with regard to treatment assignments until all subjects left the study, all queries had been resolved, a signed final Statistical Analysis Plan was available and the database had been locked. The determination of inclusion and exclusion of subjects in the various analysis populations was finalized prior to database lock and unblinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Favipiravir

Arm description:

Nine tablets (1800 mg) BID for a total daily dose of 3600 mg on Day 1, followed by 4 tablets (800 mg) BID for a total daily dose of 1600 mg on Days 2 to 5.

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

Dosage and administration details:

Nine tablets (1800 mg) BID for a total daily dose of 3600 mg on Day 1, followed by 4 tablets (800 mg) BID for a total daily dose of 1600 mg on Days 2 to 5.

Arm title	Placebo

Arm description:

Nine tablets (to mimic 1800 mg) BID on Day 1, followed by 4 tablets (to mimic 800 mg) BID on Days 2 to 5.

Arm type	Placebo

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

Dosage and administration details:

Nine tablets (to mimic 1800 mg) BID on Day 1, followed by 4 tablets (to mimic 800 mg) BID on Days 2 to 5.

Number of subjects in period 1[1]	Favipiravir	Placebo
Started	426	429
Completed	404	404
Not completed	22	25
Adverse event, non-fatal	3	3
Other	2	2
Subject Withdrawal	13	11
Treatment Failure	-	1
Lost to follow-up	3	8
Protocol deviation	1	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 5 subjects were randomized but not dosed.

Baseline characteristics

Reporting groups	
Reporting group title	Favipiravir
Reporting group description:	
Nine tablets (1800 mg) BID for a total daily dose of 3600 mg on Day 1, followed by 4 tablets (800 mg) BID for a total daily dose of 1600 mg on Days 2 to 5.	
Reporting group title	Placebo
Reporting group description:	
Nine tablets (to mimic 1800 mg) BID on Day 1, followed by 4 tablets (to mimic 800 mg) BID on Days 2 to 5.	

Reporting group values	Favipiravir	Placebo	Total
Number of subjects	426	429	855
Age categorical			
Units: Subjects			
Adults (18-64 years)	391	403	794
From 65-84 years	35	26	61
Age continuous			
Units: years			
median	41	40	
full range (min-max)	18 to 79	18 to 80	-
Gender categorical			
Units: Subjects			
Female	255	259	514
Male	171	170	341

Subject analysis sets	
Subject analysis set title	Primary Efficacy Analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The ITT (Intent to Treat) population included all subjects who were randomized and received any amount of study drug. These subjects were analyzed as randomized.	
Subject analysis set title	Primary Efficacy Analysis
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
The ITTI (Intent to Treat-Infected) population, a subset of the ITT population, was the primary efficacy population and was also used for all analyses of antiviral efficacy. It included all randomized subjects who had received any amount of study drug and were subsequently confirmed as having influenza by RT- PCR from samples collected prior to first dose. Subjects were analyzed according to the treatment they were randomized to receive.	

Subject analysis set title	Primary Efficacy Analysis
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The uninfected population was a subset of the ITT population that included subjects who did not have a positive RT- PCR on Day 1 (ITT minus ITTI).	
Subject analysis set title	Safety Analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all subjects who received any amount of study drug. In the case of any discrepancy (ie, treatment misallocation) subjects were analyzed according to the treatment actually received, not as randomized.

Reporting group values	Primary Efficacy Analysis	Primary Efficacy Analysis	Primary Efficacy Analysis
Number of subjects	855	623	232
Age categorical Units: Subjects			
Adults (18-64 years)	794	580	
From 65-84 years	61	43	
Age continuous Units: years			
median	40	40	
full range (min-max)	18 to 80	18 to 80	
Gender categorical Units: Subjects			
Female	514	368	
Male	341	255	

Reporting group values	Safety Analysis		
Number of subjects	855		
Age categorical Units: Subjects			
Adults (18-64 years)			
From 65-84 years			
Age continuous Units: years			
median			
full range (min-max)			
Gender categorical Units: Subjects			
Female			
Male			

End points

End points reporting groups

Reporting group title	Favipiravir

Reporting group description:

Nine tablets (1800 mg) BID for a total daily dose of 3600 mg on Day 1, followed by 4 tablets (800 mg) BID for a total daily dose of 1600 mg on Days 2 to 5.

Reporting group title	Placebo

Reporting group description:

Nine tablets (to mimic 1800 mg) BID on Day 1, followed by 4 tablets (to mimic 800 mg) BID on Days 2 to 5.

Subject analysis set title	Primary Efficacy Analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT (Intent to Treat) population included all subjects who were randomized and received any amount of study drug. These subjects were analyzed as randomized.

Subject analysis set title	Primary Efficacy Analysis
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

The ITTI (Intent to Treat-Infected) population, a subset of the ITT population, was the primary efficacy population and was also used for all analyses of antiviral efficacy. It included all randomized subjects who had received any amount of study drug and were subsequently confirmed as having influenza by RT- PCR from samples collected prior to first dose.
Subjects were analyzed according to the treatment they were randomized to receive.

Subject analysis set title	Primary Efficacy Analysis
Subject analysis set type	Sub-group analysis

Subject analysis set description:

The uninfected population was a subset of the ITT population that included subjects who did not have a positive RT- PCR on Day 1 (ITT minus ITTI).

Subject analysis set title	Safety Analysis
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety population included all subjects who received any amount of study drug. In the case of any discrepancy (ie, treatment misallocation) subjects were analyzed according to the treatment actually received, not as randomized.

Primary: Time to alleviation of symptoms and resolution of fever (“alleviation”).

End point title	Time to alleviation of symptoms and resolution of fever (“alleviation”).

End point description:

The time to alleviation of symptoms and resolution of fever (“alleviation”), defined as the first time point when all of the six influenza symptoms (body aches and pains, cough, fatigue, headache, nasal congestion, and sore throat) were either absent or mild and fever had resolved, with both maintained for at least 21.5 hours.

End point type	Primary

End point timeframe:

Day 1 subjects began study treatment within 48 hours after onset of influenza symptoms.Subjects returned to the clinic on Days 2 to 5 for assessments of influenza.Subjects returned to the clinic for a follow-up visit on Day 15 and a final visit on Day 22.

End point values	Favipiravir	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	301	322		
Units: hours				
median (confidence interval 95%)				
Alleviation	84.2 (77.1 to 95.7)	98.6 (94.6 to 107.1)		

Statistical analyses

Statistical analysis title	Primary efficacy endpoint

Statistical analysis description:

Statistical testing was performed using Peto-Peto Prentice test, comparing placebo vs favipiravir. Median time to alleviation was the duration between first dose to the first alleviation of all symptoms and resolution of fever. The median time to alleviation was calculated using Kaplan Meier method, which assess the time that 50% of the subjects reaching alleviation.

Comparison groups	Favipiravir v Placebo
Number of subjects included in analysis	623
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Peto-Peto Prentice test
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The Investigator was required to notify the Sponsor of the SAE within 24 hours, via the electronic data capture (EDC) system or, in the event of EDC failure, by using the email or fax number printed on the SAE form.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	Favipiravir

Reporting group description:

Nine tablets (1800 mg) BID for a total daily dose of 3600 mg on Day 1, followed by 4 tablets (800 mg) BID for a total daily dose of 1600 mg on Days 2 to 5.

Reporting group title	Placebo

Reporting group description:

Nine tablets (to mimic 1800 mg) BID on Day 1, followed by 4 tablets (to mimic 800 mg) BID on Days 2 to 5.

Serious adverse events	Favipiravir	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 428 (0.23%)	2 / 427 (0.47%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant Melanoma			
subjects affected / exposed	0 / 428 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast Cancer			
subjects affected / exposed	0 / 428 (0.00%)	1 / 427 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			

subjects affected / exposed	1 / 428 (0.23%)	0 / 427 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Favipiravir	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	110 / 428 (25.70%)	129 / 427 (30.21%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	5 / 428 (1.17%)	5 / 427 (1.17%)	
occurrences (all)	110	129	
Alanine aminotransferase increased			
subjects affected / exposed	8 / 428 (1.87%)	4 / 427 (0.94%)	
occurrences (all)	110	129	
Nervous system disorders			
Dizziness			
subjects affected / exposed	8 / 428 (1.87%)	5 / 427 (1.17%)	
occurrences (all)	110	129	
General disorders and administration site conditions			
Hypothermia			
subjects affected / exposed	6 / 428 (1.40%)	4 / 427 (0.94%)	
occurrences (all)	110	129	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	9 / 428 (2.10%)	23 / 427 (5.39%)	
occurrences (all)	110	129	
Nausea			
subjects affected / exposed	8 / 428 (1.87%)	14 / 427 (3.28%)	
occurrences (all)	110	129	
Vomiting			
subjects affected / exposed	5 / 428 (1.17%)	7 / 427 (1.64%)	
occurrences (all)	110	129	
Abdominal Pain			

subjects affected / exposed	0 / 428 (0.00%)	6 / 427 (1.41%)	
occurrences (all)	110	129	
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	4 / 428 (0.93%)	8 / 427 (1.87%)	
occurrences (all)	110	129	
Epistaxis			
subjects affected / exposed	5 / 428 (1.17%)	5 / 427 (1.17%)	
occurrences (all)	110	129	
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	9 / 428 (2.10%)	11 / 427 (2.58%)	
occurrences (all)	110	129	
Sinusitis			
subjects affected / exposed	5 / 428 (1.17%)	5 / 427 (1.17%)	
occurrences (all)	110	129	
Pneumonia			
subjects affected / exposed	0 / 428 (0.00%)	5 / 427 (1.17%)	
occurrences (all)	110	129	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 May 2013	The main changes listed below were made to the original protocol dated 15 May 2013. Treatment regimen was changed from TID to BID dosing, frequency of subjects' assessment in the subject diary of their ability to return to normal activity was changed from daily to three times daily. Text was added to indicate that subjects were required to receive the first dose of study medication within 48 hours of the initial onset of influenza symptoms. No subjects were ever enrolled under the initial protocol dated 15 May 2013.
12 February 2014	New text was added to indicate that subjects' age range could be determined in accordance with national standards in each country, new text was added to indicate that if the subject was unable or unwilling to come to the study site, study site personnel could conduct the Days 2, 3 and/or 4 visits at the subjects home, previous text advising that subjects not take more than two doses in a 24 hour period was deleted and new text was added to indicate that optimal dosing interval is 12 hours apart, addition of instruction that subjects should minimize exposure to sunlight or artificial ultraviolet light during study drug treatment, updates to information regarding the reporting of AEs, including relationship to study drug, pregnancy, and in utero drug exposure.
12 January 2015	Addition of US sites and revised the total planned number of subjects to up to 860 to provide for greater precision in the estimations of treatment effects and to increase the safety database to better meet regulatory guidelines.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported