Clinical trial results:
A Phase III Double-blind, Randomised, Parallel Group Comparison of the Efficacy and Safety of FP-1201-lyo (Recombinant Human Interferon Beta-1a) and Placebo in the Treatment of Patients with Moderate or Severe Acute Respiratory Distress Syndrome

Summary

EudraCT number	2014-005260-15
Trial protocol	DE FI BE ES CZ
Global end of trial date	23 May 2018

Results information

Result version number	v2 (current)
This version publication date	21 September 2019
First version publication date	29 June 2019
Version creation reason	• Correction of full data set Corrections to text.
Summary attachment (see zip file)	SAE listing (FPCLI002 SAE listing_EudraCT.xlsx) Adverse Events (Non-SAE) (FPCLI002 Adverse Events (non-SAE) listing_EudraCT.xlsx)

Trial information

Trial identification

Sponsor protocol code	FPCLI002 INTEREST

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02622724
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Faron Pharmaceuticals Ltd
Sponsor organisation address	Joukahaisenkatu 6 , Turku, Finland, 20520
Public contact	CMO, Faron Pharmaceuticals Ltd, matti.karvonen@faron.com
Scientific contact	CMO, Faron Pharmaceuticals Ltd, matti.karvonen@faron.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	23 May 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 May 2018
Global end of trial reached?	Yes
Global end of trial date	23 May 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate the efficacy of FP-1201-lyo in improving the clinical course and outcomes based on survival and need for mechanical ventilation in patients with moderate or severe acute respiratory distress syndrome (ARDS).

Protection of trial subjects:

The trial was performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP and applicable regulatory requirements. The informed consent process of unconscious patients was documented and approved by Ethics committee and/or competent authorities before the trial started and patients consented themselves as soon as they were medically able. An Independent Data Monitoring Committee reviewed ongoing safety data in an unblinded manner.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	23 December 2015
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	Spain: 22
Country: Number of subjects enrolled	United Kingdom: 54
Country: Number of subjects enrolled	Belgium: 24
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Finland: 30
Country: Number of subjects enrolled	France: 112
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Italy: 37
Worldwide total number of subjects	296
EEA total number of subjects	296

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)	190
From 65 to 84 years	98
85 years and over	8

Subject disposition

Recruitment

Recruitment details:

The screening period started in the first country in November 2015 and enrolment was completed in all countries in December 2017. Of the 74 study sites across 8 countries in Europe that pre-screened subjects, 47 sites randomly assigned subjects to treatment. The study was early terminated at the long-term/extended follow-up period in May 2018.

Pre-assignment

Screening details:

Subjects were randomised in a 1:1 ratio to FP-1201-lyo and placebo, using ARDS severity and country as stratification parameters. A total of 363 subjects passed screening, 301 subjects fulfilled all criteria at randomization and were randomly assigned and finally, 296 subjects received treatment in the study. Five study subjects were not dosed.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	FP-1201-lyo

Arm description: -

Arm type	Experimental
Investigational medicinal product name	FP-1201-lyo
Investigational medicinal product code	FP-1201-lyo
Other name	Recombinant Human Interferon Beta-1a
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

10 microgram FP-1201-lyo / placebo was diluted in sterile water for injection and administered as an intravenous bolus injection once daily for six consecutive days.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravenous bolus use

Dosage and administration details:

10 microgram FP-1201-lyo / placebo was diluted in sterile water for injection and administered as an intravenous bolus injection once daily for six consecutive days.

Number of subjects in period 1	FP-1201-lyo	Placebo
Started	144	152
Completed Day 28	105	115
Completed Day 90	96	101
Completed Day 180	73	74
Completed study (Day 360)	51	49
Completed	51	49
Not completed	93	103
Adverse event, serious fatal	51	53
Consent withdrawn by subject	2	3
Lost to follow-up	2	4
Early termination of the study	38	43

Baseline characteristics

Reporting groups	
Reporting group title	FP-1201-lyo
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	FP-1201-lyo	Placebo	Total
Number of subjects	144	152	296
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	58.3	58.4	
standard deviation	± 17.20	± 13.95	-
Gender categorical Units: Subjects			
Female	42	61	103
Male	102	91	193
APACHE II, baseline			
APACHE II (Acute Physiology and Chronic Health Evaluation II) was used as an assessment of the severity of the disease and estimation of mortality of the patients admitted to the ICU.			
Units: APACHE II score			
arithmetic mean	21.82	22.97	
standard deviation	± 8.75	± 7.67	-

End points

End points reporting groups

Reporting group title	FP-1201-lyo
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	All subjects
Subject analysis set type	Full analysis
Subject analysis set description:	
Full Analysis Set (FAS); all subjects who recieved at least 1 dose of study treatment	

Primary: Composite endpoint (VDFsurv) at Day 28

End point title	Composite endpoint (VDFsurv) at Day 28
End point description:	
Composite endpoint include any-cause death by Day 28 and the number of days free of mechanical ventilation (VFDsurv) within 28 days among survivors. Ventilator-free days (VDFs) correspond to those days when unassisted breathing (UAB) was possible for a complete calendar day. For the initiation of the VFD count at least two consecutive calendar days of UAB were required. UAB was defined as: sponstaneously breathing with face mask, nasal prong oxygen or room air, T-piece breathing, tracheostomy mask breathing, CPAP less than or equal to 5 cmH2O without pressure support or intermittent mandatory ventilation assistance, use of CPAP or BIPAP solely for sleep apnoea management.	
End point type	Primary
End point timeframe:	
VDFsurv is a composite measure of all-cause mortality and the number of days free of mechanical ventilation (VFD) within 28 days among survivors.	

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	152		
Units: days				
median (full range (min-max))	10 (-1 to 26)	8.5 (-1 to 26)		

Statistical analyses

Statistical analysis title	Primary Efficacy Analysis VDFsurv
Statistical analysis description:	
A non-parametric analysis has been performed as the data distribution is non-normal and negatively skewed. This involved a generalised Wilcoxon rank sum-based stratification test which assigns ranks within strata and compares two treatments within strata (Van Elteren hypothesis test)	
Comparison groups	Placebo v FP-1201-lyo

Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.8219 [2]
Method	Van Elteren hypothesis test
Parameter estimate	Median difference (net)

Notes:

[1] - Analysis were performed on Full Analysis Set (FAS, n=296), defined as all randomised subjects that received atleast one dose of study drug. Primary endpoint was analysed also for the Per Protocol population (PP, n=285), which consisted of subjects from FAS population but excluded subjects with major protocol deviations and subjects who received less than three doses of study drug.

[2] - For the Per Protocol population (PP, n=285) p=0.5032 (the overall median VDFsurv was 11.0 days with FP-1201-lyo and 8.0 days with placebo)

Secondary: Mortality (all causes)

End point title	Mortality (all causes)

End point description:

Full Analysis Set (FAS), defined as all randomised subjects that received atleast one dose of study drug. Mortality all-causes and mortality in ICU from randomisation up to day 28.

End point type	Secondary

End point timeframe:

Mortality all-causes from randomisation up to day 28.

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	152		
Units: Percentage of subjects				
number (confidence interval 95%)				
Mortality, day 28	26.4 (19 to 34)	23.0 (17 to 31)		
Mortality in ICU, day 28	25.7 (19 to 34)	23.0 (17 to 31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Days free of Mechanical Ventilation

End point title	Days free of Mechanical Ventilation

End point description:

The Total number of days free of Mechanical ventilation has been derived from the Patient Status report recorded on each day during the 28-day period. Patients who died during this period have been assigned a value of zero. This variable differs from the calculated Ventilation Free Days (VFD) endpoint which contributes to the VFDsurv primary efficacy endpoint as it require additional conditions of unassisted breating (UAB) to be met.

End point type	Secondary

End point timeframe:

The Total number of days free of Mechanical ventilation has been derived from the Patient Status report recorded on each day during the 28-day period.

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	152		
Units: Days				
median (full range (min-max))	10 (0 to 26)	9.0 (0 to 26)		

Statistical analyses

Statistical analysis title	Days free of Mechanical Ventilation

Statistical analysis description:

Van Elteren hypothesis test as the distribution was non-normal and negatively skewed by patients who are assigned scores of zero (0) in the event of death.

Comparison groups	FP-1201-lyo v Placebo
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4678
Method	Van Elteren p-values

Secondary: Days free of Organ Failure

End point title	Days free of Organ Failure

End point description:

End point type	Secondary

End point timeframe:

The total number of days free of Organ Failure (Sequential Organ Failure Assessment, SOFA) has been derived from the Patient Status report recorded on each day during the 28-day period.

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	152		
Units: Days				
median (full range (min-max))	0 (0 to 28)	0 (0 to 28)		

Statistical analyses

Statistical analysis title	Days free of Organ Failure
Comparison groups	FP-1201-lyo v Placebo
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1547
Method	Van Elteren p-values

Secondary: Days free of Renal Support

End point title	Days free of Renal Support

End point description:

End point type	Secondary

End point timeframe:

The total number of days free of Renal Support has been derived from the Patient Status report recorded on each day during the 28-day period.

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	152		
Units: Days				
median (full range (min-max))	28 (0 to 28)	27 (0 to 28)		

Statistical analyses

Statistical analysis title	Days free of Renal Support
Comparison groups	FP-1201-lyo v Placebo
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7243
Method	Van Elteren p-values

Secondary: Days free of Vasoactive Support

End point title	Days free of Vasoactive Support

End point description:

End point type	Secondary

End point timeframe:

The total number of days free of vasoactive support has been derived from the Patient Status report recorded on each day during the 28-day period.

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	152		
Units: Days				
median (full range (min-max))	20 (0 to 28)	21 (0 to 28)		

Statistical analyses

Statistical analysis title	Days free of Vasoactive Support
Comparison groups	FP-1201-lyo v Placebo
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.939
Method	Van Elteren p-values

Secondary: Number of ICU Care free Days

End point title	Number of ICU Care free Days

End point description:

End point type	Secondary

End point timeframe:

The total number of days free of ICU care has been derived from the Patient Status report recorded on each day during the 28-day period.

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	152		
Units: Days				
median (full range (min-max))	6 (0 to 24)	3.50 (0 to 24)		

Statistical analyses

Statistical analysis title	ICU Care-Free Days
Comparison groups	FP-1201-lyo v Placebo

Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3392
Method	Van Elteren p-values

Secondary: Number of days in hospital

End point title	Number of days in hospital

End point description:

End point type	Secondary

End point timeframe:

The total number of days in hospital has been derived from the Patient Status report recorded on each day during the 28-day period.

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	152		
Units: Days				
median (full range (min-max))	28 (8 to 28)	28 (8 to 28)		

Statistical analyses

Statistical analysis title	Number of days in hospital
Comparison groups	FP-1201-lyo v Placebo
Number of subjects included in analysis	296
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7029
Method	Van Elteren p-values

Secondary: Neutralising Antibodies to IFN Beta-1a

End point title	Neutralising Antibodies to IFN Beta-1a

End point description:

Neutralizing antibodies can interfere with the biological and clinical response to treatment. The ADAs were determined first and if present, the NAbs were also determined. The last observation performed, whether at Day 28, upon last day in the ICU or upon early termination, was derived. Interferon beta-1a ADA (BAb) and NAb were summarised categorically (using Positive/Negative classification). As a very high proportion of the results in both treatment groups was negative, no formal statistical testing was done. The majority of subjects were not tested for IFN beta NAb; of those tested on pre-dose, 1 (0.3 %) study subject in the FP-1201-lyo group was positive, whilst no positive results were observed on the last day in ICU.

End point type	Secondary

End point timeframe:

The immunological response to FP-1201-lyo was assessed through monitoring of anti-drug antibodies (ADAs) and Neutralising Antibodies to IFN beta 1a (NAbs) on pre-dose Day 1 and at Day 28, the last day in ICU or early termination, if earlier

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	144	150		
Units: Subjects				
number (not applicable)				
Presence of IFN beta-1a BAb, pre-dose	2	2		
Presence of IFN beta-1a BAb, D28/last day in ICU	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Evaluation of Pharmacodynamics with MxA

End point title	Evaluation of Pharmacodynamics with MxA

End point description:

To evaluate the pharmacodynamics of FP-1201-lyo with Myxovirus resistance protein A (MxA), as one of the best markers for IFN beta bioactivity. This response was measured on Day 1 Pre-dose and daily thereafter until Day 14 in the ICU. The Last observation performed whether Day 14 or earlier has been derived. The change from baseline (Day 1 Pre-dose) has been calculated. The mean (adjusted) difference in blood MxA response was significantly higher ($p<0.05$) in the active group versus the placebo group by 23.76 (95% CI: 12.77, 34.75). There was substantial variation in individual MxA responses.

End point type	Secondary

End point timeframe:

Evaluation of pharmacodynamics using MxA biomarker from baseline to Day 14

End point values	All subjects			
Subject group type	Subject analysis set			
Number of subjects analysed	296[3]			
Units: ng/mL				
least squares mean (confidence interval 95%)	23.8 (12.8 to 34.8)			

Notes:

[3] - MxA LS(adjusted) mean change PF-1201-lyo and Placebo from baseline to Last Observation Performed.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

The Adverse Event reporting period extended from signing of informed consent to Day 28. All deaths were reported as SAEs throughout the study, up until Day 360.

See attachments:

Adverse event reporting additional description:

The Adverse Event reporting period extended from signing of informed consent to Day 28. AEs occuring after Day 28 were to be reported if the investigator considered a causal relationship with the study drug. However, all deaths were reported as SAEs throughout the study, up until day 360.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The adverse events are reported in the attachments; FPCLI002 SAE listing contain information on all SAEs and FPCLI002 adverse events listing contain information on all non-serious events

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2015	Defining and describing in more detail the study monitoring procedures of IDMC
22 October 2015	The substantial changes included: - addition of APACHEII scoring to access severity of disease - prolongation of reporting time for deaths as SAE to the end of study and clarification on collection of AEs. - clarifying the rigth of the investigator to make an independent decision to break the treatment code in case of an emergency - Addition of an ECG to the Six-Minute Walk Test as a safety precaution
29 August 2017	The main analysis of the study and reporting use Day 28 and Day 90 data instead of Day 180 data.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/29132404