Clinical trial results:
A Phase II Double-blind, Randomised, Parallel Group 2:1 Comparison of the Efficacy and Safety of FP-1201-lyo (Recombinant Human Interferon Beta-1a) and Placebo in the Prevention of Multi-Organ Failure on Patients Surviving Open Surgery for a Ruptured Abdominal Aortic Aneurysm

Summary

EudraCT number	2014-000899-25
Trial protocol	FI EE LT GB
Global end of trial date	23 September 2019

Results information

Result version number	v1 (current)
This version publication date	10 October 2020
First version publication date	10 October 2020
Summary attachment (see zip file)	Adverse events (non-SAE) listing (FP1CLI006_Non-SAE_Listing EudraCT.xlsx) SAE listing (FP1CLI006_SAE_Listing EudraCT.xlsx)

Trial information

Trial identification

Sponsor protocol code	FP1CLI006 INFORAAA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03119701
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Faron Pharmaceuticals Ltd
Sponsor organisation address	Joukahaisenkatu 6 , Turku, Finland, 20520
Public contact	Chief Medical Officer, Faron Pharmaceuticals Ltd, +358 4005529411, medical@faron.com
Scientific contact	Chief Medical Officer, Faron Pharmaceuticals Ltd, +358 4005529411, medical@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	03 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 September 2019
Global end of trial reached?	Yes
Global end of trial date	23 September 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of FP-1201-lyo over placebo on all-cause mortality at trial day 30 (D30, 30 days from the first dose of trial medication).

Protection of trial subjects:

The trial was performed in compliance with the protocol, International Conference of Harmonisation Good Clinical Practice (ICH GCP), the applicable regulatory requirement(s) and the Declaration of Helsinki. If the patient was unable to sign the consent document due to ongoing preparations for operation or e.g. stomach pain, or any other relevant reason, and inability to sit up for signing, a verbal consent could be given with one of the medical staff members acting as a witness, excluding the study personnel. When the Emergency Room, Operation Room and Intensive Care Unit standard procedures were in line with trial procedures and if the timing of RAAA diagnosis, consent, open aortic repair and dosing precluded repetition of procedures for the purposes of the trial, standard patient care test results could be used for screening even prior to consent.
An Independent Data Monitoring Committee reviewed ongoing safety data in an unblinded manner.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 February 2017
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	Estonia: 3
Country: Number of subjects enrolled	Finland: 33
Country: Number of subjects enrolled	Lithuania: 4
Worldwide total number of subjects	40
EEA total number of subjects	40

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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	29
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

The first patient first visit was on 18 Feb 2017. Last patient last visit was on 03 Oct 2019. The trial was conducted in 9 sites of which 6 were in Finland, 1 in Estonia, and 2 in Lithuania. 4 additional sites in United Kingdom were intended to participate in the trial, but were not initiated for trial conduct. The trial was early terminated.

Pre-assignment

Screening details:

Patients were randomised in a 2:1 ratio to FP-1201-lyo and placebo. A total of 50 patients were screened, 40 patients fulfilled all criteria at randomization, were randomly assigned and all of them received at least one dose of investigational product.

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:

A total of 29 patients received at least 1 dose of FP-1201-lyo. 2 patients, who received FP-1201-lyo, were excluded from Full Analysis Set for Efficacy (FAS-E) and Per Protocol Set (PPS) populations due to early deaths (within 36 hours from first dose of the study treatment). Therefore, FAS-E and PPS populations consisted of 27 patients in this arm.

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	29	11
Completed	20	9
Not completed	9	2
Adverse event, serious fatal	9	2

Baseline characteristics

Reporting groups

Reporting group title	FP-1201-lyo

Reporting group description:

A total of 29 patients received at least 1 dose of FP-1201-lyo. 2 patients, who received FP-1201-lyo, were excluded from Full Analysis Set for Efficacy (FAS-E) and Per Protocol Set (PPS) populations due to early deaths (within 36 hours from first dose of the study treatment). Therefore, FAS-E and PPS populations consisted of 27 patients in this arm.

Reporting group title	Placebo

Reporting group description: -

Reporting group values	FP-1201-lyo	Placebo	Total
Number of subjects	29	11	40
Age categorical Units: Subjects			
< 70 years	7	3	10
70-80 years	15	6	21
> 80 years	7	2	9
Gender categorical Units: Subjects			
Female	4	0	4
Male	25	11	36
Baseline height Units: centimetres			
arithmetic mean	172.1	177.5	
standard deviation	± 6.93	± 7.59	-
Baseline weight Units: kilograms			
arithmetic mean	84.5	95.9	
standard deviation	± 18.31	± 21.21	-

Subject analysis sets

Subject analysis set title	The Full Analysis Set for Efficacy (FAS-E)
Subject analysis set type	Full analysis

Subject analysis set description:

FAS-E consisted of all randomised patients who received study treatment, excluding the early deaths (within 36 hours from first dose of the study treatment) and comprised the analysis set on which the primary efficacy analysis was based.

Reporting group values	The Full Analysis Set for Efficacy (FAS-E)		
Number of subjects	38		
Age categorical Units: Subjects			
< 70 years	10		
70-80 years	20		
> 80 years	8		

Gender categorical Units: Subjects			
Female	4		
Male	34		
Baseline height Units: centimetres			
arithmetic mean	173.8		
standard deviation	± 7.05		
Baseline weight Units: kilograms			
arithmetic mean	86.0		
standard deviation	± 18.58		

End points

End points reporting groups

Reporting group title	FP-1201-lyo
Reporting group description:	
A total of 29 patients received at least 1 dose of FP-1201-lyo. 2 patients, who received FP-1201-lyo, were excluded from Full Analysis Set for Efficacy (FAS-E) and Per Protocol Set (PPS) populations due to early deaths (within 36 hours from first dose of the study treatment). Therefore, FAS-E and PPS populations consisted of 27 patients in this arm.	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	The Full Analysis Set for Efficacy (FAS-E)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS-E consisted of all randomised patients who received study treatment, excluding the early deaths (within 36 hours from first dose of the study treatment) and comprised the analysis set on which the primary efficacy analysis was based.	

Primary: The efficacy of FP-1201-lyo compared to placebo concerning all cause mortality

End point title	The efficacy of FP-1201-lyo compared to placebo concerning all cause mortality
End point description:	
Number of fatalities	
End point type	Primary
End point timeframe:	
Day 30	

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	11		
Units: participants	6	2		

Statistical analyses

Statistical analysis title	Primary endpoint all cause mortality
Statistical analysis description:	
The primary efficacy analysis was performed using a logistic regression model for the observed all-cause mortality in the two treatment groups.	
Comparison groups	FP-1201-lyo v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.3

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.21
upper limit	8.19

Notes:

[1] - The threshold for statistical significance was p = 0.05

Secondary: The efficacy of FP-1201-lyo compared to placebo concerning all cause mortality

End point title	The efficacy of FP-1201-lyo compared to placebo concerning all cause mortality

End point description:

Number of fatalities

End point type	Secondary

End point timeframe:

Day 90

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	11		
Units: participants	7	2		

Statistical analyses

Statistical analysis title	Secondary endpoint all cause mortality

Statistical analysis description:

This efficacy analysis was performed using logistic regression model the same as used with the all-cause mortality at D30 in the two treatment groups.

Comparison groups	FP-1201-lyo v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.57 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.28
upper limit	10.52

Notes:

[2] - The threshold for statistical significance was p = 0.05

Secondary: The efficacy of FP-1201-lyo compared to placebo concerning number of

ventilator free days (VFDs)

End point title	The efficacy of FP-1201-lyo compared to placebo concerning number of ventilator free days (VFDs)

End point description:

Number of ventilator free days. VFDs to Day 30 were defined as the number of calendar days after initiating unassisted breathing (UAB) to Day 30 from first treatment, assuming that a patient survives at least 48 consecutive hours after initiating UAB. Patients who die without initiating UAB were assigned a VFD value of zero.

End point type	Secondary

End point timeframe:

Day 30

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	11		
Units: days				
median (full range (min-max))	25.0 (0.0 to 30.0)	29.0 (0.0 to 29.0)		

Statistical analyses

Statistical analysis title	Analysis for number of VFDs
Comparison groups	FP-1201-lyo v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.08 [3]
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - The threshold for statistical significance was p = 0.05

Secondary: The efficacy of FP-1201-lyo compared to placebo concerning number of days receiving hemodialysis

End point title	The efficacy of FP-1201-lyo compared to placebo concerning number of days receiving hemodialysis

End point description:

Number of days receiving hemodialysis. There were only few reported values other than zero. As the study was terminated early and due to there being limited data available, number of days receiving hemodialysis at D90 was not assessed.

End point type	Secondary

End point timeframe:

Day 30 and Day 90

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	10		
Units: days				
arithmetic mean (standard deviation)	0.9 (± 4.15)	0.0 (± 0.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: The efficacy of FP-1201-lyo compared to placebo concerning number of organ failure free days by means of the sequential organ failure assessment (SOFA) score

End point title	The efficacy of FP-1201-lyo compared to placebo concerning number of organ failure free days by means of the sequential organ failure assessment (SOFA) score

End point description:

Organ failure free days were defined as the number of days in the first 30 days after the first dose of study medication that the patient was alive and free of organ failure with a SOFA score of zero for the following six organ parameters: respiration, coagulation, liver, cardiovascular, central nervous system and renal function. It is graded from 0 to 4 according to the degree of dysfunction/ failure (higher scores indicate more severe organ failure). Patients who died without achieving a SOFA score of zero was assigned an organ failure free days value of zero.
Note: the information for organ failure free days has been only collected when the patients have been in the Intensive Care Unit (ICU). As ICU free days have been reported in a separate variable, it was decided that presented information will be kept, without trying to conduct imputation.

End point type	Secondary

End point timeframe:

Day 30

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	11		
Units: days				
arithmetic mean (standard deviation)	0.0 (± 0.00)	0.0 (± 0.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: The efficacy of FP-1201-lyo compared to placebo concerning prevalence of abdominal compartment syndrome by intra-abdominal pressure (IAP)

End point title	The efficacy of FP-1201-lyo compared to placebo concerning prevalence of abdominal compartment syndrome by intra-abdominal pressure (IAP)

End point description:

Intra-abdominal pressure values, which were routinely measured during ICU stay via urine bladder

catheter. The number of participants analyzed differ during the days 1 - 6, D9 and D13 and reflects the number of patients that were alive and had sufficient data to allow for calculation of the outcome measure.

End point type	Secondary

End point timeframe:

Days 1 - 6, D9 and D13 during Intensive Care Unit (ICU) stay

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	9		
Units: mmHg				
arithmetic mean (standard deviation)				
Day 1	15.4 (± 12.37)	10.3 (± 4.80)		
Day 2	12.2 (± 3.58)	12.1 (± 6.01)		
Day 3	13.1 (± 4.62)	10.3 (± 5.35)		
Day 4	11.4 (± 6.60)	8.6 (± 5.32)		
Day 5	10.5 (± 3.14)	12.5 (± 5.45)		
Day 6	11.4 (± 5.29)	15.0 (± 0.00)		
Day 9	11.0 (± 5.48)	0 (± 0)		
Day 13	10.8 (± 4.49)	0 (± 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: The efficacy of FP-1201-lyo compared to placebo concerning neutralizing antibodies against IFN beta-1a (NAbs) in whole blood samples

End point title	The efficacy of FP-1201-lyo compared to placebo concerning neutralizing antibodies against IFN beta-1a (NAbs) in whole blood samples

End point description:

IFN beta-1a neutralizing antibodies immune response. Blood samples for the NAbs assessments were collected at Day 0 pre-dose (baseline) and at Day 30. At the Baseline Visit, 2 patients in the FP-1201-lyo treatment group and 1 patient in the placebo treatment group were not tested for anti-drug antibodies. At Day 30 Visit, 8 patients in the FP-1201-lyo treatment group and 2 patient in the placebo treatment group were not tested for anti-drug antibodies. All observations for the tested patients (at the Baseline Visit and D30) were negative.

End point type	Secondary

End point timeframe:

Day 30

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	10		
Units: participants				
Baseline	0	0		
Day 30	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: The efficacy of FP-1201-lyo compared to placebo concerning disability by modified ranking scale (mRS).

End point title	The efficacy of FP-1201-lyo compared to placebo concerning disability by modified ranking scale (mRS).

End point description:

Scale gives the degree of disability or dependence in the daily activities. Single mRS value is applied for every patient based on patient or caregiver interview. The scale runs from 0-6, from perfect health without symptoms to death. Pre-operation Baseline Visit mRS value is collected for reference.

End point type	Secondary

End point timeframe:

Day 90

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	11		
Units: participants				
No symptoms - 0	5	2		
No significant disability - 1	5	5		
Slight disability - 2	3	1		
Moderate disability - 3	2	0		
Moderately severe disability - 4	3	0		
Severe disability - 5	2	1		
Death - 6	7	2		

Statistical analyses

Statistical analysis title	Analysis of disability by mRS

Statistical analysis description:

Treatment Difference (Exact Mantel-Haenszel Chi-Square Test)

Comparison groups	Placebo v FP-1201-lyo

Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.362 [4]
Method	Mantel-Haenszel

Notes:

[4] - The threshold for statistical significance was p = 0.05

Secondary: Safety parameters of clinically significant treatment emergent adverse events (TEAEs), serious adverse events, vital signs and clinical laboratory parameters

End point title	Safety parameters of clinically significant treatment emergent adverse events (TEAEs), serious adverse events, vital signs and clinical laboratory parameters

End point description:

Number of TEAEs from vital signs data, laboratory data, physical examinations and spontaneous reporting when conscious. The Full Analysis Set for Safety (FAS-S) consisted of all randomised patients receiving study treatment and comprised the analysis set on which the evaluation of safety is based.

End point type	Secondary

End point timeframe:

Day 0 to Day 30

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	11		
Units: Events				
number (not applicable)				
Product-related TEAEs	17	1		
Severe TEAEs	28	2		
Serious TEAEs	26	5		
TEAEs leading to study product discontinuation	7	1		
TEAEs leading to death	7	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacoeconomic information of length of ICU stay, length of hospital stay, length of stay at another health care facility, length of hemodialysis needed, ventilation free days

End point title	Pharmacoeconomic information of length of ICU stay, length of hospital stay, length of stay at another health care facility, length of hemodialysis needed, ventilation free days

End point description:

Economic measurement:
Length of ICU stay, in terms of ICU free days at D30
Length of hospital stay, in terms of hospital free days at D90
Length of stay at another health care facility at D90

The number of days on hemodialysis from at D30 and at D90
The number of organ failure free days at D30
The number of ventilation free days at D30

As the study was discontinued, analyses were performed on the available data gathered thus far. The number of participants analyzed differ for the listed categories and reflects the patients with sufficient data for calculation of the outcome measure.
Analyses regarding pharmacoeconomic endpoints at D90 were not performed as not relevant due to limited data availability and study discontinuation.

End point type	Secondary

End point timeframe:

Day 30 or Day 90

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	11		
Units: days				
arithmetic mean (standard deviation)				
ICU free days at Day 30	16.8 (± 12.39)	21.9 (± 11.06)		
Days in hospital at Day 30	16.5 (± 9.68)	12.4 (± 9.32)		
Days in another facility at Day 30	10.0 (± 0.00)	21.0 (± 0.00)		
Days on hemodialysis from at Day 30	0.9 (± 4.15)	0.0 (± 0.00)		
Organ failure free days at Day 30	0.0 (± 0.00)	0.0 (± 0.00)		
Ventilation free days at Day 30	20.6 (± 10.62)	25.1 (± 8.85)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Myxovirus resistant protein A (MxA) concentration in whole blood samples as pharmacodynamic marker

End point title	Myxovirus resistant protein A (MxA) concentration in whole blood samples as pharmacodynamic marker

End point description:

The pharmacodynamics of FP-1201-lyo with Myxovirus resistance protein A (MxA), as one of the best markers for IFN beta bioactivity, was evaluated. MxA was seen to behave differently between the treatment groups (treatment-visit interaction p-value<.0001). In all visits MxA values were greater in the active treatment group when compared to placebo p-values ranging from 0.009 to less than 0.0001, except at baseline before dosing (p=0.13) and D13 (p=0.10).

The number of participants analyzed is different for given categories and reflects the number of patients that were alive and had data to allow for calculation of the outcome measure.

End point type	Other pre-specified

End point timeframe:

Day 0 up to Day 13

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	11		
Units: ng/ml				
geometric mean (confidence interval 95%)				
Baseline	3.5 (2.4 to 5.1)	6.0 (3.3 to 11.0)		
Day 1	15.0 (10.2 to 22.1)	5.1 (2.8 to 9.3)		
Day 2	19.8 (13.5 to 29.1)	3.8 (2.1 to 7.0)		
Day 3	21.2 (14.3 to 31.4)	3.3 (1.8 to 6.2)		
Day 4	36.4 (24.4 to 54.2)	4.1 (2.2 to 7.7)		
Day 5	48.3 (32.3 to 72.3)	3.1 (1.6 to 5.8)		
Day 6	50.4 (33.9 to 75.1)	3.6 (1.9 to 6.8)		
Day 9	14.3 (9.5 to 21.5)	4.8 (2.4 to 9.7)		
Day 13	3.9 (2.5 to 5.9)	8.7 (3.7 to 20.7)		

Statistical analyses

Statistical analysis title	Analysis of MxA concentration

Statistical analysis description:

The lower limit of quantification (LLOQ) is equal 5 ng/ml. Values below the LLOQ were set to LLOQ/2 = 2.5 ng/ml. Values over the upper limit of quantitation (ULOQ) were set to 320 ng/ml.

Comparison groups	FP-1201-lyo v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	ANOVA

Other pre-specified: Tentative disease specific marker CD73 (Ecto-5'-nucleotidase enzyme) concentration in serum samples

End point title	Tentative disease specific marker CD73 (Ecto-5'-nucleotidase enzyme) concentration in serum samples

End point description:

The number of participants analyzed is different for given categories and reflects the number of patients that were alive and had data to allow for calculation of the outcome measure.

For CD73 concentration in serum visit was the only statistically significant effect (p<.0001).

End point type	Other pre-specified

End point timeframe:

Day 0 up to Day 13

End point values	FP-1201-lyo	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	11		
Units: ng/ml				
geometric mean (confidence interval 95%)				
Baseline	2.1 (1.8 to 2.5)	2.2 (1.7 to 2.9)		
Day 1	2.0 (1.7 to 2.4)	2.2 (1.6 to 2.8)		
Day 2	2.2 (1.8 to 2.6)	2.2 (1.7 to 3.0)		
Day 3	2.0 (1.7 to 2.4)	2.3 (1.7 to 3.1)		
Day 4	2.3 (1.9 to 2.8)	2.6 (1.9 to 3.5)		
Day 5	3.0 (2.4 to 3.6)	3.5 (2.6 to 4.8)		
Day 6	3.8 (3.2 to 4.6)	3.8 (2.7 to 5.2)		
Day 9	3.9 (3.2 to 4.8)	3.8 (2.6 to 5.4)		
Day 13	2.9 (2.3 to 3.6)	2.7 (1.7 to 4.3)		

Statistical analyses

Statistical analysis title	Analysis of CD73 concentration

Statistical analysis description:

Patients with an observation below the lower limit of quantification (LLOQ) value at baseline for CD73 were set to have the LLOQ value (LLOQ = 4 ng/ml) at baseline for subgroup determination purposes (2-fold increase in CD73 from baseline). Values below the LLOQ were set to LLOQ/2 = 2 ng/mL.

Comparison groups	FP-1201-lyo v Placebo
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.66
Method	ANOVA

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

The Adverse Event reporting period was up to study D30. The investigators reported AEs occurring after D30 only if the investigator considered a causal relationship with the study drug. All deaths were reported as SAE up until D90. See attachments.

Adverse event reporting additional description:

The list of SAEs and the Non-serious AEs present all reported Treatment Emergent Adverse Events (AEs that begins or that worsens in severity after at least one dose of study drug). In 3 patients a non-treatment emergent SAE began before first dose of the study drug (included in mortality numbers because these SAEs led to death)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

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. FP1CLI006 SAE listing contain information on all SAEs and FP1CLI006 Non-SAE listing contain information on all non-serious adverse events.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2016	Amendment included modifications as commented by Fimea after review of the clinical trial application. Additionally, some clarifications were implemented, and some typos corrected as well. The information which was to be collected during ruptured abdominal aortic aneurysm surgical procedure was included in the protocol Section 6.4.
19 June 2017	This was a non-substantial Protocol Amendment 02 which was made to clarify the content of the protocol by using more precise text, to provide more detailed information and facilitate readability of the protocol as well as other non-substantial changes.
21 February 2019	The following is a summary of the major substantial changes implemented with this amendment: • Timing of the first futility/interim/ analysis added after 40 patients have become evaluable for D30 and subsequent changes in wording due to 2 interim analyses were made. • The definition of discontinuation criteria and replacement was unified throughout the protocol to match the section on statistical methods. • As precaution for a potential post-Brexit conditions, Ireland was added as an additional country for the IP QP release and distribution to ensure the IP supply chain in EU. Protocol Amendment 03 also contained non-substantial changes. This was created to clarify the content of the protocol by using more precise text and facilitate readability of the protocol.
16 April 2019	Protocol Amendment 04 had the following major substantial changes - the first interim/futility analysis was brought further up so that it will be performed once there are at least 31 evaluable patients (instead of 40 patients). The reason for this amendment was that the recruitment rate has markedly stagnated, mainly due to changes in treatment practices of ruptured abdominal aortic aneurysm. The sample size calculations had to be re-evaluated after the first interim analysis has been performed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
09 May 2018	The clinical trial was halted temporarily on 09 May 2018 and the decision to restart the trial was taken on 17 Sep 2018. The Sponsor's justification for a temporary halt of the trial was based on the findings from the other study (protocol code FPCLI002). The recruitment was temporarily on hold and there were no patients on the treatment phase at that time of trial put on hold. The clinical trial was restarted based on the benefit-risk balance conclusion by the IDMC.	17 September 2018

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was prematurely stopped and due to this the planned statistical power for the primary comparisons was not reached.

Notes: