



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 standard deviation | 173.8 ± 7.05 | | |
| Baseline weight Units: kilograms arithmetic mean standard deviation | 86.0 ± 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 (\pm 4.15) | 0.0 (\pm 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 (\pm 0.00) | 0.0 (\pm 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 (NAb) in whole blood samples

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

End point description:

IFN beta-1a neutralizing antibodies immune response. Blood samples for the NAb 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 | <p>The following is a summary of the major substantial changes implemented with this amendment:</p> <ul style="list-style-type: none">• 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. <p>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.</p> |
| 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: