



Clinical trial results:

Study of efficacy and safety of V0305 solution in children suffering from Iron Deficiency Anaemia (IDA).

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2015-000995-88 |
| Trial protocol | PL |
| Global end of trial date | 24 January 2019 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 24 July 2019 |
| First version publication date | 24 July 2019 |

Trial information

Trial identification

| | |
|-----------------------|-------------|
| Sponsor protocol code | V00305SB301 |
|-----------------------|-------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name | PIERRE FABRE MEDICAMENT |
| Sponsor organisation address | 45 Place Abel Gance, Boulogne-Billancourt, France, 92100 |
| Public contact | Clinical Development Physician A.Boudribila, Institut de Recherche Pierre Fabre, +33 5 34 50 60 98, asmaa.boudribila@pierre-fabre.com |
| Scientific contact | Clinical Development Physician A.Boudribila, Institut de Recherche Pierre Fabre, +33 5 34 50 60 98, asmaa.boudribila@pierre-fabre.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 | 24 January 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 25 October 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 24 January 2019 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To document the effect of V0305 (ferrous sulphate solution: Tardyferon solution 20 mg/mL) administered during 3 months (princeps period) on the blood haemoglobin level in children with IDA .

Protection of trial subjects:

The study was conducted in accordance with Good Clinical Practice (CPMP/ICH/135/95), the Declaration of Helsinki and its subsequent amendments thereto, and national regulations.

In case of gastro-intestinal disorders, reported by the parent(s)/guardian(s) to the Investigator (phone call or visit), the following guidance was recommended to adapt the daily posology (initially planned to be an equivalent of 2 mg/kg once daily):

- Firstly, the daily dosage of an equivalent of 2 mg/kg/day had to be administered in two intakes.
- Secondly, if the intolerance persisted, the daily dosage had to be reduced to an equivalent of 1 mg/kg/day.
- Finally, if the intolerance persisted, the Investigator had to discontinue the treatment and, in case of intolerance reported at phone call, an unscheduled visit had to be performed to withdraw the subject from the study.

Background therapy:

There was no systematic concomitant administration of any other product than the investigational product.

Evidence for comparator:

The primary objective of this clinical study was to document the efficacy of this new formulation of ferrous sulphate in children with mild-to-moderate IDA. The assessment of the main and key criteria, i.e., the level of the blood haemoglobin (Hb) and the level of serum ferritin, is particularly objective. Furthermore, considering the consequences of IDA (fatigue, impaired growth and development in infants), it would not have been ethical to maintain children suffering from IDA on placebo.

| | |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment | 06 June 2016 |
| 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: 100 |
| Worldwide total number of subjects | 100 |
| EEA total number of subjects | 100 |

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) | 100 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

13 centres located in Poland were initiated and 10 recruited patients. 100 patients were screened and enrolled, 21 were included, treated and analysed.

Pre-assignment

Screening details:

Female or male child,

- aged between 6 and 53 months (inclusive),
- with $7.0 \text{ kg} \leq \text{body weight} \leq 20.0 \text{ kg}$,
- with a mild or moderate IDA:
 - o blood Hb level: 70 to 109 g/L
 - o serum ferritin $< 12 \mu\text{g/L}$

79/100 enrolled patients were not included as their blood Hb level and serum ferritin level did not meet the minimal threshold for IDA diagnosis.

Period 1

| | |
|------------------------------|--------------------------|
| Period 1 title | 3-month Treatment Period |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Blinding implementation details:

N/A

Arms

| | |
|------------------------------|--------------|
| Are arms mutually exclusive? | No |
| Arm title | Baseline FAS |

Arm description:

As it is a single-arm study, the Baseline data of the FAS group (see definition of full analysis set) are considered to be those of this arm.

| | |
|----------------------------------------|------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tardyferon solution 20 mg/mL |
| Investigational medicinal product code | V0305 |
| Other name | Liquid ferrous sulphate |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

The prescribed initial dosage per day had to be an equivalent of 2 mg/kg/day of V0305 administered once a day. The daily dosage had to be administered considering the child's weight measured at screening (V1) and had not to be adjusted according to the weight during the study.

The daily posology (number of intake(s) and/or dosage) could be modified in case of gastrointestinal disorders reported to the Investigator at each time during the treatment periods (phone calls or visits):

- Firstly, this daily dosage had to be administered in 2 intakes,
- Secondly, if the intolerance persisted, the daily dosage had to be reduced to an equivalent of 1 mg/kg/day (once daily)
- Finally, if the intolerance still persisted, the treatment had to be stopped.

| | |
|------------------|-------------|
| Arm title | 3-month FAS |
|------------------|-------------|

Arm description:

As it is a single-arm study, the Month 3 data of the FAS group (see definition of full analysis set) are considered to be those of this arm.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|----------------------------------------|------------------------------|
| Investigational medicinal product name | Tardyferon solution 20 mg/mL |
| Investigational medicinal product code | V0305 |
| Other name | Liquid ferrous sulphate |
| Pharmaceutical forms | Oral solution |
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Dosage and administration details:

The prescribed initial dosage per day had to be an equivalent of 2 mg/kg/day of V0305 administered once a day. The daily dosage had to be administered considering the child's weight measured at screening (V1) and had not to be adjusted according to the weight during the study.

The daily posology (number of intake(s) and/or dosage) could be modified in case of gastrointestinal disorders reported to the Investigator at each time during the treatment periods (phone calls or visits):

- Firstly, this daily dosage had to be administered in 2 intakes,
- Secondly, if the intolerance persisted, the daily dosage had to be reduced to an equivalent of 1 mg/kg/day (once daily)
- Finally, if the intolerance still persisted, the treatment had to be stopped.

| | |
|------------------|-----------------|
| Arm title | Baseline PP set |
|------------------|-----------------|

Arm description:

As it is a single-arm study, the Baseline data of the PP set (see PP set definition) are considered to be those of this arm

| | |
|----------------------------------------|------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tardyferon solution 20 mg/mL |
| Investigational medicinal product code | V0305 |
| Other name | Liquid ferrous sulphate |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

The prescribed initial dosage per day had to be an equivalent of 2 mg/kg/day of V0305 administered once a day. The daily dosage had to be administered considering the child's weight measured at screening (V1) and had not to be adjusted according to the weight during the study.

The daily posology (number of intake(s) and/or dosage) could be modified in case of gastrointestinal disorders reported to the Investigator at each time during the treatment periods (phone calls or visits):

- Firstly, this daily dosage had to be administered in 2 intakes,
- Secondly, if the intolerance persisted, the daily dosage had to be reduced to an equivalent of 1 mg/kg/day (once daily)
- Finally, if the intolerance still persisted, the treatment had to be stopped.

| | |
|------------------|----------------|
| Arm title | 3-month PP set |
|------------------|----------------|

Arm description:

As it is a single-arm study, the Month 3 data of the PP set (see PP set definition) are considered to be those of this arm

| | |
|----------------------------------------|------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Tardyferon solution 20 mg/mL |
| Investigational medicinal product code | V0305 |
| Other name | Liquid ferrous sulphate |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

The prescribed initial dosage per day had to be an equivalent of 2 mg/kg/day of V0305 administered once a day. The daily dosage had to be administered considering the child's weight measured at screening (V1) and had not to be adjusted according to the weight during the study.

The daily posology (number of intake(s) and/or dosage) could be modified in case of gastrointestinal disorders reported to the Investigator at each time during the treatment periods (phone calls or visits):

- Firstly, this daily dosage had to be administered in 2 intakes,
- Secondly, if the intolerance persisted, the daily dosage had to be reduced to an equivalent of 1 mg/kg/day (once daily)
- Finally, if the intolerance still persisted, the treatment had to be stopped.

| Number of subjects in period 1 | Baseline FAS | 3-month FAS | Baseline PP set |
|--------------------------------|--------------|-------------|-----------------|
| Started | 21 | 21 | 11 |
| Completed | 17 | 17 | 11 |
| Not completed | 4 | 4 | 0 |
| Adverse event, non-fatal | 2 | 2 | - |
| Wrong inclusion | 2 | 2 | - |

| Number of subjects in period 1 | 3-month PP set |
|--------------------------------|----------------|
| Started | 11 |
| Completed | 11 |
| Not completed | 0 |
| Adverse event, non-fatal | - |
| Wrong inclusion | - |

Period 2

| | |
|-----------------------------------------|-------------------------------------|
| Period 2 title | Additional 3-month Treatment Period |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |
| Blinding implementation details: N/A | |

Arms

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|
| Arm title | 6-month FAS |
| Arm description: As it is a single-arm study, the Month 6 data of the FAS patient(s) who entered the additional 3-month period are considered to be those of this arm. | |
| Arm type | Experimental |
| Investigational medicinal product name | Tardyferon solution 20 mg/mL |
| Investigational medicinal product code | V0305 |
| Other name | Liquid ferrous sulphate |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

The prescribed initial dosage per day had to be an equivalent of 2 mg/kg/day of V0305 administered once a day. The daily dosage had to be administered considering the child's weight measured at screening (V1) and had not to be adjusted according to the weight during the study.

The daily posology (number of intake(s) and/or dosage) could be modified in case of gastrointestinal disorders reported to the Investigator at each time during the treatment periods (phone calls or visits):

- Firstly, this daily dosage had to be administered in 2 intakes,
- Secondly, if the intolerance persisted, the daily dosage had to be reduced to an equivalent of 1 mg/kg/day (once daily)
- Finally, if the intolerance still persisted, the treatment had to be stopped.

| Number of subjects in period 2 | 6-month FAS |
|---------------------------------------|-------------|
| Started | 1 |
| Completed | 1 |

Baseline characteristics

Reporting groups^[1]

| | |
|-----------------------|--------------------------|
| Reporting group title | 3-month Treatment Period |
|-----------------------|--------------------------|

Reporting group description:

As it is a single-arm study, the 21 patients of this group are those who were included and treated.

Notes:

[1] - The number of subjects reported to be in the baseline period is not equal to the worldwide number of subjects enrolled in the trial. It is expected that these numbers will be the same.

Justification: The protocol defined the enrolled patients as the patients selected at the end of the pre-assignment/-enrolment visit (V1) and whose parents signed an informed consent of participation. Patients were definitely included after all selection criteria were met as attested at the end of the assignment/inclusion visit (V2). At the end of V2, 21 patients were definitely included and assigned to treatment.

| Reporting group values | 3-month Treatment Period | Total | |
|----------------------------------------------------|--------------------------|-------|--|
| Number of subjects | 21 | 21 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 21 | 21 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: months | | | |
| arithmetic mean | 10.4 | | |
| standard deviation | ± 3.9 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 4 | |
| Male | 17 | 17 | |
| Race | | | |
| Units: Subjects | | | |
| White | 21 | 21 | |
| Asian | 0 | 0 | |
| Black | 0 | 0 | |
| Other | 0 | 0 | |
| Breastfeeding at enrolment | | | |
| Units: Subjects | | | |
| Yes | 9 | 9 | |
| No | 12 | 12 | |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 9.54 | | |
| standard deviation | ± 1.79 | - | |

Subject analysis sets

| | |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: | |
| All patients treated: analysed for all efficacy and safety outcomes. | |
| Subject analysis set title | PP set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: | |
| Patients treated with available data at baseline and at Month 3 on blood Hb and without major protocol deviations or other potential risk of primary analysis bias | |

| Reporting group values | Full Analysis Set (FAS) | PP set | |
|----------------------------------------------------|-------------------------|--------|--|
| Number of subjects | 21 | 11 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 21 | 11 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: months | | | |
| arithmetic mean | 10.4 | | |
| standard deviation | ± 3.9 | ± | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 2 | |
| Male | 17 | 9 | |
| Race | | | |
| Units: Subjects | | | |
| White | 21 | 11 | |
| Asian | 0 | 0 | |
| Black | 0 | 0 | |
| Other | 0 | 0 | |
| Breastfeeding at enrolment | | | |
| Units: Subjects | | | |
| Yes | 9 | | |
| No | 12 | | |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | 9.54 | | |
| standard deviation | ± 1.79 | ± | |

End points

End points reporting groups

| | |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
| Reporting group title | Baseline FAS |
| Reporting group description: As it is a single-arm study, the Baseline data of the FAS group (see definition of full analysis set) are considered to be those of this arm. | |
| Reporting group title | 3-month FAS |
| Reporting group description: As it is a single-arm study, the Month 3 data of the FAS group (see definition of full analysis set) are considered to be those of this arm. | |
| Reporting group title | Baseline PP set |
| Reporting group description: As it is a single-arm study, the Baseline data of the PP set (see PP set definition) are considered to be those of this arm | |
| Reporting group title | 3-month PP set |
| Reporting group description: As it is a single-arm study, the Month 3 data of the PP set (see PP set definition) are considered to be those of this arm | |
| Reporting group title | 6-month FAS |
| Reporting group description: As it is a single-arm study, the Month 6 data of the FAS patient(s) who entered the additional 3-month period are considered to be those of this arm. | |
| Subject analysis set title | Full Analysis Set (FAS) |
| Subject analysis set type | Full analysis |
| Subject analysis set description: All patients treated: analysed for all efficacy and safety outcomes. | |
| Subject analysis set title | PP set |
| Subject analysis set type | Per protocol |
| Subject analysis set description: Patients treated with available data at baseline and at Month 3 on blood Hb and without major protocol deviations or other potential risk of primary analysis bias | |

Primary: Blood Hb Level

| | |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| End point title | Blood Hb Level ^[1] |
| End point description: All statistical results were considered within a descriptive perspective and no statistical test was performed. The primary efficacy outcome, blood Hb at Month 3, was analysed in terms of value and change from baseline. Handling of drop-outs (for efficacy outcomes): in case of premature withdrawal between Week 3 (inclusive) and Month 3, the Observed Cases approach was used with the premature withdrawal visit replacing the Month 3 visit. In case of premature withdrawal before Week 3, Hb value was considered as missing at Month 3. | |
| End point type | Primary |
| End point timeframe: - For the Baseline group: last sampling before administration (Day 1) - For the 3-month group: between Day 83 and Day 97 | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The statistical analysis was purely descriptive with no test performed. It can only be added that the 95% CI of the mean at Month 3 was [116.1;123.2] g/L, with a CI half-width of 3.6 g/L. The CI half-width was inferior to that initially planned for sample size determination (4 g/L), confirming the

accuracy of the primary outcome CI.

| End point values | Baseline FAS | 3-month FAS | Baseline PP set | 3-month PP set |
|--------------------------------------|-------------------|-------------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 19 ^[2] | 19 ^[3] | 11 | 11 |
| Units: g/l | | | | |
| arithmetic mean (standard deviation) | 99.7 (± 7.6) | 119.7 (± 7.4) | 96.9 (± 7.8) | 121.1 (± 7.6) |

Notes:

[2] - 2 subjects with missing data

[3] - 2 subjects with missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Hb Responders

| | |
|---------------------------------------------------------------------------------|------------------------------|
| End point title | Hb Responders ^[4] |
| End point description: Number of subjects with blood Hb level \geq 110 g/L | |
| End point type | Secondary |
| End point timeframe: Day 83 - 97 | |

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As it is a single-arm, open-label study, the Baseline-FAS and the 3-Month FAS are the same groups. This endpoint was analysed at Month 3 and, as it was a secondary endpoint, was only analysed in the FAS. Therefore, the statistics are only reported in the 3-month FAS arm.

| End point values | 3-month FAS | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 19 | | | |
| Units: Number of subjects | 18 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Serum ferritin level

| | |
|-----------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------|
| End point title | Serum ferritin level ^[5] |
| End point description: | |
| End point type | Secondary |
| End point timeframe: - For the Baseline group: last sampling before administration (Day 1) - For the 3-month group: between Day 83 and Day 97 | |

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As this endpoint was a secondary endpoint, it was only analysed in the FAS. Therefore, the statistics are only reported in the Baseline FAS arm (baseline data) and the 3-month FAS arm (Month 3 data).

| End point values | Baseline FAS | 3-month FAS | | |
|--------------------------------------|-------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 19 ^[6] | 19 | | |
| Units: µg/L | | | | |
| arithmetic mean (standard deviation) | 6.4 (± 3.0) | 31.5 (± 19.4) | | |

Notes:

[6] - 2 missing data

Statistical analyses

No statistical analyses for this end point

Secondary: Ferritin Responders

| | |
|---------------------------------------------------------------------|------------------------------------|
| End point title | Ferritin Responders ^[7] |
| End point description: | |
| Number of subjects with serum ferritin level $\geq 12\mu\text{g/L}$ | |
| End point type | Secondary |
| End point timeframe: | |
| Day 83-97 | |

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As it is a single-arm, open-label study, the Baseline-FAS and the 3-Month FAS are the same groups. This endpoint was analysed at Month 3 and, as it was a secondary endpoint, was only analysed in the FAS. Therefore, the statistics are only reported in the 3-month FAS arm.

| End point values | 3-month FAS | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 19 | | | |
| Units: subjects | 16 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Acceptability (for parents)

| | |
|-----------------------------------------------------------------------------------|--------------------------------------------|
| End point title | Acceptability (for parents) ^[8] |
| End point description: | |
| Parents rated the acceptability of the treatment (taste-tolerability-ease of use) | |
| End point type | Secondary |
| End point timeframe: | |
| Day 83-97 or end of study if before Month 3 | |

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As it is a single-arm, open-label study, the Baseline-FAS and the 3-Month FAS are the same groups. This endpoint was analysed at Month 3 and, as it was a secondary endpoint, was only analysed in the FAS. Therefore, the statistics are only reported in the 3-month FAS arm.

| End point values | 3-month FAS | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: subjects | | | | |
| Very good | 5 | | | |
| Good | 12 | | | |
| Moderate | 3 | | | |
| Not good | 1 | | | |
| Not good at all | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall satisfaction (of Investigators)

| | |
|-----------------------------------------------------------------------------------|--------------------------------------------------------|
| End point title | Overall satisfaction (of Investigators) ^[9] |
| End point description: | |
| Investigators rated their satisfaction regarding the effect on the child's status | |
| End point type | Secondary |
| End point timeframe: | |
| Day 83-97 or end of study if before Month 3 | |

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: As it is a single-arm, open-label study, the Baseline-FAS and the 3-Month FAS are the same groups. This endpoint was analysed at Month 3 and, as it was a secondary endpoint, was only analysed in the FAS. Therefore, the statistics are only reported in the 3-month FAS arm.

| End point values | 3-month FAS | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: Subjects | | | | |
| Very satisfied | 8 | | | |
| Satisfied | 11 | | | |
| Moderately satisfied | 2 | | | |
| Not satisfied | 0 | | | |
| Not satisfied at all | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Ease of dose adaptation (for Investigators)

| | |
|-----------------|-------------------------------------------------------------|
| End point title | Ease of dose adaptation (for Investigators) ^[10] |
|-----------------|-------------------------------------------------------------|

End point description:

Investigators rated the ease of dose adaptation with the pipette

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 83-97 or end of study if before Month 3

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As it is a single-arm, open-label study, the Baseline-FAS and the 3-Month FAS are the same groups. This endpoint was analysed at Month 3 and, as it was a secondary endpoint, was only analysed in the FAS. Therefore, the statistics are only reported in the 3-month FAS arm.

| End point values | 3-month FAS | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 21 | | | |
| Units: Subjects | | | | |
| Very easy | 8 | | | |
| Easy | 13 | | | |
| Moderately easy | 0 | | | |
| Not easy | 0 | | | |
| Not easy at all | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Whole study period + 30 days for serious AEs; treatment period for non serious treatment-emergent AEs

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------------|
| Reporting group title | Full analysis set |
|-----------------------|-------------------|

Reporting group description:

All patients treated

| Serious adverse events | Full analysis set | | |
|---------------------------------------------------|-------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 21 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |

Frequency threshold for reporting non-serious adverse events: 4 %

| Non-serious adverse events | Full analysis set | | |
|-------------------------------------------------------|----------------------------------------------------------------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 21 (33.33%) | | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences (all) | 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | Additional description: Reported term "Stomachache" = only drug related AE | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences (all) | 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Dermatitis allergic | | | |
| subjects affected / exposed | 1 / 21 (4.76%) | | |
| occurrences (all) | 1 | | |

| | | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|
| Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Exanthema subitum subjects affected / exposed occurrences (all) Gastroenteritis rotavirus subjects affected / exposed occurrences (all) Laryngitis viral subjects affected / exposed occurrences (all) Respiratory tract infection subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) Viral rash subjects affected / exposed occurrences (all) | 1 / 21 (4.76%) 1 1 / 21 (4.76%) 1 1 / 21 (4.76%) 1 1 / 21 (4.76%) 1 2 / 21 (9.52%) 2 2 / 21 (9.52%) 2 1 / 21 (4.76%) 1 1 / 21 (4.76%) 1 | | |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--|--|

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 29 November 2017 | Besides administrative changes, the section on adverse events was updated to mention the new current version of the Investigator's Brochure, the expected date of last completed subject was updated, and the definition of the Per Protocol set was modified (the minimal treatment exposure was modified from 90 days to 83 days, to be in line with the possibility for the Subject to perform V4 at 90 ± 7 days) . Moreover, the opening of 5 new study centres was recorded. |
| 05 June 2018 | Mentioned the Local Study Manager leaving (with no replacement). Changed the expected date of the last patient's study end |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date | Interruption | Restart date |
|--------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 31 July 2018 | Despite measures were taken to help with recruitment, recruitment difficulties persisted, and it was decided to prematurely stop the recruitment on July 31, 2018 after 100 subjects had been screened. For all patients already recruited, the study was continued. | - |

Notes:

Limitations and caveats

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

- The number of included patients was lower than expected (21 vs 50) due to premature recruitment stop.
- A high % of patients was excluded from the PP set (48%). Nevertheless, the primary outcome results were supported by the PP analysis.

Notes: