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 kg ≤ body weight ≤ 20.0 kg,
- with a mild or moderate IDA:
    - o blood Hb level: 70 to 109 g/L
    - o serum ferritin < 12 µg/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
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	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 oucomes.

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 oucomes.	
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 >= 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 >= 12µg/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	1 / 21 (4.76%)		
occurrences (all)	1		
Exanthema subitum			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Gastroenteritis rotavirus			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Laryngitis viral			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Upper respiratory tract infection			
subjects affected / exposed	2 / 21 (9.52%)		
occurrences (all)	2		
Urinary tract infection			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	1		
Viral rash			
subjects affected / exposed	1 / 21 (4.76%)		
occurrences (all)	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: