Clinical trial results:
A RANDOMISED, SINGLE-BLIND, ACTIVE CONTROLLED, MULTI-CENTRE TRIAL TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY, ACCEPTABILITY AND PALATABILITY OF PMF104 COMPARED TO A CONVENTIONAL PEG-ELECTROLYTE SOLUTION IN CHILDREN AGED FROM 2 TO LESS THAN 6, FROM 6 TO LESS THAN 12 AND ADOLESCENTS FROM 12 TO LESS THAN 18 YEARS OF AGE REQUIRING A DIAGNOSTIC PROCEDURE CONCERNING THE COLON

Summary

EudraCT number	2015-002969-27
Trial protocol	IT BE FR
Global end of trial date	22 January 2021

Results information

Result version number	v1 (current)
This version publication date	09 July 2022
First version publication date	09 July 2022

Trial information

Trial identification

Sponsor protocol code	PMF104 PD1-2-3/2013

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	CRO-15-125: CRO code

Notes:

Sponsors

Sponsor organisation name	Alfasigma S.p.A.
Sponsor organisation address	Via Ragazzi del '99, 5, Bologna, Italy,
Public contact	Raffaella Tacchi, Alfasigma S.p.A., raffaella.tacchi@alfasigma.com
Scientific contact	Raffaella Tacchi, Alfasigma S.p.A., raffaella.tacchi@alfasigma.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001356-PIP02-12
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 January 2021
Global end of trial reached?	Yes
Global end of trial date	22 January 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to evaluate efficacy, safety, tolerability, acceptability and palatability of PMF104 compared to Klean-prep® in children aged from 2 to less than 18 years old requiring a diagnostic procedure of the colon.

Protection of trial subjects:

Before initiating the trial, the Sponsor and the investigators/institutions obtained written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent and assent forms and any other written/oral information provided to the paediatric subjects and their parents or legal representatives. The Sponsor provided the IRB/IEC with a current copy of the Investigator's Brochure and any updated copy prepared during the trial, when requested. The Sponsor and the investigators/Institutions obtained approval/favourable opinion from the IRB/IEC for change(s) to any aspect of the trial, such as modification(s) of the protocol, written informed consent form, written information provided to subjects.
The Sponsor had to promptly report any new information that could affect the safety of the paediatric subjects or the conduct of the trial to both the IRB/IEC and the Regulatory Authorities, if applicable.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 April 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	Belgium: 14
Country: Number of subjects enrolled	France: 51
Country: Number of subjects enrolled	Italy: 291
Worldwide total number of subjects	356
EEA total number of subjects	356

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)	201
Adolescents (12-17 years)	155
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed in 8 clinical centres in Europe: 5 centres in Italy, 1 centre in Belgium and 2 centres in France.

Pre-assignment

Screening details:

Overall 357 subjects were screened

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

During the study a single-blind design with respect to the investigational products was achieved by providing the randomisation list only to the unblinded study staff personnel who handled study drug management, preparation, dispensation and collection but who was not involved in colonoscopy performing. Only the endoscopist performing the colonoscopy was blinded regarding the treatment assigned.

Arms

Are arms mutually exclusive?	Yes
Arm title	PMF104

Arm description: -

Arm type	Experimental
Investigational medicinal product name	PMF104
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

PMF104 solution was administered the day before the diagnostic procedure concerning the colon, starting in the mid-late afternoon (4-6 p.m.), as a single dose by oral route. A nasogastric tube was inserted in children unable to drink the required amount of solution (in-patients only).

Arm title	Klean-Prep®

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Klean-Prep®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Klean-Prep® solution was administered the day before the diagnostic procedure concerning the colon, starting in the mid-late afternoon (4-6 p.m.), as a single dose by oral route. A nasogastric tube was placed in children unable to drink the required amount of solution (in-patients only).

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: During the study a single-blind design with respect to the investigational products was

achieved by providing the randomisation list only to the unblinded study staff personnel who handled study drug management, preparation, dispensation and collection but who was not involved in colonoscopy performing. Only the endoscopist performing the colonoscopy was blinded regarding the treatment assigned.

Number of subjects in period 1	PMF104	Klean-Prep®
Started	179	177
Completed	169	176
Not completed	10	1
Physician decision	2	-
Adverse event, non-fatal	4	-
Technical problems	1	-
Lost to follow-up	2	1
Withdrawal by parent/guardian	1	-

Baseline characteristics

Reporting groups	
Reporting group title	PMF104
Reporting group description: -	
Reporting group title	Klean-Prep®
Reporting group description: -	

Reporting group values	PMF104	Klean-Prep®	Total
Number of subjects	179	177	356
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	101	100	201
Adolescents (12-17 years)	78	77	155
Adults (18-64 years)	0	0	0
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	10.6	10.5	
standard deviation	± 3.9	± 3.9	-
Gender categorical Units: Subjects			
Female	82	76	158
Male	97	101	198

End points

End points reporting groups

Reporting group title	PMF104
Reporting group description: -	
Reporting group title	Klean-Prep®
Reporting group description: -	
Subject analysis set title	Per Protocol Set (PP) PMF104 2-<6 years
Subject analysis set type	Per protocol

Subject analysis set description:

The PP set includes the subjects (age stratum 2-<6 years) of the FAS (i.e. all randomised patients who received at least a fraction of the dose of the investigational product and have at least the BBPS score of any of the 3 broad regions of the colon [right colon, transverse colon or left colon]) who have a Good or Optimal compliance to PMF104 (regardless of the intake of a rescue dose) and have the BBPS scores of all the 3 broad regions of the colon (right colon, transverse colon and left colon), without any major protocol deviation that has an impact on the efficacy outcomes.

Subject analysis set title	Per Protocol Set (PP) Klean-Prep® 2-<6 years
Subject analysis set type	Per protocol

Subject analysis set description:

The PP set includes the subjects (age stratum 2-<6 years) of the FAS (i.e. all randomised patients who received at least a fraction of the dose of the investigational product and have at least the BBPS score of any of the 3 broad regions of the colon [right colon, transverse colon or left colon]) who have a Good or Optimal compliance to Klean-Prep® (regardless of the intake of a rescue dose) and have the BBPS scores of all the 3 broad regions of the colon (right colon, transverse colon and left colon), without any major protocol deviation that has an impact on the efficacy outcomes.

Subject analysis set title	Safety Set PMF104
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety set includes all subjects who received at least a fraction of the dose of PMF104. These subjects were included in the safety analysis.

Subject analysis set title	Safety Set Klean-Prep®
Subject analysis set type	Safety analysis

Subject analysis set description:

The safety set includes all subjects who received at least a fraction of the dose of Klean-Prep®. These subjects were included in the safety analysis.

Subject analysis set title	Per Protocol Set (PP) PMF104 6-<12 years
Subject analysis set type	Per protocol

Subject analysis set description:

The PP set includes the subjects (age stratum 6-<12 years) of the FAS (i.e. all randomised patients who received at least a fraction of the dose of the investigational product and have at least the BBPS score of any of the 3 broad regions of the colon [right colon, transverse colon or left colon]) who have a Good or Optimal compliance to PMF104 (regardless of the intake of a rescue dose) and have the BBPS scores of all the 3 broad regions of the colon (right colon, transverse colon and left colon), without any major protocol deviation that has an impact on the efficacy outcomes.

Subject analysis set title	Per Protocol Set (PP) Klean-Prep® 6-<12 years
Subject analysis set type	Per protocol

Subject analysis set description:

The PP set includes the subjects (age stratum 6-<12 years) of the FASc(i.e. all randomised patients who received at least a fraction of the dose of the investigational product and have at least the BBPS score of any of the 3 broad regions of the colon [right colon, transverse colon or left colon]) who have a Good or Optimal compliance to Klean-Prep® (regardless of the intake of a rescue dose) and have the BBPS scores of all the 3 broad regions of the colon (right colon, transverse colon and left colon), without any major protocol deviation that has an impact on the efficacy outcomes.

Subject analysis set title	Per Protocol Set (PP) PMF104 12-<18 years
Subject analysis set type	Per protocol

Subject analysis set description:

The PP set includes the subjects (age stratum 12-<18 years) of the FAS (i.e. all randomised patients who received at least a fraction of the dose of the investigational product and have at least the BBPS score of any of the 3 broad regions of the colon [right colon, transverse colon or left colon]) who have a Good or Optimal compliance to PMF104 (regardless of the intake of a rescue dose) and have the BBPS scores of all the 3 broad regions of the colon (right colon, transverse colon and left colon), without any major protocol deviation that has an impact on the efficacy outcomes.

Subject analysis set title	Per Protocol Set (PP) Klean-Prep® 12-<18 years
Subject analysis set type	Per protocol

Subject analysis set description:

The PP set includes the subjects (age stratum 12-<18 years) of the FAS (i.e. all randomised patients who received at least a fraction of the dose of the investigational product and have at least the BBPS score of any of the 3 broad regions of the colon [right colon, transverse colon or left colon]) who have a Good or Optimal compliance to Klean-Prep® (regardless of the intake of a rescue dose) and have the BBPS scores of all the 3 broad regions of the colon (right colon, transverse colon and left colon), without any major protocol deviation that has an impact on the efficacy outcomes.

Primary: Mean (total) BBPS score - Age stratum 2-<6 years

End point title	Mean (total) BBPS score - Age stratum 2-<6 years

End point description:

The primary endpoint is the difference between Clensia (PMF104) and Klean-Prep in terms of colon cleansing at day 2 as assessed by the Boston Bowel Preparation Scale (BBPS) score, with the objective of demonstrating non inferiority of PMF104 compared to the reference product (Klean-Prep).

Age stratum 2-<6 years.

End point type	Primary

End point timeframe:

Day 1: drug administration.
Day 2: evaluation of primary endpoint.

End point values	Per Protocol Set (PP) PMF104 2-<6 years	Per Protocol Set (PP) Klean-Prep® 2-<6 years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	16		
Units: BBPS score				
arithmetic mean (standard deviation)	5.9 (± 2.2)	6.6 (± 2.3)		

Statistical analyses

Statistical analysis title	Efficacy statistical analysis
Comparison groups	Per Protocol Set (PP) PMF104 2-<6 years v Per Protocol Set (PP) Klean-Prep® 2-<6 years

Number of subjects included in analysis	32
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Adjusted Mean Difference
Point estimate	-0.7357
Confidence interval	
level	90 %
sides	1-sided
lower limit	-1.6962
Variability estimate	Standard deviation

Primary: Mean (total) BBPS score - Age stratum 6-<12 years

End point title	Mean (total) BBPS score - Age stratum 6-<12 years

End point description:

The primary endpoint is the difference between Clensia (PMF104) and Klean-Prep in terms of colon cleansing at day 2 as assessed by the Boston Bowel Preparation Scale (BBPS) score, with the objective of demonstrating non inferiority of PMF104 compared to the reference product (Klean-Prep).

Age stratum 6 - <12 years

End point type	Primary

End point timeframe:

Day 1: drug administration.
Day 2: evaluation of primary endpoint.

End point values	Per Protocol Set (PP) PMF104 6-<12 years	Per Protocol Set (PP) Klean-Prep® 6-<12 years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	59		
Units: BBPS score				
arithmetic mean (standard deviation)	6.6 (± 1.9)	6.5 (± 1.8)		

Statistical analyses

Statistical analysis title	Efficacy statistical analysis
Comparison groups	Per Protocol Set (PP) PMF104 6-<12 years v Per Protocol Set (PP) Klean-Prep® 6-<12 years
Number of subjects included in analysis	109
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Adjusted Mean Difference
Point estimate	0.1309

Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-0.5097
Variability estimate	Standard deviation

Primary: Mean (total) BBPS score - Age stratum 12-<18 years

End point title	Mean (total) BBPS score - Age stratum 12-<18 years

End point description:

The primary endpoint is the difference between Clensia (PMF104) and Klean-Prep in terms of colon cleansing at day 2 as assessed by the Boston Bowel Preparation Scale (BBPS) score, with the objective of demonstrating non inferiority of PMF104 compared to the reference product (Klean-Prep).

Age stratum 12 - <18 years.

End point type	Primary

End point timeframe:

Day 1: drug administration.
Day 2: evaluation of primary endpoint.

End point values	Per Protocol Set (PP) PMF104 12-<18 years	Per Protocol Set (PP) Klean-Prep® 12-<18 years		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	61		
Units: BBPS score				
arithmetic mean (standard deviation)	6.1 (± 2.1)	6.0 (± 2.0)		

Statistical analyses

Statistical analysis title	Efficacy statistical analysis
Comparison groups	Per Protocol Set (PP) PMF104 12-<18 years v Per Protocol Set (PP) Klean-Prep® 12-<18 years
Number of subjects included in analysis	117
Analysis specification	Pre-specified
Analysis type	non-inferiority
Parameter estimate	Adjusted Mean Difference
Point estimate	0.1781
Confidence interval	
level	Other: 97.5 %
sides	1-sided
lower limit	-0.5035
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Overall study period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups	
Reporting group title	Safety Set PMF104 2-<6 years
Reporting group description: -	
Reporting group title	Safety Set PMF104 6-<12 years
Reporting group description: -	
Reporting group title	Safety Set PMF104 12-<18 years
Reporting group description: -	
Reporting group title	Safety Set Klean-Prep 2-<6 years
Reporting group description: -	
Reporting group title	Safety Set Klean-Prep 6-<12 years
Reporting group description: -	
Reporting group title	Safety Set Klean-Prep 12-<18 years
Reporting group description: -	

Serious adverse events	Safety Set PMF104 2-<6 years	Safety Set PMF104 6-<12 years	Safety Set PMF104 12-<18 years
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 22 (4.55%)	1 / 77 (1.30%)	0 / 75 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Congenital, familial and genetic disorders			
Haemorrhagic arteriovenous malformation			
subjects affected / exposed	0 / 22 (0.00%)	0 / 77 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericarditis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 77 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			

Pyrexia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 77 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	1 / 77 (1.30%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 77 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 22 (0.00%)	0 / 77 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 22 (0.00%)	0 / 77 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 22 (0.00%)	0 / 77 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Oral herpes			
subjects affected / exposed	1 / 22 (4.55%)	0 / 77 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Safety Set Klean-Prep 2-<6 years	Safety Set Klean-Prep 6-<12 years	Safety Set Klean-Prep 12-<18 years
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 26 (3.85%)	0 / 74 (0.00%)	4 / 77 (5.19%)
number of deaths (all causes)	0	0	0

number of deaths resulting from adverse events	0	0	0
Congenital, familial and genetic disorders			
Haemorrhagic arteriovenous malformation			
subjects affected / exposed	1 / 26 (3.85%)	0 / 74 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Pericarditis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 74 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 26 (0.00%)	0 / 74 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrointestinal polyp haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	0 / 74 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain			
subjects affected / exposed	0 / 26 (0.00%)	0 / 74 (0.00%)	3 / 77 (3.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 26 (0.00%)	0 / 74 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 26 (0.00%)	0 / 74 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	0 / 26 (0.00%)	0 / 74 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Oral herpes			
subjects affected / exposed	0 / 26 (0.00%)	0 / 74 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Safety Set PMF104 2-<6 years	Safety Set PMF104 6-<12 years	Safety Set PMF104 12-<18 years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 22 (59.09%)	48 / 77 (62.34%)	59 / 75 (78.67%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 22 (0.00%)	1 / 77 (1.30%)	0 / 75 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 22 (9.09%)	19 / 77 (24.68%)	14 / 75 (18.67%)
occurrences (all)	2	20	14
Asthenia			
subjects affected / exposed	0 / 22 (0.00%)	3 / 77 (3.90%)	8 / 75 (10.67%)
occurrences (all)	0	3	8
pyrexia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 77 (0.00%)	2 / 75 (2.67%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	4 / 22 (18.18%)	31 / 77 (40.26%)	35 / 75 (46.67%)
occurrences (all)	4	34	38
Abdominal pain			
subjects affected / exposed	6 / 22 (27.27%)	19 / 77 (24.68%)	35 / 75 (46.67%)
occurrences (all)	6	21	37
Abdominal distension			

subjects affected / exposed	3 / 22 (13.64%)	12 / 77 (15.58%)	27 / 75 (36.00%)
occurrences (all)	3	12	28
Vomiting			
subjects affected / exposed	5 / 22 (22.73%)	20 / 77 (25.97%)	16 / 75 (21.33%)
occurrences (all)	5	21	17
Anorectal discomfort			
subjects affected / exposed	2 / 22 (9.09%)	5 / 77 (6.49%)	10 / 75 (13.33%)
occurrences (all)	2	5	10
Diarrhoea			
subjects affected / exposed	0 / 22 (0.00%)	0 / 77 (0.00%)	3 / 75 (4.00%)
occurrences (all)	0	0	3
Gastritis			
subjects affected / exposed	0 / 22 (0.00%)	2 / 77 (2.60%)	0 / 75 (0.00%)
occurrences (all)	0	2	0
Rectal haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	0 / 77 (0.00%)	2 / 75 (2.67%)
occurrences (all)	0	0	2
Haematochezia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 77 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Enterobiasis			
subjects affected / exposed	0 / 22 (0.00%)	2 / 77 (2.60%)	0 / 75 (0.00%)
occurrences (all)	0	2	0
Pharyngitis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 77 (0.00%)	0 / 75 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Safety Set Klean-Prep 2-<6 years	Safety Set Klean-Prep 6-<12 years	Safety Set Klean-Prep 12-<18 years
Total subjects affected by non-serious adverse events			
subjects affected / exposed	15 / 26 (57.69%)	50 / 74 (67.57%)	60 / 77 (77.92%)
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 26 (0.00%)	2 / 74 (2.70%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
General disorders and administration site conditions			

Fatigue			
subjects affected / exposed	3 / 26 (11.54%)	16 / 74 (21.62%)	25 / 77 (32.47%)
occurrences (all)	3	16	27
Asthenia			
subjects affected / exposed	0 / 26 (0.00%)	4 / 74 (5.41%)	9 / 77 (11.69%)
occurrences (all)	0	4	9
pyrexia			
subjects affected / exposed	0 / 26 (0.00%)	2 / 74 (2.70%)	3 / 77 (3.90%)
occurrences (all)	0	2	3
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 26 (19.23%)	26 / 74 (35.14%)	48 / 77 (62.34%)
occurrences (all)	6	27	53
Abdominal pain			
subjects affected / exposed	6 / 26 (23.08%)	22 / 74 (29.73%)	23 / 77 (29.87%)
occurrences (all)	6	23	29
Abdominal distension			
subjects affected / exposed	1 / 26 (3.85%)	19 / 74 (25.68%)	31 / 77 (40.26%)
occurrences (all)	1	19	32
Vomiting			
subjects affected / exposed	7 / 26 (26.92%)	15 / 74 (20.27%)	21 / 77 (27.27%)
occurrences (all)	9	17	28
Anorectal discomfort			
subjects affected / exposed	1 / 26 (3.85%)	8 / 74 (10.81%)	17 / 77 (22.08%)
occurrences (all)	1	8	19
Diarrhoea			
subjects affected / exposed	0 / 26 (0.00%)	0 / 74 (0.00%)	4 / 77 (5.19%)
occurrences (all)	0	0	4
Gastritis			
subjects affected / exposed	0 / 26 (0.00%)	2 / 74 (2.70%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Rectal haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)	0 / 74 (0.00%)	2 / 77 (2.60%)
occurrences (all)	0	0	2
Haematochezia			

subjects affected / exposed	1 / 26 (3.85%)	0 / 74 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Enterobiasis			
subjects affected / exposed	0 / 26 (0.00%)	1 / 74 (1.35%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 26 (0.00%)	0 / 74 (0.00%)	2 / 77 (2.60%)
occurrences (all)	0	0	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2015	An exclusion criterion was modified and an additional exclusion criterion was added.
23 November 2016	• The number of participating clinical sites was increased in order to increase the low enrolment rate observed in the first months of the study. • The analysis model was integrated, with an additional analysis to be performed beside the originally planned analysis. • The inclusion criterion concerning fertile subjects was integrated. • Modification of a pre-screening clinical laboratory test schedule.
15 September 2017	This amendment was released to notify the change in the study Sponsor and legal representative. On 01 August 2017 Alfa Wassermann S.p.A. was merged with and incorporated in Alfasigma S.p.A. The latter became the study Sponsor and legal representative.
02 July 2018	• Reduction in the number of subjects to be included in the first (2-<6 years) age stratum as compared to the original protocol. • Change in the Statistical Plan with respect to the study population in the age stratum 2-<6 years. • Extension of enrolment period up to July 2020. • Reference to General Data Protection Regulation and data breach management was enclosed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported