Clinical trial results:
A randomised, assessor-blinded, multi-centre trial comparing the efficacy, safety and tolerability of the PICOPREP tailored dosing schedule to the PICOPREP day-before dosing schedule for colon cleansing in preparation for colonoscopy.

Summary

EudraCT number	2014-001062-10
Trial protocol	NL DE
Global end of trial date	08 June 2015

Results information

Result version number	v1 (current)
This version publication date	02 June 2016
First version publication date	02 June 2016

Trial information

Trial identification

Sponsor protocol code	000121

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02239692
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ferring Pharmaceuticals A/S
Sponsor organisation address	Kay Fiskers Plads 11, Copenhagen S, Denmark, 2300
Public contact	Clinical Development Support, Ferring Pharmaceuticals, DK0-Disclosure@ferring.com
Scientific contact	Clinical Development Support, Ferring Pharmaceuticals, DK0-Disclosure@ferring.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	18 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 June 2015
Global end of trial reached?	Yes
Global end of trial date	08 June 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This was a phase 3, randomised, assessor-blinded, multi-centre trial comparing the efficacy, safety and tolerability of a PICOPREP tailored dosing schedule to the PICOPREP day-before dosing schedule for colon cleansing in preparation for colonoscopy.

Protection of trial subjects:

Before obtaining the consent from patients, the Investigator appropriately explained the aims, methods, anticipated benefits, potential hazards, and any other aspects of the trial which are relevant to the patient's decision to participate, in a language understood by the patient. The Investigator explained to the patients about their right of freedom to refuse to enter the trial or to withdraw from it at any time, without any consequences on their further care and without the need to justify their decision. The trial was conducted in accordance with the Declaration of Helsinki and in compliance with the International Conference on Harmonization-Good Clinical Practice guidelines.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 November 2014
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	France: 15
Country: Number of subjects enrolled	Germany: 152
Country: Number of subjects enrolled	Netherlands: 37
Worldwide total number of subjects	204
EEA total number of subjects	204

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)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	134
From 65 to 84 years	70
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Subjects were recruited from 11 sites in Germany, France and the Netherlands from Nov 2014 to May 2015.

Pre-assignment

Screening details:

A total of 218 subjects were screened for this trial. Out of which 204 subjects fulfilled all inclusion and none of the exclusion criteria and were randomly assigned in a 2:1 ratio to either the PICOPREP tailored dosing schedule (n=131) or to the PICOPREP day-before dosing schedule (n=73).

Period 1

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

Blinding implementation details:

Subjects were randomised to one of the two dosing schedules according to a computer generated randomisation list prepared for all trial sites. The dosing schedule was not available to any member of the site staff involved in the conduct and evaluation of the trial, except the Investigator, and the unblinded trial coordinator, until the trial database was locked. The participating subjects and the monitor knew the treatment allocation once the subject was randomised.

Arms

Are arms mutually exclusive?	Yes
Arm title	PICOPREP day-before dosing schedule

Arm description:

PICOPREP Dose 1 was given before 8:00 AM on day before colonoscopy and Dose 2 was given 6-8 hours after Dose 1.

Arm type	Active comparator
Investigational medicinal product name	PICOPREP (Sodium picosulfate 10 mg, Magnesium oxide 3.5 g, and Citric acid 12 g)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Dose 1 was given before 8:00 AM on day before colonoscopy and Dose 2 was given 6-8 hours after Dose 1.

Arm title	PICOPREP tailored dosing schedule

Arm description:

PICOPREP Dose 1 was given 10-18 hours before colonoscopy and Dose 2 was given 4-6 hours before colonoscopy.

Arm type	Experimental
Investigational medicinal product name	PICOPREP (Sodium picosulfate 10 mg, Magnesium oxide 3.5 g, and Citric acid 12 g)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for oral solution

Routes of administration	Oral use

Dosage and administration details:

Dose 1 was given 10-18 hours before colonoscopy and Dose 2 was given 4-6 hours before colonoscopy.

Notes:

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

Justification: Considering the dosage regimens used in this trial, both Investigator and subjects (once randomised to a treatment group) were aware of the treatment provided. All members of the site personnel involved in the conduct and/or evaluation of the trial remained blinded to the treatment.

Number of subjects in period 1	PICOPREP day-before dosing schedule	PICOPREP tailored dosing schedule
Started	73	131
Completed	67	118
Not completed	6	13
Consent withdrawn by subject	3	5
Physician decision	-	1
Adverse event, non-fatal	-	1
Other reason	1	-
Incomplete colonoscopy	1	2
Lost to follow-up	1	4

Baseline characteristics

Reporting groups	
Reporting group title	PICOPREP day-before dosing schedule

Reporting group description:

PICOPREP Dose 1 was given before 8:00 AM on day before colonoscopy and Dose 2 was given 6-8 hours after Dose 1.

Reporting group title	PICOPREP tailored dosing schedule

Reporting group description:

PICOPREP Dose 1 was given 10-18 hours before colonoscopy and Dose 2 was given 4-6 hours before colonoscopy.

Reporting group values	PICOPREP day-before dosing schedule	PICOPREP tailored dosing schedule	Total
Number of subjects	73	131	204
Age Categorical Units: subjects			
<=18 years	0	0	0
Between 18 and 65 years	49	85	134
>=65 years	24	46	70
Age Continuous Units: years			
arithmetic mean	56.6	58.4	
standard deviation	± 15.1	± 13.3	-
Gender, Male/Female Units: subjects			
Female	43	77	120
Male	30	54	84
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2	3	5
Not Hispanic or Latino	71	128	199
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	73	130	203
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Height Units: meter (m)			
arithmetic mean	1.71	1.71	
standard deviation	± 0.088	± 0.094	-

Weight			
Units: kilogram(Kg)			
arithmetic mean	75.3	77.4	
standard deviation	± 14.9	± 16.1	-
Body Mass Index (BMI)			
Units: kg/m^2			
arithmetic mean	25.6	26.5	
standard deviation	± 4.33	± 4.71	-

Subject analysis sets

Subject analysis set title	Intention-to-Treat (ITT) Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT analysis set consisted of all randomised subjects.

Subject analysis set title	Per-Protocol (PP) Analysis Set
Subject analysis set type	Per protocol

Subject analysis set description:

The PP analysis set consisted of ITT analysis set subjects who had no major protocol deviations that would impact efficacy analysis.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set comprised of all treated subjects and was analysed according to the actual treatment received.

Reporting group values	Intention-to-Treat (ITT) Analysis Set	Per-Protocol (PP) Analysis Set	Safety Analysis Set
Number of subjects	204	186	195
Age Categorical			
Units: subjects			
<=18 years	0	0	0
Between 18 and 65 years	134	122	129
>=65 years	70	64	66
Age Continuous			
Units: years			
arithmetic mean	57.8	57.8	57.7
standard deviation	± 13.9	± 14.3	± 14.1
Gender, Male/Female			
Units: subjects			
Female	120	108	115
Male	84	78	80
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	5	5	5
Not Hispanic or Latino	199	181	190
Unknown or Not Reported	0	0	0
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	1	1
Native Hawaiian or Other Pacific Islander	0	0	0

Black or African American	0	0	0
White	203	185	194
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Height			
Units: meter (m)			
arithmetic mean	1.71	1.71	1.71
standard deviation	± 0.091	± 0.092	± 0.092
Weight			
Units: kilogram(Kg)			
arithmetic mean	76.6	76.5	76.6
standard deviation	± 15.7	± 15.5	± 15.5
Body Mass Index (BMI)			
Units: kg/m^2			
arithmetic mean	26.2	26.1	26.2
standard deviation	± 4.58	± 4.49	± 4.53

End points

End points reporting groups

Reporting group title	PICOPREP day-before dosing schedule

Reporting group description:

PICOPREP Dose 1 was given before 8:00 AM on day before colonoscopy and Dose 2 was given 6-8 hours after Dose 1.

Reporting group title	PICOPREP tailored dosing schedule

Reporting group description:

PICOPREP Dose 1 was given 10-18 hours before colonoscopy and Dose 2 was given 4-6 hours before colonoscopy.

Subject analysis set title	Intention-to-Treat (ITT) Analysis Set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT analysis set consisted of all randomised subjects.

Subject analysis set title	Per-Protocol (PP) Analysis Set
Subject analysis set type	Per protocol

Subject analysis set description:

The PP analysis set consisted of ITT analysis set subjects who had no major protocol deviations that would impact efficacy analysis.

Subject analysis set title	Safety Analysis Set
Subject analysis set type	Safety analysis

Subject analysis set description:

The Safety Analysis Set comprised of all treated subjects and was analysed according to the actual treatment received.

Primary: Overall colon cleansing procedure (ITT) measured by the total Ottawa Scale

End point title	Overall colon cleansing procedure (ITT) measured by the total Ottawa Scale

End point description:

Measured by the total Ottawa Scale score during the colonoscopy performed by a colonoscopist blinded to the dosing schedules. Total Ottawa Scale score was computed by adding the ratings (0 to 4; 0=excellent, 1=good, 2=fair, 3=poor, 4=inadequate) for each of the three colon segments and the overall fluid quality rating (0 to 2). The final score ranged from 0 (excellent) to 14 (solid stool in each colon segment and lots of fluid).

End point type	Primary

End point timeframe:

Day 1 (day of colonoscopy)

End point values	PICOPREP day-before dosing schedule	PICOPREP tailored dosing schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	131		
Units: score on a scale				
arithmetic mean (standard deviation)	8.2 (± 3.54)	4.2 (± 3.75)		

Statistical analyses

Statistical analysis title	Analysis of overall colon cleansing (ITT)

Statistical analysis description:

Null hypothesis was no treatment difference between the two dosing schedules. Adjusted estimated treatment mean difference was calculated as PICOPREP tailored dosing schedule minus PICOPREP day-before dosing schedule.

Comparison groups	PICOPREP day-before dosing schedule v PICOPREP tailored dosing schedule
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	Adjusted estimated mean difference
Point estimate	-3.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.99
upper limit	-2.87

Notes:

[1] - Non-inferiority is assessed by examining whether the upper limit of the 95% confidence interval is less than the specified non-inferiority margin of 1.5 points.
[2] - p-value corresponds to a two-sided test of superiority.

Primary: Overall Colon Cleansing Procedure (PP) Measured by the total Ottawa Scale

End point title	Overall Colon Cleansing Procedure (PP) Measured by the total Ottawa Scale

End point description:

Measured by the total Ottawa Scale score during the colonoscopy which is performed by a colonoscopist blinded to the dosing schedules. Total Ottawa Scale score was computed by adding the ratings (0 to 4; 0=excellent, 1=good, 2=fair, 3=poor, 4=inadequate) for each of the three colon segments and the overall fluid quality rating (0 to 2). The final score ranged from 0 (excellent) to 14 (solid stool in each colon segment and lots of fluid).

End point type	Primary

End point timeframe:

Day 1 (day of colonoscopy)

End point values	PICOPREP day-before dosing schedule	PICOPREP tailored dosing schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	120		
Units: score on a scale				
arithmetic mean (standard deviation)	8.1 (± 3.38)	3.7 (± 3.14)		

Statistical analyses

Statistical analysis title	Analysis of overall colon cleansing (PP)

Statistical analysis description:

Null hypothesis was no treatment difference between the two dosing schedules. Adjusted estimated treatment mean difference was calculated as PICOPREP tailored dosing schedule minus PICOPREP day-before dosing schedule.

Comparison groups	PICOPREP day-before dosing schedule v PICOPREP tailored dosing schedule
Number of subjects included in analysis	186
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	< 0.0001 [4]
Method	ANCOVA
Parameter estimate	Adjusted estimated mean difference
Point estimate	-4.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.34
upper limit	-3.41

Notes:

[3] - Non-inferiority is assessed by examining whether the upper limit of the 95% confidence interval is less than the specified non-inferiority margin of 1.5 points.

[4] - p-value corresponds to a two-sided test of superiority.

Secondary: Ascending colon cleansing responder status (ITT)

End point title	Ascending colon cleansing responder status (ITT)

End point description:

Percentage of subjects classified as responders, i.e. Ottawa Scale score of either 0 (excellent) or 1 (good), during colonoscopy performed by a colonoscopist blinded to the dosing schedules.

End point type	Secondary

End point timeframe:

Day 1 (day of colonoscopy)

End point values	PICOPREP day-before dosing schedule	PICOPREP tailored dosing schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	131		
Units: Percentage of subject				
number (not applicable)	15.1	61.1		

Statistical analyses

Statistical analysis title	Analysis of ascending colon cleansing (ITT)

Statistical analysis description:

Null hypothesis was no treatment difference between the two dosing schedules. The estimated odds ratio compares the odds of being a responder in the PICOPREP tailored dosing schedule vs. the PICOPREP day-before dosing schedule.

Comparison groups	PICOPREP day-before dosing schedule v PICOPREP tailored dosing schedule
Number of subjects included in analysis	204
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001 [5]
Method	Regression, Logistic
Parameter estimate	Adjusted estimated odds ratio
Point estimate	9.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.36
upper limit	19.32

Notes:

[5] - p-value corresponds to a two-sided test of superiority.

Secondary: Frequency and intensity of adverse events

End point title	Frequency and intensity of adverse events

End point description:

End point type	Secondary

End point timeframe:

From baseline (screening) up to day 10 after colonoscopy

End point values	PICOPREP day-before dosing schedule	PICOPREP tailored dosing schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	125		
Units: Number of subject				
Frequency of all adverse events	4	15		
Frequency of mild adverse events	4	12		

Frequency of moderate adverse events	0	2		
Frequency of severe adverse events	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinically significant changes in vital signs (pulse and blood pressure)

End point title	Clinically significant changes in vital signs (pulse and blood pressure)

End point description:

Mean change from baseline to the end-of-trial was observed for pulse and blood pressure (systolic and diastolic).

End point type	Secondary

End point timeframe:

From baseline (screening) up to day 10 after colonoscopy (inclusive of assessment at each visit)

End point values	PICOPREP day-before dosing schedule	PICOPREP tailored dosing schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	125		
Units: Number of subject				
Clinically significant change in pulse	0	0		
Clinically significant change in blood pressure	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinically significant changes in laboratory values (haematology, clinical chemistry, coagulation and urinalysis)

End point title	Clinically significant changes in laboratory values (haematology, clinical chemistry, coagulation and urinalysis)

End point description:

Laboratory parameters included routine haematology, clinical chemistry, coagulation and urinalysis. With the exception of urinalysis and urine pregnancy test, which was performed as dip-stick analyses at the trial site, all laboratory tests were analysed by a central laboratory.

End point type	Secondary

End point timeframe:

From baseline (screening) up to day 10 after colonoscopy (inclusive of assessment at each visit)

End point values	PICOPREP day-before dosing schedule	PICOPREP tailored dosing schedule		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	70	125		
Units: Number of subject				
Clinically significant change in haematology	0	0		
Clinically significant change in clinical chem	0	0		
Clinically significant change in coagulation	0	0		
Clinically significant change in urinalysis	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from baseline till the end-of-trial (10 days after colonoscopy).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	PICOPREP tailored dosing schedule

Reporting group description:

Subjects in this group received Dose 1 of PICOPREP 10-18 hours before colonoscopy and Dose 2 at 4-6 hours before colonoscopy.

Reporting group title	PICOPREP day-before dosing schedule

Reporting group description:

Subjects in this group received Dose 1 of PICOPREP before 8:00 AM on day before colonoscopy and received Dose 2 at 6-8 hours after Dose 1.

Serious adverse events	PICOPREP tailored dosing schedule	PICOPREP day-before dosing schedule	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 125 (0.80%)	0 / 70 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Large intestinal obstruction			
subjects affected / exposed	1 / 125 (0.80%)	0 / 70 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	PICOPREP tailored dosing schedule	PICOPREP day-before dosing schedule	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 125 (11.20%)	4 / 70 (5.71%)	
Investigations			
Blood glucose increased			

subjects affected / exposed	1 / 125 (0.80%)	0 / 70 (0.00%)	
occurrences (all)	1	0	
Congenital, familial and genetic disorders			
Gilbert's syndrome			
subjects affected / exposed	0 / 125 (0.00%)	1 / 70 (1.43%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 125 (0.80%)	1 / 70 (1.43%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	0 / 125 (0.00%)	1 / 70 (1.43%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	5 / 125 (4.00%)	0 / 70 (0.00%)	
occurrences (all)	5	0	
Diarrhoea			
subjects affected / exposed	1 / 125 (0.80%)	1 / 70 (1.43%)	
occurrences (all)	1	1	
Nausea			
subjects affected / exposed	1 / 125 (0.80%)	1 / 70 (1.43%)	
occurrences (all)	1	1	
Anorectal discomfort			
subjects affected / exposed	1 / 125 (0.80%)	0 / 70 (0.00%)	
occurrences (all)	1	0	
Dyspepsia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 70 (0.00%)	
occurrences (all)	1	0	
Eructation			
subjects affected / exposed	0 / 125 (0.00%)	1 / 70 (1.43%)	
occurrences (all)	0	1	
Gastrointestinal pain			
subjects affected / exposed	1 / 125 (0.80%)	0 / 70 (0.00%)	
occurrences (all)	1	0	

Vomiting			
subjects affected / exposed	1 / 125 (0.80%)	0 / 70 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 70 (0.00%)	
occurrences (all)	1	0	
Sleep disorder			
subjects affected / exposed	1 / 125 (0.80%)	0 / 70 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 125 (0.00%)	1 / 70 (1.43%)	
occurrences (all)	0	1	
Hypermagnesaemia			
subjects affected / exposed	1 / 125 (0.80%)	0 / 70 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 September 2014	The main reason for this amendment was to include the contraindications mentioned in the summary of products characteristics of PICOPREP, 'Rhabdomyolysis, Nausea and vomiting, Severe dehydration, and Hypermagnesaemia' to the list of exclusion criteria, as suggested by the Agence Nationale de Sécurité du Medicament et des Produits de Santé (ANMS) in France. In addition, minor changes and editorial clarifications have been made to the protocol. This was applicable for all sites.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported