Clinical trial results:
Efficacy, safety and tolerability of a bowel cleansing preparation (Eziclen®/Izinova®) in paediatric subjects undergoing colonoscopy: a Phase III, multicentre, randomised, comparative study versus Klean-Prep® (PEG-Electrolytes), administered on the day before colonoscopy, investigator-blinded, non-inferiority in adolescents of 12 to 17 years of age (inclusive) >40 kg

Summary

EudraCT number	2016-002265-60
Trial protocol	DE FR NL CZ PL IT
Global end of trial date	29 June 2020

Results information

Result version number	v1 (current)
This version publication date	14 February 2021
First version publication date	14 February 2021

Trial information

Trial identification

Sponsor protocol code	F-FR-58800-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03008460
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ipsen Pharma SAS
Sponsor organisation address	65 quai Georges Gorse, Boulogne-Billancourt, France, 92100
Public contact	Medical Director, Ipsen Pharma SAS, clinical.trials@ipsen.com
Scientific contact	Medical Director, Ipsen Consumer Healthcare, clinical.trials@ipsen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000816-PIP02-10
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	29 June 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that Eziclen®/Izinova®, an osmotic sulphate-based laxative preparation given on the day before colonoscopy has non-inferior efficacy to Klean-Prep® (polyethylene glycol [PEG]-electrolytes) on colon cleansing in adolescents aged 12 to 17 years (inclusive) with a body weight > 40 kilograms (kg), scheduled to undergo a colonoscopy for a routinely accepted diagnostic indication.

Protection of trial subjects:

The study was conducted under the provisions of the Declaration of Helsinki, in accordance with the International Conference on Harmonisation Consolidated Guideline on Good Clinical Practice, and in compliance with Independent Ethics Committee and informed consent regulations, and adhered to all local regulatory requirements. Written informed consent was obtained from the subject's parent(s)/legal representative(s) and as a signed assent from the adolescent prior to the subject entering the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 October 2017
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	Netherlands: 40
Country: Number of subjects enrolled	Poland: 139
Country: Number of subjects enrolled	Czechia: 6
Country: Number of subjects enrolled	France: 18
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Italy: 21
Worldwide total number of subjects	250
EEA total number of subjects	250

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)	250
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in adolescents who were undergoing a colonoscopy for a routinely accepted indication. Subjects were randomised 1:1 to Eziclen®/Izinova® (¾ of adult dose; 750 millilitres [mL] of preparation plus 1500 mL of water) or Klean-Prep® (70 mL/kg; maximum of 4000 mL). Subjects were randomised at 22 study centres in 6 countries.

Pre-assignment

Screening details:

The study consisted of a 1-day enrolment (Day 1, baseline) and investigator-blind label dosing period, a colonoscopy (Day 2) and a 30-day follow-up period (Day 32 [-5/+15, i.e. Day 27 to Day 47]). Subjects were expected to participate in the study for a minimum of 27 days and up to 47 days.

Period 1

Period 1 title	Randomisation Through Start of Treatment
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Arms

Are arms mutually exclusive?	Yes
Arm title	Eziclen®/Izinova®

Arm description:

Subjects randomised to the Eziclen®/Izinova® treatment group.

Arm type	Experimental
Investigational medicinal product name	Eziclen®/Izinova®
Investigational medicinal product code	
Other name	Eziclen®, Izinova®
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

Period is prior to the start of treatment; no study drug administered.

Arm title	Klean-Prep®

Arm description:

Subjects randomised to the Klean-Prep® treatment group.

Arm type	Active comparator
Investigational medicinal product name	Klean-Prep®
Investigational medicinal product code	
Other name	Macrogol 3350 plus electrolytes
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Period is prior to the start of treatment; no study drug administered.

Notes:

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

Justification: This was a single-blinded study in which the investigator (i.e. colonoscopist) was blinded to ensure an unbiased evaluation of the study preparations.

Number of subjects in period 1	Eziclen®/Izinova®	Klean-Prep®
Started	126	124
Completed	125	116
Not completed	1	8
Consent withdrawn by subject	1	4
Adverse event, non-fatal	-	1
Study drug not dispensed	-	1
Protocol deviation	-	2

Period 2

Period 2 title	Treatment Through End of Study
Is this the baseline period?	Yes[2]
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[3]

Blinding implementation details:

In this single-blinded (investigator-blinded) study, to ensure an unbiased evaluation of the study preparations, the colonoscopist was not allowed to perform any study treatment-related activities (drug dispensing, return and accountability, acceptability, tolerability, and review of subject's leaflet/questionnaires). Subjects and caregivers/nurses did not discuss their study preparation with the colonoscopist or any staff member other than with the study nurse who collected the questionnaires.

Arms

Are arms mutually exclusive?	Yes
Arm title	Eziclen®/Izinova®

Arm description:

Subjects received Eziclen®/Izinova® oral sulphate salt solution, administered as ¾ of the adult dose, as a 1-day regimen on the evening of the day before colonoscopy (Day 1). The 750 mL preparation was administered in 2 half doses as follows: the first half of preparation (375 mL) was drunk slowly in 30 minutes to 1 hour, followed by 750 mL of water over the next hour. Approximately 2 hours after starting the first half of preparation, the second half (375 mL) was drunk slowly in 30 minutes to 1 hour, followed by 750 mL of water over the next hour. Overall total volume (preparation + water) was 2250 mL (1125 mL per dose).

Arm type	Experimental
Investigational medicinal product name	Eziclen®/Izinova®
Investigational medicinal product code	
Other name	Eziclen®, Izinova®
Pharmaceutical forms	Concentrate for oral solution
Routes of administration	Oral use

Dosage and administration details:

Eziclen®/Izinova® is a concentrate for oral solution packaged in 2 bottles, each containing: sodium sulphate anhydrous: 17.510 grams (g), magnesium sulphate heptahydrate: 3.276 g and potassium sulphate: 3.130 g. The 2 bottles were diluted up to 1000 mL with water and 250 mL were discarded, with the remaining 750 mL preparation being given on the evening of the day before colonoscopy.

Arm title	Klean-Prep®

Arm description:

Subjects received Klean-Prep® oral solution, administered as a 70 mL/kg dose (calculated based on subject's weight) as a 1-day regimen on the evening of the day before colonoscopy (Day 1). The whole

solution was administered in 2 half doses (1 litre per hour), with a 1-hour pause between the 2 half doses. Approximately 2 hours after starting the first half of preparation, the second half was drunk. The maximum global volume administered was 4000 mL (2000 mL per dose).

Arm type	Active comparator
Investigational medicinal product name	Klean-Prep®
Investigational medicinal product code	
Other name	Macrogol 3350 plus electrolytes
Pharmaceutical forms	Powder for oral solution
Routes of administration	Oral use

Dosage and administration details:

Each sachet of Klean-prep® contains the following active ingredients: macrogol 3350: 59.000 g, anhydrous sodium sulphate: 5.685 g, sodium bicarbonate: 1.685 g, sodium chloride: 1.465 g, potassium chloride: 0.7425 g. Each treatment pack was composed of 4 sachets with a total of 69 g of the product included in each sachet. Each sachet was diluted in 1000 mL of water and dosage was 70 mL/kg (calculated based on subject's weight). Klean-Prep® was given on the evening of the day before colonoscopy.

Notes:

[2] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Period 1 presents data for all subjects randomised until the start of treatment and Period 2 presents data for all subjects who received study drug. Baseline characteristics are based on subjects who were randomised and who received even a partial dose of study drug; Period 2 is therefore the baseline period.

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

Justification: This was a single-blinded study in which the investigator (i.e. colonoscopist) was blinded to ensure an unbiased evaluation of the study preparations.

Number of subjects in period 2[4]	Eziclen®/Izinova®	Klean-Prep®
Started	125	116
Completed	119	110
Not completed	6	6
Consent withdrawn by subject	4	2
End of study visit outside permitted time window	-	1
Lost to follow-up	1	3
COVID-19 pandemic - consent withdrawn	1	-

Notes:

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

Justification: Baseline characteristics are based on subjects who were randomised and who received even a partial dose of study drug.

Baseline characteristics

Reporting groups	
Reporting group title	Eziclen®/Izinova®
Reporting group description:	
Subjects received Eziclen®/Izinova® oral sulphate salt solution, administered as ¾ of the adult dose, as a 1-day regimen on the evening of the day before colonoscopy (Day 1). The 750 mL preparation was administered in 2 half doses as follows: the first half of preparation (375 mL) was drunk slowly in 30 minutes to 1 hour, followed by 750 mL of water over the next hour. Approximately 2 hours after starting the first half of preparation, the second half (375 mL) was drunk slowly in 30 minutes to 1 hour, followed by 750 mL of water over the next hour. Overall total volume (preparation + water) was 2250 mL (1125 mL per dose).	
Reporting group title	Klean-Prep®
Reporting group description:	
Subjects received Klean-Prep® oral solution, administered as a 70 mL/kg dose (calculated based on subject's weight) as a 1-day regimen on the evening of the day before colonoscopy (Day 1). The whole solution was administered in 2 half doses (1 litre per hour), with a 1-hour pause between the 2 half doses. Approximately 2 hours after starting the first half of preparation, the second half was drunk. The maximum global volume administered was 4000 mL (2000 mL per dose).	

Reporting group values	Eziclen®/Izinova®	Klean-Prep®	Total
Number of subjects	125	116	241
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)	0	0	0
Adolescents (12-17 years)	125	116	241
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	15.1	15.3	
standard deviation	± 1.6	± 1.6	-
Gender categorical Units: Subjects			
Female	60	47	107
Male	65	69	134
Region of Enrollment Units: Subjects			
France	9	9	18
Germany	13	11	24
Italy	10	8	18
Netherlands	20	20	40
Poland	70	65	135
Czechia	3	3	6

End points

End points reporting groups

Reporting group title	Eziclen®/Izinova®
Reporting group description:	
Subjects randomised to the Eziclen®/Izinova® treatment group.	
Reporting group title	Klean-Prep®
Reporting group description:	
Subjects randomised to the Klean-Prep® treatment group.	
Reporting group title	Eziclen®/Izinova®
Reporting group description:	
Subjects received Eziclen®/Izinova® oral sulphate salt solution, administered as ¾ of the adult dose, as a 1-day regimen on the evening of the day before colonoscopy (Day 1). The 750 mL preparation was administered in 2 half doses as follows: the first half of preparation (375 mL) was drunk slowly in 30 minutes to 1 hour, followed by 750 mL of water over the next hour. Approximately 2 hours after starting the first half of preparation, the second half (375 mL) was drunk slowly in 30 minutes to 1 hour, followed by 750 mL of water over the next hour. Overall total volume (preparation + water) was 2250 mL (1125 mL per dose).	
Reporting group title	Klean-Prep®
Reporting group description:	
Subjects received Klean-Prep® oral solution, administered as a 70 mL/kg dose (calculated based on subject's weight) as a 1-day regimen on the evening of the day before colonoscopy (Day 1). The whole solution was administered in 2 half doses (1 litre per hour), with a 1-hour pause between the 2 half doses. Approximately 2 hours after starting the first half of preparation, the second half was drunk. The maximum global volume administered was 4000 mL (2000 mL per dose).	
Subject analysis set title	Eziclen®/Izinova®
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received Eziclen®/Izinova® oral sulphate salt solution, administered as ¾ of the adult dose, as a 1-day regimen on the evening of the day before colonoscopy (Day 1). The 750 mL preparation was administered in 2 half doses as follows: the first half of preparation (375 mL) was drunk slowly in 30 minutes to 1 hour, followed by 750 mL of water over the next hour. Approximately 2 hours after starting the first half of preparation, the second half (375 mL) was drunk slowly in 30 minutes to 1 hour, followed by 750 mL of water over the next hour. Overall total volume (preparation + water) was 2250 mL (1125 mL per dose).	
Subject analysis set title	Klean-Prep®
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received Klean-Prep® oral solution, administered as a 70 mL/kg dose (calculated based on subject's weight) as a 1-day regimen on the evening of the day before colonoscopy (Day 1). The whole solution was administered in 2 half doses (1 litre per hour), with a 1-hour pause between the 2 half doses. Approximately 2 hours after starting the first half of preparation, the second half was drunk. The maximum global volume administered was 4000 mL (2000 mL per dose).	

Primary: Percentage of Subjects With Successful Overall Colon Preparation, Assessed With the Cleansing Score (4-point Scale)

End point title	Percentage of Subjects With Successful Overall Colon Preparation, Assessed With the Cleansing Score (4-point Scale)

End point description:

Blinded overall assessment of preparation efficacy (Cleansing Score) was determined by the colonoscopist upon completion of the examination, based on a 4-point scale as follows:
- 4 (Excellent) = No more than small bits of adherent faeces/fluid
- 3 (Good) = Small amounts of faeces or fluid not interfering with examination
- 2 (Fair) = Enough faeces or fluid to prevent a completely reliable examination
- 1 (Poor) = Large amounts of faecal residue, additional cleansing required.

Only perfect preparations graded as excellent (4) or good (3), which allowed full, reliable examination of the mucosa were considered as successful. The adjusted percentage of subjects with a successful preparation was determined using a logistic regression model, including treatment and country as covariates.

The modified intention-to-treat population included all randomised subjects who received even a partial dose of study drug and produced a primary efficacy assessment.

End point type	Primary

End point timeframe:

At Day 2 (colonoscopy visit)

End point values	Eziclen®/Izinova®	Klean-Prep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	116		
Units: adjusted percentage of subjects				
number (confidence interval 95%)	71.42 (56.33 to 82.89)	79.03 (65.34 to 88.28)		

Statistical analyses

Statistical analysis title	Adjusted treatment difference

Statistical analysis description:

Analysis of the treatment difference (Eziclen®/Izinova® minus Klean-Prep®) was performed using a logistic regression model, including treatment and country as covariates.

Comparison groups	Eziclen®/Izinova® v Klean-Prep®
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.0907 [2]
Method	Regression, Logistic
Parameter estimate	Adjusted treatment difference
Point estimate	-7.61
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.45
upper limit	3.24

Notes:

[1] - Non-inferiority would be demonstrated if the lower limit of the 95% confidence interval of the adjusted treatment difference was higher than -15%.

[2] - P-value for non-inferiority was estimated from the adjusted treatment difference.

Secondary: Mean Colon Cleansing Score (4-point Scale)

End point title	Mean Colon Cleansing Score (4-point Scale)

End point description:

The Cleansing Score was determined by the blinded colonoscopist, based on a 4-point scale as follows:
- 4 (Excellent) = No more than small bits of adherent faeces/fluid
- 3 (Good) = Small amounts of faeces or fluid not interfering with examination
- 2 (Fair) = Enough faeces or fluid to prevent a completely reliable examination
- 1 (Poor) = Large amounts of faecal residue, additional cleansing required.

The adjusted mean score was estimated using a 2-way analysis of variance (ANOVA), including treatment and country as covariates.
The intention-to-treat (ITT) population included all randomised subjects who received even a partial dose of study drug.

End point type	Secondary

End point timeframe:

At Day 2 (colonoscopy visit)

End point values	Eziclen®/Izinova®	Klean-Prep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	116		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)	2.83 (2.67 to 2.99)	3.02 (2.85 to 3.18)		

Statistical analyses

Statistical analysis title	Adjusted treatment difference

Statistical analysis description:

Analysis of the treatment difference (Eziclen®/Izinova® minus Klean-Prep®) was performed using a 2-way ANOVA, including treatment and country as covariates.

Comparison groups	Eziclen®/Izinova® v Klean-Prep®
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0428
Method	ANOVA
Parameter estimate	Adjusted treatment difference
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	-0.01

Secondary: Mean Boston Bowel Preparation Scale (BBPS) Global Score and BBPS Scores by Colon Segment

End point title	Mean Boston Bowel Preparation Scale (BBPS) Global Score and BBPS Scores by Colon Segment

End point description:

The BBPS score for each colon segment (left, transverse, right) was determined by the blinded colonoscopist as follows:
• 0 = Unprepared colon segment with mucosa not seen due to solid stool that cannot be cleared
• 1 = Portion of mucosa of the segment seen, but other areas of the colon segment not well seen due to staining, residual stool and/or opaque liquid
• 2 = Minor amount of residual staining, small fragments of stool and/or opaque liquid, but mucosa of segment seen well
• 3 = Entire mucosa of segment seen well with no residual staining, small fragments of stool and/or opaque liquid.
Each segment score ranged from 0-3. Global score was sum of the 3 segment scores and ranged from 0-9 (worst to best). Successful colon cleansing was defined as a global BBPS score ≥6. The adjusted

mean score was estimated using a 2-way ANOVA, including treatment and country as covariates.
The ITT population included all randomised subjects who received even a partial dose of study drug.

End point type	Secondary

End point timeframe:

At Day 2 (colonoscopy visit)

End point values	Eziclen®/Izinova®	Klean-Prep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	116		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)				
Left colon (n=124, 116)	2.05 (1.89 to 2.22)	2.12 (1.95 to 2.29)		
Transverse colon (n=124, 115)	2.25 (2.10 to 2.40)	2.33 (2.18 to 2.48)		
Right colon (n=123, 115)	1.92 (1.74 to 2.09)	2.16 (1.98 to 2.34)		
Global score (n=123, 115)	6.25 (5.86 to 6.63)	6.61 (6.21 to 7.01)		

Statistical analyses

Statistical analysis title	Adjusted treatment difference: Left colon

Statistical analysis description:

Analysis of the treatment difference (Eziclen®/Izinova® minus Klean-Prep®) was performed using a 2-way ANOVA, including treatment and country as covariates.

Comparison groups	Eziclen®/Izinova® v Klean-Prep®
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4676
Method	ANOVA
Parameter estimate	Adjusted treatment difference
Point estimate	-0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.12

Statistical analysis title	Adjusted treatment difference: Transverse colon

Statistical analysis description:

Analysis of the treatment difference (Eziclen®/Izinova® minus Klean-Prep®) was performed using a 2-way ANOVA, including treatment and country as covariates.

Comparison groups	Eziclen®/Izinova® v Klean-Prep®

Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3076
Method	ANOVA
Parameter estimate	Adjusted treatment difference
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.25
upper limit	0.08

Statistical analysis title	Adjusted treatment difference: Right colon
Statistical analysis description:	
Analysis of the treatment difference (Eziclen®/Izinova® minus Klean-Prep®) was performed using a 2-way ANOVA, including treatment and country as covariates.	
Comparison groups	Eziclen®/Izinova® v Klean-Prep®
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0155
Method	ANOVA
Parameter estimate	Adjusted treatment difference
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.44
upper limit	-0.05

Statistical analysis title	Adjusted treatment difference: Global score
Statistical analysis description:	
Analysis of the treatment difference (Eziclen®/Izinova® minus Klean-Prep®) was performed using a 2-way ANOVA, including treatment and country as covariates.	
Comparison groups	Eziclen®/Izinova® v Klean-Prep®
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0975
Method	ANOVA
Parameter estimate	Adjusted treatment difference
Point estimate	-0.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.79
upper limit	0.07

Secondary: Percentage of Subjects With Need for Rescue Treatment

End point title	Percentage of Subjects With Need for Rescue Treatment

End point description:

The percentage of subjects who needed rescue treatment (saline enema) prior to colonoscopy because of inadequate preparation intake was assessed.
The ITT population included all randomised subjects who received even a partial dose of study drug.

End point type	Secondary

End point timeframe:

At Day 2 (colonoscopy visit, before colonoscopy)

End point values	Eziclen®/Izinova®	Klean-Prep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	116		
Units: percentage of subjects				
number (confidence interval 95%)	20.2 (13.1 to 27.2)	14.7 (8.2 to 21.1)		

Statistical analyses

Statistical analysis title	Adjusted treatment difference rate

Statistical analysis description:

Analysis was performed using Cochran-Mantel-Haenszel (CMH) chi-square method (using the general association statistic), stratified on country.

Comparison groups	Eziclen®/Izinova® v Klean-Prep®
Number of subjects included in analysis	240
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.2428
Method	CMH chi-square
Parameter estimate	Adjusted treatment difference rate
Point estimate	1.3847
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	2.4

Secondary: Percentage of Subjects With Need for Nasogastric Tube To Complete Preparation

End point title	Percentage of Subjects With Need for Nasogastric Tube To Complete Preparation

End point description:

The percentage of subjects who needed placement of a nasogastric tube to achieve administration of the complete preparation was assessed.
The ITT population included all randomised subjects who received even a partial dose of study drug.

End point type	Secondary

End point timeframe:

At Day 1 (treatment visit)

End point values	Eziclen®/Izinova®	Klean-Prep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	116		
Units: percentage of subjects				
number (confidence interval 95%)	7.2 (2.7 to 11.7)	31.0 (22.6 to 39.5)		

Statistical analyses

Statistical analysis title	Adjusted treatment difference rate

Statistical analysis description:

Analysis was performed using CMH chi-square method (using the general association statistic), stratified on country.

Comparison groups	Eziclen®/Izinova® v Klean-Prep®
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	CMH chi-square
Parameter estimate	Adjusted treatment difference rate
Point estimate	24.0219
Confidence interval	
level	95 %
sides	2-sided
lower limit	12.6
upper limit	45.9

Secondary: Percentage of Subjects With Colonoscopy Procedure Documented as Completed

End point title	Percentage of Subjects With Colonoscopy Procedure Documented as Completed

End point description:

The percentage of subjects with a complete colonoscopy, defined as a procedure that reached the caecum, was assessed.
The ITT population included all randomised subjects who received even a partial dose of study drug.

End point type	Secondary

End point timeframe:

At Day 2 (colonoscopy visit)

End point values	Eziclen®/Izinova®	Klean-Prep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	116		
Units: percentage of subjects				
number (confidence interval 95%)	96.8 (93.7 to 99.9)	96.6 (93.2 to 99.9)		

Statistical analyses

Statistical analysis title	Adjusted treatment difference rate

Statistical analysis description:

Analysis was performed using CMH chi-square method (using the general association statistic), stratified on country.

Comparison groups	Eziclen®/Izinova® v Klean-Prep®
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.9257
Method	CMH chi-square
Parameter estimate	Adjusted treatment difference rate
Point estimate	1.0022
Confidence interval	
level	95 %
sides	2-sided
lower limit	1
upper limit	1.1

Secondary: Median Time to Caecal Intubation

End point title	Median Time to Caecal Intubation

End point description:

The time to caecal intubation was defined as the time from colonoscope introduction to caecal intubation, estimated using the Kaplan-Meier product limit method. In the event the procedure did not reach the caecum, the subject was censored at time of withdrawal of colonoscope.
The ITT population included all randomised subjects who received even a partial dose of study drug.
Note: for 2 subjects in the Eziclen®/Izinova® group and 1 subject in the Klean-Prep® group, although the procedure reached the caecum, the time was not reported and consequently, these subjects could

not be included in the analysis.

End point type	Secondary

End point timeframe:

At Day 2 (colonoscopy visit)

End point values	Eziclen®/Izinova®	Klean-Prep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	123	115		
Units: minutes				
median (confidence interval 95%)	13.0 (10.0 to 15.0)	15.0 (12.0 to 15.0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Duration of Examination

End point title	Mean Duration of Examination

End point description:

The duration of examination for colonoscopy (in minutes) was measured by the difference between the time of caecum intubation and the time of withdrawal of the colonoscope. The adjusted mean duration of examination was estimated using a 2-way ANOVA, including treatment and country as covariates. Subjects for whom the caecum was not reached were excluded from the analysis.
The ITT population included all randomised subjects who received even a partial dose of study drug.

End point type	Secondary

End point timeframe:

At Day 2 (colonoscopy visit)

End point values	Eziclen®/Izinova®	Klean-Prep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	119	111		
Units: minutes				
arithmetic mean (confidence interval 95%)	14.77 (12.63 to 16.92)	15.70 (13.50 to 17.90)		

Statistical analyses

Statistical analysis title	Adjusted treatment difference

Statistical analysis description:

Analysis of the treatment difference (Eziclen®/Izinova® minus Klean-Prep®) was performed using 2-way ANOVA, including treatment and country as covariates.

Comparison groups	Eziclen®/Izinova® v Klean-Prep®

Number of subjects included in analysis	230
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.4459
Method	ANOVA
Parameter estimate	Adjusted treatment difference
Point estimate	-0.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.32
upper limit	1.47

Secondary: Mean Score for Overall Treatment Acceptability, Assessed Using Treatment Acceptability Questionnaire

End point title	Mean Score for Overall Treatment Acceptability, Assessed Using Treatment Acceptability Questionnaire

End point description:

The Treatment Acceptability Questionnaire was completed by the caregiver or subject after the subject ended the intake of preparation. Subject acceptability was rated as follows:
• 1 = Very badly accepted/unacceptable
• 2 = Badly but accepted
• 3 = Neither good nor bad
• 4 = Well accepted
• 5 = Very well accepted.
Overall acceptability score is the average of scores from the 2 doses ranging from 1 - 5 (worst to best). The adjusted mean score was estimated using a 2-way ANOVA, including treatment and country as covariates.
The ITT population included all randomised subjects who received even a partial dose of study drug.

End point type	Secondary

End point timeframe:

At Day 1 (treatment visit)

End point values	Eziclen®/Izinova®	Klean-Prep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	110		
Units: scores on a scale				
arithmetic mean (confidence interval 95%)	2.93 (2.65 to 3.21)	2.22 (1.92 to 2.51)		

Statistical analyses

Statistical analysis title	Adjusted treatment difference

Statistical analysis description:

Analysis of the treatment difference (Eziclen®/Izinova® minus Klean-Prep®) was performed using 2-way ANOVA, including treatment and country as covariates.

Comparison groups	Eziclen®/Izinova® v Klean-Prep®

Number of subjects included in analysis	235
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.0001
Method	ANOVA
Parameter estimate	Adjusted treatment difference
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.03

Secondary: Mean Overall Treatment Compliance

End point title	Mean Overall Treatment Compliance

End point description:

Treatment compliance according the instructions of use provided in the prescription was assessed as the percentage of volume of fluid taken relative to the planned volume of fluid to be taken (measured by the caregiver and reported in the treatment questionnaire of subject's leaflet during treatment administration). Overall treatment compliance was derived from the total volumes of fluid (i.e. preparation + hydration for Eziclen®/Izinova® and preparation only for Klean-Prep®) and was assessed for dose 1, dose 2 and globally (accounting for both doses). The adjusted mean overall treatment compliance (%) was estimated using a 2-way ANOVA, including treatment and country as covariates. The ITT population included all randomised subjects who received even a partial dose of study drug.

End point type	Secondary

End point timeframe:

At Day 1 (treatment visit)

End point values	Eziclen®/Izinova®	Klean-Prep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	116		
Units: adjusted percentage of subjects				
arithmetic mean (confidence interval 95%)				
Dose 1	96.74 (94.19 to 99.30)	95.52 (92.90 to 98.13)		
Dose 2	93.53 (89.24 to 97.81)	87.14 (82.76 to 91.53)		
Global	96.82 (93.32 to 100.31)	89.34 (85.74 to 92.93)		

Statistical analyses

Statistical analysis title	Adjusted treatment difference rate: Dose 1

Statistical analysis description:

Analysis of the treatment difference (Eziclen®/Izinova® minus Klean-Prep®) was performed using 2-way ANOVA, including treatment and country as covariates.

Comparison groups	Eziclen®/Izinova® v Klean-Prep®
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.3945
Method	ANOVA
Parameter estimate	Adjusted treatment difference rate
Point estimate	1.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	4.05

Statistical analysis title	Adjusted treatment difference rate: Dose 2
Statistical analysis description:	
Analysis of the treatment difference (Eziclen®/Izinova® minus Klean-Prep®) was performed using 2-way ANOVA, including treatment and country as covariates.	
Comparison groups	Eziclen®/Izinova® v Klean-Prep®
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0085
Method	ANOVA
Parameter estimate	Adjusted treatment difference rate
Point estimate	6.38
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.65
upper limit	11.12

Statistical analysis title	Adjusted treatment difference rate: Global
Statistical analysis description:	
Analysis of the treatment difference (Eziclen®/Izinova® minus Klean-Prep®) was performed using 2-way ANOVA, including treatment and country as covariates.	
Comparison groups	Eziclen®/Izinova® v Klean-Prep®
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0036
Method	ANOVA
Parameter estimate	Adjusted treatment difference rate
Point estimate	7.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	2.46
upper limit	12.5

Secondary: Mean Subject Tolerability Total Score, Assessed using a Symptom Scale

End point title	Mean Subject Tolerability Total Score, Assessed using a Symptom Scale

End point description:

Tolerability was assessed using a Symptom Scale after each dose of treatment for stomach cramping, stomach bloating and nausea on a paediatric 5-point scale as follows:
• 1 = No symptom
• 2 = Mild
• 3 = Bothersome
• 4 = Distressing
• 5 = Severely distressing symptoms.
The total tolerability score is the sum of the scores for the 3 symptoms ranging from 3 to 15 (best to worst). Mean total tolerability scores after dose 1 and dose 2 are presented.
The safety population included all randomised subjects who received even a partial dose of study drug. Subjects were assessed according to the treatment received (1 subject randomised to the Eziclen®/Izinova® group was mistakenly administered Klean-Prep®; this subject was therefore included in the Klean-Prep® safety population).

End point type	Secondary

End point timeframe:

At Day 1 (treatment visit)

End point values	Eziclen®/Izinova®	Klean-Prep®		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	124	117		
Units: scores on a scale				
arithmetic mean (standard deviation)				
Dose 1 (n=124, 117)	5.48 (± 2.42)	6.34 (± 2.78)		
Dose 2 (n=122, 113)	5.93 (± 2.58)	6.71 (± 3.07)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Median Time to Clear Effluent

End point title	Median Time to Clear Effluent

End point description:

The time to clear effluent, as reported by the subject, was defined as the time between first intake of prescription and first clear watery stool, estimated using the Kaplan-Meier product limit method. In the event of no clear watery stools, subjects with colonoscopy were censored at the time of colonoscope introduction, and subjects without colonoscopy were censored at time of start of treatment + 12 hours. Although time to clear effluent was pre-specified as a secondary endpoint in the study protocol, in a change to the planned analysis, it was subsequently analysed and reported as an 'other' efficacy

endpoint.
The ITT population included all randomised subjects who received even a partial dose of study drug.

End point type	Other pre-specified

End point timeframe:

At Day 2 (colonoscopy visit)

End point values	Eziclen®/Izinova®	Klean-Prep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	116		
Units: hours				
median (confidence interval 95%)	4.3 (3.5 to 5.3)	4.8 (3.8 to 5.8)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Time Between Last Intake of Fluids and Start of Colonoscopy Procedure

End point title	Mean Time Between Last Intake of Fluids and Start of Colonoscopy Procedure

End point description:

The time between the end of treatment administration (on Day 1) and the start of colonoscopy (on Day 2) was determined. The adjusted mean time between the last intake of fluids and the start of colonoscopy procedure was estimated using a 2-way ANOVA, including treatment and country as covariates.
The ITT population included all randomised subjects who received even a partial dose of study drug.

End point type	Other pre-specified

End point timeframe:

Day 1 (treatment visit) and Day 2 (colonoscopy visit)

End point values	Eziclen®/Izinova®	Klean-Prep®		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	125	116		
Units: hours				
arithmetic mean (confidence interval 95%)	15.30 (14.72 to 15.88)	14.25 (13.65 to 14.84)		

Statistical analyses

Statistical analysis title	Adjusted treatment difference

Statistical analysis description:

Analysis of the treatment difference (Eziclen®/Izinova® minus Klean-Prep®) was performed using 2-

way ANOVA, including treatment and country as covariates.

Comparison groups	Eziclen®/Izinova® v Klean-Prep®
Number of subjects included in analysis	241
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.0015
Method	ANOVA
Parameter estimate	Adjusted treatment difference
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.41
upper limit	1.69

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) were collected from Day 1 up to Day 32 (30 days [-5+/15] after colonoscopy).

Adverse event reporting additional description:

The safety population included all randomised subjects who received even a partial dose of study drug. Subjects were assessed according to the treatment received (1 subject randomised to the Eziclen®/Izinova® group was mistakenly administered Klean-Prep®; this subject was therefore included in the Klean-Prep® safety population).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Eziclen®/Izinova®

Reporting group description:

Subjects received Eziclen®/Izinova® oral sulphate salt solution, administered as ¾ of the adult dose, as a 1-day regimen on the evening of the day before colonoscopy (Day 1). The 750 mL preparation was administered in 2 half doses as follows: the first half of preparation (375 mL) was drunk slowly in 30 minutes to 1 hour, followed by 750 mL of water over the next hour. Approximately 2 hours after starting the first half of preparation, the second half (375 mL) was drunk slowly in 30 minutes to 1 hour, followed by 750 mL of water over the next hour. Overall total volume (preparation + water) was 2250 mL (1125 mL per dose).

Reporting group title	Klean-Prep®

Reporting group description:

Subjects received Klean-Prep® oral solution, administered as a 70 mL/kg dose (calculated based on subject's weight) as a 1-day regimen on the evening of the day before colonoscopy (Day 1). The whole solution was administered in 2 half doses (1 litre per hour), with a 1-hour pause between the 2 half doses. Approximately 2 hours after starting the first half of preparation, the second half was drunk. The maximum global volume administered was 4000 mL (2000 mL per dose).

Serious adverse events	Eziclen®/Izinova®	Klean-Prep®	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 124 (3.23%)	3 / 117 (2.56%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 124 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	0 / 124 (0.00%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 124 (0.81%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Crohn's disease	Additional description: Diagnostic finding at colonoscopy, reported as non-related TEAE and related to the indication for colonoscopy.		
subjects affected / exposed	2 / 124 (1.61%)	1 / 117 (0.85%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal polyp			
subjects affected / exposed	1 / 124 (0.81%)	0 / 117 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal stenosis			
subjects affected / exposed	1 / 124 (0.81%)	0 / 117 (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: 2 %

Non-serious adverse events	Eziclen®/Izinova®	Klean-Prep®	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	111 / 124 (89.52%)	105 / 117 (89.74%)	
Nervous system disorders			
Headache			
subjects affected / exposed	9 / 124 (7.26%)	2 / 117 (1.71%)	
occurrences (all)	9	2	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	90 / 124 (72.58%)	84 / 117 (71.79%)	
occurrences (all)	123	115	
Abdominal distension			

subjects affected / exposed	67 / 124 (54.03%)	77 / 117 (65.81%)	
occurrences (all)	91	107	
Abdominal pain upper			
subjects affected / exposed	64 / 124 (51.61%)	64 / 117 (54.70%)	
occurrences (all)	83	84	
Vomiting			
subjects affected / exposed	11 / 124 (8.87%)	10 / 117 (8.55%)	
occurrences (all)	11	11	
Crohn's disease	Additional description: Diagnostic finding at colonoscopy, reported as non-related TEAE and related to the indication for colonoscopy.		
subjects affected / exposed	9 / 124 (7.26%)	2 / 117 (1.71%)	
occurrences (all)	9	2	
Abdominal pain			
subjects affected / exposed	6 / 124 (4.84%)	3 / 117 (2.56%)	
occurrences (all)	6	3	
Colitis ulcerative	Additional description: Diagnostic finding at colonoscopy, reported as non-related TEAE and related to the indication for colonoscopy.		
subjects affected / exposed	1 / 124 (0.81%)	6 / 117 (5.13%)	
occurrences (all)	1	6	
Gastritis			
subjects affected / exposed	4 / 124 (3.23%)	3 / 117 (2.56%)	
occurrences (all)	4	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 January 2017	• Modification of the minimum weight for inclusion, from ≥40 kg to >40 kg; • Update of the pharmacovigilance/emergency contact address; • Update of exclusion criterion 1 to include advanced carcinoma; • Clarification of exclusion criterion 5; • Update of exclusion criterion 6 to include ascites, congestive heart failure of all grades, and hyperuricemia; • Update of exclusion criterion 10 to include asthma; • Modification of urine pregnancy test in blood pregnancy test and specification that urine pregnancy test was performed only when blood tests including pregnancy test were performed prior to Visit 1; • Clarification with regards to blood sampling (laboratory assessments performed within ≤10 days prior to inclusion could be used to determine eligibility upon investigator agreement) and addition of a footnote in the schedule of study procedures; • Addition of an Expert Committee to review safety data; • Addition of caution for subjects taking some types of medications; • Addition of medical care in the follow-up of adverse events (AEs).
16 March 2018	• Update of the department name of the sponsor's medically responsible person; • Update of the pharmacovigilance/emergency contact; • Update of the sponsor signatory; • Clarification of colonoscopy assessment and addition of the collection of colonoscopy diagnosis or diagnostic findings as part of safety and tolerability variables; • Update of the AE definition with regards to colonoscopy diagnosis or diagnostic findings; • Deletion from the safety and tolerability variables of the description and histological examination of any colonic biopsy specimens of mucosal lesions suspected by the investigator to have been caused by colonic lavage.
26 July 2018	• Deletion of the collection of colonoscopy diagnosis or diagnostic findings as part of safety and tolerability variables; • Addition from the safety and tolerability variables of the description and histological examination of any colonic biopsy specimens of mucosal lesions suspected by the investigator to have been caused by colonic lavage; • Deletion of International Normalised Ratio (INR) from the assessments of biochemistry parameters and addition of INR in the assessments of haematology parameters; • Update of the AE definition with regards to colonoscopy diagnosis or diagnostic findings.
02 March 2020	• Redefinition of the end of study and update of overall study duration and planned study period; • Removal of the investigator from the unblinded personnel who ensured of the proper investigational medicinal product storage, reconstitution, and dispensation; • Update in case the investigator had to break the blind for an emergency: the monitor to be informed was not blind; • Update with regards to the data review on unblinded data; • Update with regards to the review of safety data by the Expert Committee: this review was to be performed on blind data.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported