Clinical trial results:
A Randomized, Double-Blind, Placebo-Controlled Phase 4 Study to Evaluate the Efficacy and Safety of Entyvio (Vedolizumab IV) in the Treatment of Chronic Pouchitis (EARNEST)

Summary

EudraCT number	2015-003472-78
Trial protocol	DE GB BE ES NL IT
Global end of trial date	02 February 2021

Results information

Result version number	v1
This version publication date	25 June 2021
First version publication date	25 June 2021

Trial information

Trial identification

Sponsor protocol code	Vedolizumab-4004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02790138
WHO universal trial number (UTN)	U1111-1171-0918

Notes:

Sponsors

Sponsor organisation name	Takeda
Sponsor organisation address	95 Hayden Avenue, Lexington, United States, MA 02421
Public contact	Study Director, Takeda, TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda, TrialDisclosures@takeda.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	Interim
Date of interim/final analysis	11 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 June 2020
Global end of trial reached?	Yes
Global end of trial date	02 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to compare the efficacy of vedolizumab intravenous (IV) and placebo in terms of the percentage of participants with chronic or recurrent pouchitis achieving clinically relevant remission.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	12 October 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Spain: 1
Country: Number of subjects enrolled	United Kingdom: 15
Worldwide total number of subjects	102
EEA total number of subjects	48

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)	97
From 65 to 84 years	5
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 31 investigative sites in Canada, United States, Belgium, France, Germany, Italy, Netherlands, Spain, and United Kingdom from 12 October 2016 to 2 February 2021. Data is reported for primary outcome measures up to 11 June 2020.

Pre-assignment

Screening details:

Participants with a diagnosis of chronic or recurrent pouchitis were enrolled in a 1:1 ratio to receive placebo IV or vedolizumab IV 300 mg.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo IV

Arm description:

Vedolizumab placebo-matching intravenous (IV) infusion, once at Day 1, Weeks 2, 6, 14, 22, and 30 along with ciprofloxacin 500 mg, tablet, orally twice daily up to Week 4.

Arm type	Placebo
Investigational medicinal product name	Ciprofloxacin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ciprofloxacin tablets

Investigational medicinal product name	Vedolizumab Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Vedolizumab placebo-matching IV infusion

Arm title	Vedolizumab IV 300 mg

Arm description:

Vedolizumab 300 mg, IV infusion, once at Day 1, Weeks 2, 6, 14, 22, and 30 along with ciprofloxacin 500 mg, tablet, orally twice daily up to Week 4.

Arm type	Experimental
Investigational medicinal product name	Vedolizumab
Investigational medicinal product code	
Other name	Entyvio, MLN0002 IV, Kynteles
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

Vedolizumab IV infusion

Investigational medicinal product name	Ciprofloxacin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ciprofloxacin tablets

Number of subjects in period 1	Placebo IV	Vedolizumab IV 300 mg
Started	51	51
Completed	30	32
Not completed	21	19
Adverse event, non-fatal	5	2
Voluntary Withdrawal	8	9
Significant Protocol Deviation	-	1
Lost to follow-up	1	-
Reason not Specified	1	-
Lack of efficacy	6	7

Baseline characteristics

Reporting groups	
Reporting group title	Placebo IV
Reporting group description:	
Vedolizumab placebo-matching intravenous (IV) infusion, once at Day 1, Weeks 2, 6, 14, 22, and 30 along with ciprofloxacin 500 mg, tablet, orally twice daily up to Week 4.	
Reporting group title	Vedolizumab IV 300 mg
Reporting group description:	
Vedolizumab 300 mg, IV infusion, once at Day 1, Weeks 2, 6, 14, 22, and 30 along with ciprofloxacin 500 mg, tablet, orally twice daily up to Week 4.	

Reporting group values	Placebo IV	Vedolizumab IV 300 mg	Total
Number of subjects	51	51	102
Age categorical Units: Subjects			
Adults (18-64 years)	47	50	97
From 65-84 years	4	1	5
Age Continuous Units: years			
arithmetic mean	42.9	40.8	
standard deviation	± 13.48	± 11.32	-
Sex: Female, Male Units: participants			
Female	13	19	32
Male	38	32	70
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	6	3	9
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	42	44	86
More than one race	0	1	1
Unknown or Not Reported	2	2	4
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	11	12	23
Unknown or Not Reported	40	39	79
Region of Enrollment Units: Subjects			
Canada	7	9	16
United States	11	12	23
Belgium	6	1	7
France	2	5	7
Germany	1	2	3
Italy	10	10	20

Netherlands	6	4	10
Spain	1	0	1
United Kingdom	7	8	15
Height			
Units: cm			
arithmetic mean	175.3	172.4	
standard deviation	± 9.10	± 10.79	-
Weight			
Units: kg			
arithmetic mean	79.60	72.13	
standard deviation	± 19.115	± 17.588	-
Body Mass Index (BMI)			
BMI = weight (kg)/[height (m)^2			
Units: kg/m^2			
arithmetic mean	25.74	24.13	
standard deviation	± 5.125	± 4.891	-

End points

End points reporting groups

Reporting group title	Placebo IV
Reporting group description:	
Vedolizumab placebo-matching intravenous (IV) infusion, once at Day 1, Weeks 2, 6, 14, 22, and 30 along with ciprofloxacin 500 mg, tablet, orally twice daily up to Week 4.	
Reporting group title	Vedolizumab IV 300 mg
Reporting group description:	
Vedolizumab 300 mg, IV infusion, once at Day 1, Weeks 2, 6, 14, 22, and 30 along with ciprofloxacin 500 mg, tablet, orally twice daily up to Week 4.	

Primary: Percentage of Participants with Chronic or Recurrent Pouchitis Achieving Clinically Relevant Remission at Week 14

End point title	Percentage of Participants with Chronic or Recurrent Pouchitis Achieving Clinically Relevant Remission at Week 14
End point description:	
Clinically relevant remission is defined as modified Pouchitis Disease Activity Index (mPDAI) score <5 and a reduction of mPDAI score by ≥2 points from Baseline. The 12-point mPDAI score is calculated from two 6-point subscales: 1) Clinical Symptoms: Stool Frequency (0=usual to postoperative stool frequency to 2=three or more stools/day>postoperative usual); Rectal bleeding (0=None or rare to 1=Present daily); Fecal urgency or abdominal cramps (0=None to 2=Usual), Fever [temperature >37.8 degrees C] (0=Absent and 1=Present) for a clinical symptoms subscore of 0 (best) to 6 (worse); 2) Endoscopic Inflammation Findings: Edema, Granularity, Friability, Loss of vascular pattern, Mucous exudates and Ulcerations. Each item is scored on a scale of 0=not present to 1=present summed up to an endoscopic subscore ranging from 0 (best) to 6 (worst). Full Analysis Set (FAS) included all randomized participants who received at least 1 dose of study medication, as randomized.	
End point type	Primary
End point timeframe:	
Week 14	

End point values	Placebo IV	Vedolizumab IV 300 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	51	51		
Units: percentage of participants				
number (confidence interval 95%)	9.8 (3.3 to 21.4)	31.4 (19.1 to 45.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Placebo IV v Vedolizumab IV 300 mg

Number of subjects included in analysis	102
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.013 [1]
Method	Fisher’s Exact Test
Parameter estimate	Percentage Difference
Point estimate	21.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.9
upper limit	37.5

Notes:

[1] - The significance level was 0.05.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug up to 18 weeks after last dose (Up to 50 weeks).

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Vedolizumab IV 300 mg

Reporting group description:

Vedolizumab 300 mg, IV infusion, once at Day 1, Weeks 2, 6, 14, 22, and 30 along with ciprofloxacin 500 mg, tablet, orally twice daily up to Week 4.

Reporting group title	Placebo IV

Reporting group description:

Vedolizumab placebo-matching IV infusion, once at Day 1, Weeks 2, 6, 14, 22, and 30 along with ciprofloxacin 500 mg, tablet, orally twice daily up to Week 4.

Serious adverse events	Vedolizumab IV 300 mg	Placebo IV	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 51 (5.88%)	4 / 51 (7.84%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
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	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pouchitis			

subjects affected / exposed	2 / 51 (3.92%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 51 (0.00%)	1 / 51 (1.96%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 51 (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: 5 %

Non-serious adverse events	Vedolizumab IV 300 mg	Placebo IV	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	42 / 51 (82.35%)	35 / 51 (68.63%)	
Nervous system disorders			
Headache			
subjects affected / exposed	10 / 51 (19.61%)	3 / 51 (5.88%)	
occurrences (all)	11	4	
Gastrointestinal disorders			
Pouchitis			
subjects affected / exposed	23 / 51 (45.10%)	20 / 51 (39.22%)	
occurrences (all)	31	24	
Nausea			
subjects affected / exposed	5 / 51 (9.80%)	5 / 51 (9.80%)	
occurrences (all)	5	6	
Abdominal pain			
subjects affected / exposed	4 / 51 (7.84%)	2 / 51 (3.92%)	
occurrences (all)	5	2	
Frequent bowel movements			
subjects affected / exposed	4 / 51 (7.84%)	2 / 51 (3.92%)	
occurrences (all)	5	2	

Gastroenteritis			
subjects affected / exposed	1 / 51 (1.96%)	3 / 51 (5.88%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 51 (0.00%)	3 / 51 (5.88%)	
occurrences (all)	0	4	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 51 (13.73%)	9 / 51 (17.65%)	
occurrences (all)	7	11	
Back pain			
subjects affected / exposed	2 / 51 (3.92%)	5 / 51 (9.80%)	
occurrences (all)	2	5	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 51 (11.76%)	6 / 51 (11.76%)	
occurrences (all)	9	9	
Influenza			
subjects affected / exposed	4 / 51 (7.84%)	1 / 51 (1.96%)	
occurrences (all)	4	1	
Upper respiratory tract infection			
subjects affected / exposed	5 / 51 (9.80%)	1 / 51 (1.96%)	
occurrences (all)	5	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 October 2016	The primary purpose of this amendment was to make following changes: Updated the protocol to clarify the exclusion criteria, excluded medications, and proper post-study care. Chest X-ray added to exclusion criterion for latent tuberculosis (TB). Text modified for subjects receiving investigational nonbiologic therapy or an approved nonbiologic in an investigational protocol to extend the exclusion period. Modified exclusion criterion for subjects with a history of tendon rupture to include tendon disease related to quinolone treatment. New exclusion criterion added for subjects with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Added disopyramide, probenecid, and omeprazole to list of excluded medications. Deleted methotrexate from list of permitted immunomodulators. Added text regarding post-study care for subjects upon completion of the study or early withdrawal. Corrected typographical errors, punctuation, grammar, and formatting.
21 April 2017	The primary purpose of this amendment was to make following changes: Changed primary endpoint from Pouchitis Disease Activity Index (PDAI) score to modified Pouchitis Disease Activity Index (mPDAI) score. Reduced number of biopsy samples. Added minimum endoscopic subscore of 2 and specified definitions of chronic and recurrent pouchitis for study inclusion. Adjusted sample size calculation and decreased the total sample size from 200 to 110 participants. Added a futility analysis after 25 patients per arm reach Week 14. Added exclusion criteria. Added collection of stool sample for Clostridium (C) difficile testing to the Screening visit. Changed the maximum dose of oral corticosteroids from 30 to 20 mg/day and removed the recommended tapering schedule. Removed some of the exclusion criteria. Added a section on the Steering Committee. Added an investigator responsibility per updated International Conference on Harmonisation guideline. Updated indications for vedolizumab in the background information. Updated background information on the basis of the current Investigator’s Brochure. Updated the approximate total blood volume from 65 to 75 mL. Added a section on participant rescreening. Changed wording in the safety section from severity to intensity. Added frequency to the list of pretreatment event and AE reporting. Corrected an item in the PDAI and mPDAI to fecal urgency or abdominal cramps as per the original tool. Modified the criteria for discontinuation or withdrawal to add monitoring for leukopenia and lymphopenia and to clarify other criteria. Added clarifications to the Schedule of Study Procedures table.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported