ID: C13007 | Study of Vedolizumab (MLN0002) in Patients With Moderate to Severe Crohn's Disease | NCT00783692

Results Preview

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Participant Flow

Recruitment Details: Participants took part in the study at 285 investigative sites worldwide from 23 December 2008 to 08 May 2012. The Induction Phase contained 2 cohorts. The eligibility criteria for both cohorts were identical. The purpose of Cohort 2 was to provide enough responders to power the Maintenance Phase primary efficacy analysis.

Pre-Assignment Details: In Cohort 1, eligible patients who met entry criteria were randomized to treatment with double-blind vedolizumab 300 mg or placebo in a 3:2 ratio. All Cohort 2 patients were treated with open-label vedolizumab. In the Maintenance Phase participants were assigned to treatment groups based on their Induction Phase treatment and response to therapy.

Arm/Group Title	Placebo	Induction Phase: DB Vedolizumab	Induction Phase: OL Vedolizumab	Maintenance Phase: Placebo	Maintenance Phase: Vedolizumab Q8W	Maintenance Phase: Vedolizumab Q4W	Maintenance Phase: Non-Responders	Total (Not public)
Arm/Group Description	In the Induction Phase participants in Cohort 1 were randomized to receive double-blind placebo intravenous infusions at Week 0 and Week 2. Participants continued to receive placebo every 4 weeks from Week 6 through Week 50 during the Maintenance Phase, regardless of treatment response during induction.	In the Induction Phase participants in Cohort 1 were randomized to receive double-blind (DB) vedolizumab 300 mg, administered by intravenous infusion at Week 0 and Week 2.	In the Induction Phase participants in Cohort 2 received open-label (OL) vedolizumab 300 mg, administered by intravenous infusion at Week 0 and Week 2.	Participants who received vedolizumab during the Induction Phase and demonstrated a clinical response at Week 6 were then randomized to receive double-blind treatment with placebo every 4 weeks up to Week 50 during the Maintenance Phase.	Participants who received vedolizumab during the Induction Phase and demonstrated a clinical response at Week 6 were then randomized to receive double-blind treatment with vedolizumab 300 mg every 8 weeks (Q8W) at Weeks 6, 14, 22, 30, 38, and 46, and, to maintain blinding, placebo infusions at Weeks 10, 18, 26, 34, 42, and 50.	Participants who received vedolizumab during the Induction Phase and demonstrated a clinical response at Week 6 were then randomized to receive double-blind treatment with vedolizumab 300 mg every 4 weeks (Q4W) from Week 6 to Week 50.	Participants who received vedolizumab during the Induction Phase who did not demonstrate a clinical response at Week 6 received open-label treatment with vedolizumab 300 mg every 4 weeks from Week 6 to Week 50.	
Period Title: Induction Phase								
Started	148	220	748	0	0	0	0	1116
Treated	148	220	747	0	0	0	0	1115
Completed	137	199	674	0	0	0	0	1010
Not Completed	11	21	74	0	0	0	0	106
Reason Not Completed								
Adverse Event	7	9	24	0	0	0	0	40
Protocol Violation	0	0	1	0	0	0	0	1
Lack of Efficacy	1	3	28	0	0	0	0	32
Withdrawal by Subject	3	9	16	0	0	0	0	28
Lost to Follow-up	0	0	3	0	0	0	0	3
Other	0	0	2	0	0	0	0	2
NOTE : "Other" is not sufficiently descriptive for "Other" Reason Not Completed. Please provide a more descriptive label. (Not Public)	Not Completed = 11 Total from all reasons = 11	Not Completed = 21 Total from all reasons = 21	Not Completed = 74 Total from all reasons = 74	Not Completed = 0 Total from all reasons = 0	Not Completed = 0 Total from all reasons = 0	Not Completed = 0 Total from all reasons = 0	Not Completed = 0 Total from all reasons = 0	
Period Title: Maintenance Phase								
Started	137	0 NOTE : The number of participants to start a Period is not equal to the number who completed previous Period.	0 NOTE : The number of participants to start a Period is not equal to the number who completed previous Period.	153 NOTE : The number of participants to start a Period is not equal to the number who completed previous Period.	154 NOTE : The number of participants to start a Period is not equal to the number who completed previous Period.	154 NOTE : The number of participants to start a Period is not equal to the number who completed previous Period.	412 NOTE : The number of participants to start a Period is not equal to the number who completed previous Period.	1010
Completed	42	0	0	64	73	82	163	424
Not Completed	95	0	0	89	81	72	249	586
Reason Not Completed								
Adverse Event	7	0	0	15	12	9	38	81
Protocol Violation	0	0	0	1	2	3	4	10
Lack of Efficacy	79	0	0	64	58	48	177	426
Withdrawal by Subject	7	0	0	7	6	9	24	53
Lost to Follow-up	2	0	0	1	3	2	5	13
Other	0	0	0	1	0	1	1	3
NOTE : "Other" is not sufficiently descriptive for "Other" Reason Not Completed. Please provide a more descriptive label. (Not Public)	Not Completed = 95 Total from all reasons = 95	Not Completed = 0 Total from all reasons = 0	Not Completed = 0 Total from all reasons = 0	Not Completed = 89 Total from all reasons = 89	Not Completed = 81 Total from all reasons = 81	Not Completed = 72 Total from all reasons = 72	Not Completed = 249 Total from all reasons = 249	

Baseline Characteristics

Arm/Group Title	Placebo	Induction Phase: DB Vedolizumab	Induction Phase: OL Vedolizumab	Total
Arm/Group Description	In the Induction Phase participants in Cohort 1 were randomized to receive double-blind placebo intravenous infusions at Week 0 and Week 2.	In the Induction Phase participants in Cohort 1 were randomized to receive double-blind (DB) vedolizumab 300 mg, administered by intravenous infusion at Week 0 and Week 2.	In the Induction Phase participants in Cohort 2 received open-label (OL) vedolizumab 300 mg, administered by intravenous infusion at Week 0 and Week 2.	
Overall Number of Baseline Participants	148	220	747	**1115**
Baseline Analysis Population Description	The Induction Phase Safety Population, defined as all participants, in both Cohort 1 and Cohort 2, who received any amount of study drug in the Induction Phase (Weeks 0 to 6), according to the actual study drug received.			
Age, Continuous **Mean (Standard Deviation)** **Units: years**	38.6 (13.16)	36.3 (11.57)	35.6 (12.01)	36.1 (12.12)
Age, Customized **Measure Type: Number** **Units: participants**				
< 35 years	67	111	404	582
≥ 35 years	81	109	343	533
Age, Customized **Measure Type: Number** **Units: participants**				
< 65 years	142	218	732	1092
≥ 65 years	6	2	15	23
Gender, Male/Female **Measure Type: Number** **Units: participants**				
Female	79	115	401	595
Male	69	105	346	520
Ethnicity (NIH/OMB) **Measure Type: Number** **Units: participants**				
Hispanic or Latino	5	2	19	26
Not Hispanic or Latino	139	214	712	1065
Unknown or Not Reported	4	4	16	24
Race/Ethnicity, Customized **Measure Type: Number** **Units: participants**				
White	124	182	689	995
Black	3	3	17	23
Asian	19	35	35	89
Other	2	0	6	8
Region of Enrollment **Measure Type: Number** **Units: participants**				
Australia	5	10	30	45
Austria	4	3	7	14
Belgium	12	17	41	70
Bulgaria	5	7	2	14
Canada	22	12	103	137
Czech Republic	11	16	53	80
Denmark	0	2	8	10
Estonia	1	2	3	6
France	4	3	37	44
Germany	0	1	49	50
Greece	0	0	2	2
Hong Kong	2	0	0	2
Hungary	9	17	47	73
Iceland	0	0	4	4
India	10	19	5	34
Ireland	0	0	2	2
Israel	2	4	12	18
Italy	1	0	13	14
Korea, Republic of	3	12	11	26
Latvia	0	2	0	2
Malaysia	1	3	5	9
Netherlands	0	0	7	7
New Zealand	4	5	3	12
Norway	0	0	13	13
Poland	7	6	14	27
Romania	0	1	4	5
Russian Federation	4	9	15	28
Serbia	0	0	3	3
Singapore	1	0	0	1
Slovakia	3	5	10	18
South Africa	3	3	14	20
Spain	1	0	6	7
Sweden	0	1	8	9
Switzerland	0	1	9	10
Taiwan	0	0	3	3
Turkey	2	3	1	6

Ukraine	3	4	9	16
United Kingdom	0	0	6	6
United States	28	52	188	268
Body Weight				
Mean (Standard Deviation)				
Units: kg	68.7 (18.90)	67.1 (19.07)	70.8 (19.56)	69.8 (19.42)
Body Mass Index (BMI)				
Mean (Standard Deviation)				
Units: kg/m^2	23.7 (5.77)	23.1 (5.62)	24.2 (6.02)	23.9 (5.93)
Duration of Crohn's Disease (CD)				
Mean (Standard Deviation)				
Units: years	8.2 (7.80)	9.2 (8.18)	9.2 (7.63)	9.0 (7.77)
Duration of Crohn's Disease - Categorical				
Measure Type: Number				
Units: participants				
< 1 year	12	12	45	69
≥ 1 to < 3 years	27	48	126	201
≥ 3 to < 7 years	45	49	191	285
≥ 7 years	64	111	385	560
Baseline Disease Activity – Crohn's Disease Activity Index (CDAI) [1]				
Mean (Standard Deviation)				
Units: units on a scale	324.6 (78.08)	327.3 (70.67)	322.2 (67.17)	323.6 (69.37)

[1] Number of participants for whom baseline CDAI scores were available were 147, 219, and 743, respectively.
The CDAI is a numerical calculation derived from the sum of products from a list of 8 disease variables: number of liquid stools, extent of abdominal pain, general well-being, occurrence of extraintestinal symptoms, need for antidiarrheal drugs, presence of abdominal masses, hematocrit, and body weight. CDAI scores range from 0 to ~600 points with lower scores indicating disease remission and higher scores indicating disease worsening.

Baseline Disease Activity – Categorical				
Measure Type: Number				
Units: participants				
CDAI ≤ 330	81	119	418	618
CDAI > 330	66	100	325	491
Missing	1	1	4	6
Baseline C-reactive Protein (CRP) [1]				
Mean (Standard Deviation)				
Units: mg/L	23.6 (27.85)	24.1 (27.23)	20.4 (27.40)	21.5 (27.45)

[1] Baseline CRP data was only available for 147 participants in the placebo arm.

Baseline CRP - Categorical				
Measure Type: Number				
Units: participants				
≤ 2.87 mg/L	20	37	130	187
> 2.87 to ≤ 5 mg/L	14	25	75	114
> 5 to ≤ 10 mg/L	28	38	160	226
> 10 mg/L	85	120	382	587
Missing	1	0	0	1
Baseline Fecal Calprotectin [1]				
Mean (Standard Deviation)				
Units: µg/g	1421.2 (2076.11)	1839.9 (2624.92)	1050.1 (1558.93)	1254.2 (1908.82)

[1] Number of participants for whom baseline fecal calprotectin data were available were 142, 210, and 719, respectively.

Baseline Fecal Calprotectin - Categorical				
Measure Type: Number				
Units: participants				
≤ 250 µg/g	34	51	201	286
> 250 to ≤ 500 µg/g	27	25	112	164
> 500 µg/g	81	134	406	621
Missing	6	10	28	44
Disease Localization				
Measure Type: Number				
Units: participants				
Ileum only	21	37	123	181
Colon only	43	62	211	316
Ileocolonic (both ileum and colon)	84	121	413	618
History of Prior Surgery for Crohn's Disease				
Measure Type: Number				
Units: participants				
Yes	54	98	314	466
No	94	122	433	649
History of Fistulizing Disease				
Measure Type: Number				
Units: participants				
Yes	56	90	264	410
No	92	130	483	705
Draining Fistula at Baseline				
Measure Type: Number				
Units: participants				
Yes	23	38	104	165
All Closed	2	1	8	11
No	123	181	635	939
Smoking Status				
Measure Type: Number				
Units: participants				

Current smoker	34	54	210	298
Nonsmoker (never smoked)	85	120	351	556
Former smoker	29	46	185	260
Missing	0	0	1	1
Baseline Extraintestinal Manifestations **Measure Type: Number** **Units: participants**				
Yes	107	133	456	696
No	41	87	291	419
History of Extraintestinal Manifestations **Measure Type: Number** **Units: participants**				
Yes	123	177	619	919
No	25	43	128	196

Outcome Measures

1. Primary Outcome

Title: Induction Phase: Percentage of Participants Achieving Clinical Remission at Week 6

Description:
Clinical remission is defined as a Crohn's Disease Activity Index (CDAI) score ≤ 150 points.
The CDAI is used to quantify the symptoms of patients with Crohn's disease and consists of eight factors, each summed after adjustment with a weighting factor. The components of the CDAI are:

- Number of liquid or soft stools each day for 7 days;
- Abdominal pain (graded from 0-3 on severity) each day for 7 days;
- General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day for 7 days;
- Presence of complications;
- Taking Lomotil or opiates for diarrhea;
- Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite);
- Hematocrit of < 0.47 in men and < 0.42 in women;
- Percentage deviation from standard weight.

The total score ranges from 0 to approximately 600 and with higher scores indicating greater disease activity.
All participants who prematurely discontinued for any reason were considered as not achieving clinical remission.

Time Frame: Week 6

Safety Issue? No

Outcome Measure Data

Analysis Population Description
Induction Study Intention to Treat (ITT) Population, which consisted of all randomized patients in Cohort 1 who received any amount of blinded study drug.

Arm/Group Title	**Placebo**	**DB Vedolizumab**
Arm/Group Description:	Participants in Cohort 1 received double-blind placebo intravenous infusions at Week 0 and Week 2 in the Induction Phase.	Participants in Cohort 1 received double-blind vedolizumab 300 mg, administered by intravenous infusion at Week 0 and Week 2 in the Induction Phase.
Number of Participants Analyzed	148	220
Number (95% Confidence Interval) **Units: percentage of participants**	6.8 (2.7 to 10.8)	14.5 (9.9 to 19.2)

Statistical Analysis 1

Statistical Analysis Overview	**Comparison Groups**	Placebo, DB Vedolizumab
	Comments	The Hochberg method was applied to control the overall Type I error rate at a 5% significance level for the multiple comparisons of the primary endpoints. If both p-values were ≤ 0.05, both primary endpoints were to be declared significant. If 1 of the p-values for the primary endpoints was > 0.05, the other p-value was to be tested at the 0.025 level and declared significant only if the p-value was ≤ 0.025. If neither primary was declared significant, no further testing was to be conducted.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	**P-Value**	0.0206
	Comments	P-value is based on the Cochran-Mantel-Haenszel (CMH) chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNFα antagonists and/or concomitant immunomodulator use (yes/no).
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]
Method of Estimation	**Estimation Parameter**	Risk Difference (RD)
	Estimated Value	7.8
	Confidence Interval	(2-Sided) 95% 1.2 to 14.3
	Estimation Comments	Risk Difference = adjusted (for stratification factors) percent vedolizumab - adjusted percent placebo

2. Primary Outcome

Title: Induction Phase: Percentage of Participants With Enhanced Clinical Response at Week 6

Description:
Enhanced clinical response is defined as a CDAI score at least 100 points lower than Baseline. The CDAI is used to quantify the symptoms of patients with Crohn's disease and consists of eight factors, each summed after adjustment with a weighting factor. The components of the CDAI are:

- Number of liquid or soft stools each day for 7 days;
- Abdominal pain (graded from 0-3 on severity) each day for 7 days;
- General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day for 7 days;
- Presence of complications;
- Taking Lomotil or opiates for diarrhea;
- Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite);
- Hematocrit of < 0.47 in men and < 0.42 in women;
- Percentage deviation from standard weight.

The total score ranges from 0 to 600 with higher scores indicating greater disease activity.
All participants who prematurely discontinued for any reason were considered as not achieving enhanced clinical response.

Time Frame: Baseline and Week 6

Safety Issue? No

Outcome Measure Data

Analysis Population Description
Induction Study ITT Population

Arm/Group Title	Placebo	DB Vedolizumab
Arm/Group Description:	Participants in Cohort 1 received double-blind placebo intravenous infusions at Week 0 and Week 2 in the Induction Phase.	Participants in Cohort 1 received double-blind vedolizumab 300 mg, administered by intravenous infusion at Week 0 and Week 2 in the Induction Phase.
Number of Participants Analyzed	148	220
Number (95% Confidence Interval) **Units: percentage of participants**	25.7 (18.6 to 32.7)	31.4 (25.2 to 37.5)

Statistical Analysis 1

Statistical Analysis Overview	**Comparison Groups**	Placebo, DB Vedolizumab
	Comments	The Hochberg method was applied to control the overall Type I error rate at a 5% significance level for the multiple comparisons of the primary endpoints. If both p-values were ≤ 0.05, both primary endpoints were to be declared significant. If 1 of the p-values for the primary endpoints was > 0.05, the other p-value was to be tested at the 0.025 level and declared significant only if the p-value was ≤ 0.025. If neither primary was declared significant, no further testing was to be conducted.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	**P-Value**	0.2322
	Comments	P-value is based on the Cochran-Mantel-Haenszel (CMH) chi-square test, with stratification according to: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNFα antagonists and/or concomitant immunomodulator use (yes/no).
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]
Method of Estimation	**Estimation Parameter**	Risk Difference (RD)
	Estimated Value	5.7
	Confidence Interval	(2-Sided) 95% -3.6 to 15.0
	Estimation Comments	Risk Difference = adjusted (for stratification factors) percent vedolizumab - adjusted percent placebo

3. Primary Outcome

Title: Maintenance Phase: Percentage of Participants Achieving Clinical Remission at Week 52

Description:
Clinical remission is defined as a CDAI score ≤ 150. The CDAI is used to quantify the symptoms of patients with Crohn's disease and consists of eight factors, each summed after adjustment with a weighting factor. The components of the CDAI are:

- Number of liquid or soft stools each day for 7 days;
- Abdominal pain (graded from 0-3 on severity) each day for 7 days;
- General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day for 7 days;
- Presence of complications;
- Taking Lomotil or opiates for diarrhea;
- Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite);
- Hematocrit of < 0.47 in men and < 0.42 in women;
- Percentage deviation from standard weight.

The total score ranges from 0 to 600 with higher scores indicating greater disease activity.
All participants who prematurely discontinued for any reason were considered as not achieving clinical remission.

Time Frame: Week 52

Safety Issue? No

Outcome Measure Data

Analysis Population Description

Maintenance Study ITT Population, defined as all randomized participants who received vedolizumab during the Induction Phase and met the protocol definition of clinical response at Week 6, as assessed by the investigator, were randomized, and received any amount of double-blind study drug in the Maintenance Phase.

Arm/Group Title	Placebo	Vedolizumab Q8W	Vedolizumab Q4W
Arm/Group Description:	Participants who received vedolizumab during the Induction Phase and demonstrated a clinical response at Week 6 were then randomized to receive double-blind treatment with placebo every 4 weeks up to Week 50 during the Maintenance Phase.	Participants who received vedolizumab during the Induction Phase and demonstrated a clinical response at Week 6 were then randomized to receive double-blind treatment with vedolizumab 300 mg every 8 weeks (Q8W) from Week 6 to Week 50.	Participants who received vedolizumab during the Induction Phase and demonstrated a clinical response at Week 6 were then randomized to receive double-blind treatment with vedolizumab 300 mg every 4 weeks (Q4W) from Week 6 to Week 50.
Number of Participants Analyzed	153	154	154
Number (95% Confidence Interval) Units: percentage of participants	21.6 (15.1 to 28.1)	39.0 (31.3 to 46.7)	36.4 (28.8 to 44.0)

Statistical Analysis 1

Statistical Analysis Overview	**Comparison Groups**	Placebo, Vedolizumab Q8W
	Comments	The Hochberg method was applied to control the overall Type I error rate at a 5% significance level. If both p-values were ≤ 0.05, both dose regimens were to be declared significant. If 1 of the p-values for the 2 dose comparisons was > 0.05, the other p-value was to be tested at the 0.025 level and declared significant only if the p-value was ≤ 0.025. If neither dose was declared significant for the primary endpoint, no further testing was to be conducted.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	**P-Value**	0.0007
	Comments	CMH chi-square test, stratified by: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNFα antagonists and/or concomitant immunomodulator use (yes/no); 3) enrollment in Cohort 1 or Cohort 2 in the Induction Phase.
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]
Method of Estimation	**Estimation Parameter**	Risk Difference (RD)
	Estimated Value	17.4
	Confidence Interval	(2-Sided) 95% 7.3 to 27.5
	Estimation Comments	Risk Difference = adjusted (for stratification factors) percent vedolizumab - adjusted percent placebo

Statistical Analysis 2

Statistical Analysis Overview	**Comparison Groups**	Placebo, Vedolizumab Q4W
	Comments	The Hochberg method was applied to control the overall Type I error rate at a 5% significance level. If both p-values were ≤ 0.05, both dose regimens were to be declared significant. If 1 of the p-values for the 2 dose comparisons was > 0.05, the other p-value was to be tested at the 0.025 level and declared significant only if the p-value was ≤ 0.025. If neither dose was declared significant for the primary endpoint, no further testing was to be conducted.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	**P-Value**	0.0042
	Comments	CMH chi-square test, stratified by: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNFα antagonists and/or concomitant immunomodulator use (yes/no); 3) enrollment in Cohort 1 or Cohort 2 in the Induction Phase.
	Method	Cochran-Mantel-Haenszel

	Comments	[Not specified]
Method of Estimation	**Estimation Parameter**	Risk Difference (RD)
	Estimated Value	14.7
	Confidence Interval	(2-Sided) 95% 4.6 to 24.7
	Estimation Comments	Risk Difference = adjusted (for stratification factors) percent vedolizumab - adjusted percent placebo

4. Secondary Outcome

Title: Induction Phase: Change From Baseline in C-Reactive Protein (CRP) Levels at Week 6

Description: C-reactive protein (CRP) is a protein found in the blood, the levels of which rise in response to inflammation. Normal concentration in healthy human serum is usually lower than 10 mg/L, slightly increasing with age. Higher levels indicate mild inflammation (10-40 mg/L) and active inflammation (40-200 mg/L).

Time Frame: Baseline and Week 6

Safety Issue? No

Outcome Measure Data

Analysis Population Description

Induction Study ITT Population; last observation carried forward (LOCF) imputation was used. Baseline CRP was missing for one participant in the placebo group.

Arm/Group Title	**Placebo**	**DB Vedolizumab**
Arm/Group Description:	Participants in Cohort 1 received double-blind placebo intravenous infusions at Week 0 and Week 2 in the Induction Phase.	Participants in Cohort 1 received double-blind vedolizumab 300 mg, administered by intravenous infusion at Week 0 and Week 2 in the Induction Phase.
Number of Participants Analyzed	147	220
Median (Full Range) Units: mg/L	-0.5 (-27.6 to 12.1)	-0.9 (-20.6 to 10.3)

Statistical Analysis 1

Statistical Analysis Overview	**Comparison Groups**	Placebo, DB Vedolizumab
	Comments	If at least 1 of the primary endpoints was significant, the sequential Hochberg procedure was to be used to test the secondary endpoint for significance at the 0.05% level.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	**P-Value**	0.9288
	Comments	Wilcoxon Rank Sum test on the CRP change from baseline values (two-sided).
	Method	Wilcoxon (Mann-Whitney)
	Comments	[Not specified]

5. Secondary Outcome

Title: Maintenance Phase: Percentage of Participants With Enhanced Clinical Response at Week 52

Description: Enhanced clinical response is defined as a CDAI score at least 100 points lower than the Baseline value. The CDAI is used to quantify the symptoms of patients with Crohn's disease and consists of eight factors, each summed after adjustment with a weighting factor. The components of the CDAI are:

- Number of liquid or soft stools each day for 7 days;
- Abdominal pain (graded from 0-3 on severity) each day for 7 days;
- General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day for 7 days;
- Presence of complications;
- Taking Lomotil or opiates for diarrhea;
- Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite);
- Hematocrit of < 0.47 in men and < 0.42 in women;
- Percentage deviation from standard weight.

The total score ranges from 0 to 600 with higher scores indicating greater disease activity.
All participants who prematurely discontinued for any reason were considered as not achieving enhanced clinical response.

Time Frame: Baseline and Week 52

Safety Issue? No

Outcome Measure Data

Analysis Population Description

Maintenance Study ITT Population

Arm/Group Title	**Placebo**	**Vedolizumab Q8W**	**Vedolizumab Q4W**
Arm/Group Description:	Participants who received vedolizumab during the Induction Phase and demonstrated a clinical response at Week 6 were then randomized to receive double-blind treatment with placebo every 4 weeks up to Week 50 during the Maintenance Phase.	Participants who received vedolizumab during the Induction Phase and demonstrated a clinical response at Week 6 were randomized to receive double-blind treatment with vedolizumab 300 mg every 8 weeks (Q8W) from Week 6 to Week 50.	Participants who received vedolizumab during the Induction Phase and demonstrated a clinical response at Week 6 were then randomized to receive double-blind treatment with vedolizumab 300 mg every 4 weeks (Q4W) from Week 6 to Week 50.
Number of Participants Analyzed	153	154	154

Number (95% Confidence Interval) **Units: percentage of participants**	30.1 (22.8 to 37.3)	43.5 (35.7 to 51.3)	45.5 (37.6 to 53.3)

Statistical Analysis 1

Statistical Analysis Overview	**Comparison Groups**	Placebo, Vedolizumab Q8W
	Comments	To maintain the overall Type I error rate at 5% in the multiple-dose comparisons in each key secondary endpoint, the Hochberg method was used. To further maintain the overall Type I error rate at 5%, the key secondary assessments were performed sequentially. The first key secondary endpoint was tested only if 1 or both of the primary comparisons were significant and the next key secondary endpoint was to be tested only if the previous key secondary endpoint was significant for at least 1 dose.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	**P-Value**	0.0132
	Comments	CMH chi-square test, stratified by: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNFα antagonists and/or concomitant immunomodulator use (yes/no); 3) enrollment in Cohort 1 or Cohort 2 in the Induction Phase.
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]
Method of Estimation	**Estimation Parameter**	Risk Difference (RD)
	Estimated Value	13.4
	Confidence Interval	(2-Sided) 95% 2.8 to 24.0
	Estimation Comments	Risk Difference = adjusted (for stratification factors) percent vedolizumab - adjusted percent placebo

Statistical Analysis 2

Statistical Analysis Overview	**Comparison Groups**	Placebo, Vedolizumab Q4W
	Comments	To maintain the overall Type I error rate at 5% in the multiple-dose comparisons in each key secondary endpoint, the Hochberg method was used. To further maintain the overall Type I error rate at 5%, the key secondary assessments were performed sequentially. The first key secondary endpoint was tested only if 1 or both of the primary comparisons were significant and the next key secondary endpoint was to be tested only if the previous key secondary endpoint was significant for at least 1 dose.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	**P-Value**	0.0053
	Comments	CMH chi-square test, stratified by: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNFα antagonists and/or concomitant immunomodulator use (yes/no); 3) enrollment in Cohort 1 or Cohort 2 in the Induction Phase.

	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]
Method of Estimation	**Estimation Parameter**	Risk Difference (RD)
	Estimated Value	15.3
	Confidence Interval	(2-Sided) 95% 4.6 to 26.0
	Estimation Comments	Risk Difference = adjusted (for stratification factors) percent vedolizumab - adjusted percent placebo

6. Secondary Outcome

Title: Maintenance Phase: Percentage of Participants in Corticosteroid-free Clinical Remission at Week 52

Description: Participants using oral corticosteroids at Baseline, who discontinued corticosteroids and were in clinical remission (CDAI score ≤ 150) at Week 52 achieved corticosteroid-free clinical remission. The CDAI quantifies the symptoms of patients with Crohn's disease and consists of eight factors, summed after adjustment with a weighting factor. The total score ranges from 0 to 600 with higher scores indicating greater disease activity. All participants who prematurely discontinued for any reason were considered as not achieving corticosteroid-free clinical remission.

Time Frame: Week 52

Safety Issue? No

Outcome Measure Data

Analysis Population Description

Maintenance Study ITT Population, participants who were on corticosteroids at Baseline.

Arm/Group Title	**Placebo**	**Vedolizumab Q8W**	**Vedolizumab Q4W**
Arm/Group Description:	Participants who received vedolizumab during the Induction Phase and demonstrated a clinical response at Week 6 were randomized to receive double-blind treatment with placebo every 4 weeks up to Week 50 during the Maintenance Phase.	Participants who received vedolizumab during the Induction Phase and demonstrated a clinical response at Week 6 were randomized to receive double-blind treatment with vedolizumab 300 mg every 8 weeks (Q8W) from Week 6 to Week 50.	Participants who received vedolizumab during the Induction Phase and demonstrated a clinical response at Week 6 were randomized to receive double-blind treatment with vedolizumab 300 mg every 4 weeks (Q4W) from Week 6 to Week 50.
Number of Participants Analyzed	82	82	80
Number (95% Confidence Interval) **Units: percentage of participants**	15.9 (7.9 to 23.8)	31.7 (21.6 to 41.8)	28.8 (18.8 to 38.7)

Statistical Analysis 1

Statistical Analysis Overview	**Comparison Groups**	Placebo, Vedolizumab Q8W
	Comments	To maintain the overall Type I error rate at 5% in the multiple-dose comparisons in each key secondary endpoint, the Hochberg method was used. To further maintain the overall Type I error rate at 5%, the key secondary assessments were performed sequentially. The first key secondary endpoint was tested only if 1 or both of the primary comparisons were significant and the next key secondary endpoint was to be tested only if the previous key secondary endpoint was significant for at least 1 dose.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	**P-Value**	0.0154
	Comments	P-value is based on the CMH chi-square test, with stratification according to: 1) previous exposure to TNFα antagonists and/or concomitant immunomodulator use (yes/no); 2) enrollment in Cohort 1 or Cohort 2 in the Induction Phase.
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]
Method of Estimation	**Estimation Parameter**	Risk Difference (RD)
	Estimated Value	15.9
	Confidence Interval	(2-Sided) 95% 3.0 to 28.7
	Estimation Comments	Risk Difference = adjusted (for stratification factors) percent vedolizumab - adjusted percent placebo

Statistical Analysis 2

Statistical Analysis Overview	**Comparison Groups**	Placebo, Vedolizumab Q4W
	Comments	To maintain the overall Type I error rate at 5% in the multiple-dose comparisons in each key secondary endpoint, the Hochberg method was used. To further maintain the overall Type I error rate at 5%, the key secondary assessments were performed sequentially. The first key secondary endpoint was tested only if 1 or both of the primary comparisons were significant and the next key secondary endpoint was to be tested only if the previous key secondary endpoint was significant for at least 1 dose.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	**P-Value**	0.0450
	Comments	P-value is based on the CMH chi-square test, with stratification according to: 1) previous exposure to TNFα antagonists and/or concomitant immunomodulator use

(yes/no); 2) enrollment in Cohort 1 or Cohort 2 in the Induction Phase.

	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]
Method of Estimation	**Estimation Parameter**	Risk Difference (RD)
	Estimated Value	12.9
	Confidence Interval	(2-Sided) 95% 0.3 to 25.5
	Estimation Comments	Risk Difference = adjusted (for stratification factors) percent vedolizumab - adjusted percent placebo

7. Secondary Outcome

Title: Maintenance Phase: Percentage of Participants With Durable Clinical Remission

Description: Durable clinical remission is defined as CDAI score ≤ 150 points at 80% or more of study visits during the Maintenance Phase, including the Week 52 visit (11 of 13 study visits). The CDAI quantifies the symptoms of patients with Crohn's disease and consists of eight factors, summed after adjustment with a weighting factor. The total score ranges from 0 to 600 with higher scores indicating greater disease activity.
All participants who prematurely discontinued for any reason were considered as not achieving durable clinical remission

Time Frame: Assessed every 4 weeks from Week 6 to Week 50, and at Week 52

Safety Issue? No

Outcome Measure Data

Analysis Population Description
Maintenance Study ITT Population

Arm/Group Title	**Placebo**	**Vedolizumab Q8W**	**Vedolizumab Q4W**
Arm/Group Description:	Participants who received vedolizumab during the Induction Phase and demonstrated a clinical response at Week 6 were randomized to receive double-blind treatment with placebo every 4 weeks up to Week 50 during the Maintenance Phase.	Participants who received vedolizumab during the Induction Phase and demonstrated a clinical response at Week 6 were randomized to receive double-blind treatment with vedolizumab 300 mg every 8 weeks (Q8W) from Week 6 to Week 50.	Participants who received vedolizumab during the Induction Phase and demonstrated a clinical response at Week 6 were randomized to receive double-blind treatment with vedolizumab 300 mg every 4 weeks (Q4W) from Week 6 to Week 50.
Number of Participants Analyzed	153	154	154
Number (95% Confidence Interval) **Units: percentage of participants**	14.4 (8.8 to 19.9)	21.4 (14.9 to 27.9)	16.2 (10.4 to 22.1)

Statistical Analysis 1

Statistical Analysis Overview	**Comparison Groups**	Placebo, Vedolizumab Q8W
	Comments	To maintain the overall Type I error rate at 5% in the multiple-dose comparisons in each key secondary endpoint, the Hochberg method was used. To further maintain the overall Type I error rate at 5%, the key secondary assessments were performed sequentially. The first key secondary endpoint was tested only if 1 or both of the primary comparisons were significant and the next key secondary endpoint was to be tested only if the previous key secondary endpoint was significant for at least 1 dose.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical Test of Hypothesis	**P-Value**	0.1036
	Comments	CMH chi-square test, stratified by: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNFα antagonists and/or concomitant immunomodulator use (yes/no); 3) enrollment in Cohort 1 or Cohort 2 in the Induction Phase.
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]
Method of Estimation	**Estimation Parameter**	Risk Difference (RD)
	Estimated Value	7.2
	Confidence Interval	(2-Sided) 95% -1.5 to 16.0
	Estimation Comments	Risk Difference = adjusted (for stratification factors) percent vedolizumab - adjusted percent placebo

Statistical Analysis 2

Statistical Analysis Overview	**Comparison Groups**	Placebo, Vedolizumab Q4W
	Comments	To maintain the overall Type I error rate at 5% in the multiple-dose comparisons in each key secondary endpoint, the Hochberg method was used. To further maintain the overall Type I error rate at 5%, the key secondary assessments were performed sequentially. The first key secondary endpoint was tested only if 1 or both of the primary comparisons were significant and the next key secondary endpoint was to be tested only if the previous key secondary endpoint was significant for at least 1 dose.
	Non-Inferiority or Equivalence Analysis?	No
	Comments	[Not specified]
Statistical	**P-Value**	0.6413

Test of Hypothesis	**Comments**	CMH chi-square test, stratified by: 1) concomitant use of oral corticosteroids (yes/no); 2) previous exposure to TNFα antagonists and/or concomitant immunomodulator use (yes/no); 3) enrollment in Cohort 1 or Cohort 2 in the Induction Phase.
	Method	Cochran-Mantel-Haenszel
	Comments	[Not specified]
Method of Estimation	**Estimation Parameter**	Risk Difference (RD)
	Estimated Value	2.0
	Confidence Interval	(2-Sided) 95% -6.3 to 10.2
	Estimation Comments	Risk Difference = adjusted (for stratification factors) percent vedolizumab - adjusted percent placebo

Adverse Events

Time Frame	From the start of the Induction Phase until a final on-study safety assessment at Week 66 (or Final Safety visit 16 weeks after the last dose).
Additional Description	
Source Vocabulary Name	MedDRA (14.0)
Assessment Type	Systematic Assessment

Arm/Group Title	Placebo	VDZ/PBO	VDZ/VDZ
Arm/Group Description	Participants who received double-blind placebo intravenous infusions in the Induction Phase and continued to receive placebo during the Maintenance Phase.	Participants who received vedolizumab during the Induction Phase and were then randomized to receive placebo during the Maintenance Phase.	Participants who received vedolizumab during the Induction Phase and continued to receive vedolizumab during the Maintenance Phase. This includes participants who had a clinical response at Week 6 and were randomized to vedolizumab every 4 weeks or every 8 weeks in the Maintenance Phase, participants who did not achieve a clinical response at Week 6 and continued to receive vedolizumab every 4 weeks for the duration of the study, and participants who withdrew during the Induction phase.

Serious Adverse Events

	Placebo Affected / at Risk (%)	**VDZ/PBO** Affected / at Risk (%)	**VDZ/VDZ** Affected / at Risk (%)
Total	23/148 (15.54%)	23/153 (15.03%)	199/814 (24.45%)
Blood and lymphatic system disorders			
Anaemia † A	0/148 (0%)	0/153 (0%)	4/814 (0.49%)
Coagulopathy † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Cyclic neutropenia † A	0/148 (0%)	1/153 (0.65%)	0/814 (0%)
Febrile neutropenia † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Cardiac disorders			
Myocardial infarction † A	0/148 (0%)	1/153 (0.65%)	0/814 (0%)
Myocarditis † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Ventricular extrasystoles † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Eye disorders			
Vision blurred † A	0/148 (0%)	0/153 (0%)	2/814 (0.25%)
Vitreous floaters † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Gastrointestinal disorders			
Abdominal pain † A	1/148 (0.68%)	2/153 (1.31%)	3/814 (0.37%)
Abdominal pain lower † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Anal fissure † A	1/148 (0.68%)	0/153 (0%)	0/814 (0%)
Anal fistula † A	1/148 (0.68%)	0/153 (0%)	1/814 (0.12%)
Colon dysplasia † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Colonic fistula † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Colonic stenosis † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Crohn's disease † A	13/148 (8.78%)	8/153 (5.23%)	99/814 (12.16%)
Diarrhoea † A	0/148 (0%)	1/153 (0.65%)	0/814 (0%)
Diverticular perforation † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Duodenal ulcer † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Enteritis † A	0/148 (0%)	1/153 (0.65%)	2/814 (0.25%)
Enterovesical fistula † A	0/148 (0%)	0/153 (0%)	2/814 (0.25%)
Gastric ulcer † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Gastrointestinal haemorrhage † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Ileal perforation † A	0/148 (0%)	1/153 (0.65%)	0/814 (0%)
Ileal stenosis † A	0/148 (0%)	2/153 (1.31%)	2/814 (0.25%)
Ileitis † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Ileus † A	0/148 (0%)	1/153 (0.65%)	0/814 (0%)
Intestinal obstruction † A	1/148 (0.68%)	0/153 (0%)	4/814 (0.49%)
Intestinal stenosis † A	0/148 (0%)	1/153 (0.65%)	1/814 (0.12%)
Jejunal perforation † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Large intestine perforation † A	0/148 (0%)	1/153 (0.65%)	0/814 (0%)
Lower gastrointestinal haemorrhage † A	1/148 (0.68%)	0/153 (0%)	0/814 (0%)
Melaena † A	0/148 (0%)	1/153 (0.65%)	0/814 (0%)

Nausea	0/148 (0%)	0/153 (0%)	3/814 (0.37%)
Pancreatitis † A	0/148 (0%)	1/153 (0.65%)	1/814 (0.12%)
Periproctitis † A	0/148 (0%)	1/153 (0.65%)	0/814 (0%)
Peritonitis † A	0/148 (0%)	1/153 (0.65%)	1/814 (0.12%)
Proctalgia † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Proctitis † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Rectal haemorrhage † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Small intestinal obstruction † A	1/148 (0.68%)	1/153 (0.65%)	6/814 (0.74%)
Small intestinal stenosis † A	0/148 (0%)	1/153 (0.65%)	1/814 (0.12%)
Subileus † A	0/148 (0%)	1/153 (0.65%)	1/814 (0.12%)
Umbilical hernia † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Upper gastrointestinal haemorrhage † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Vomiting † A	0/148 (0%)	0/153 (0%)	3/814 (0.37%)
General disorders			
Chest discomfort † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Chest pain † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
General physical health deterioration † A	1/148 (0.68%)	0/153 (0%)	2/814 (0.25%)
Generalised oedema † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Non-cardiac chest pain † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Oedema peripheral † A	1/148 (0.68%)	0/153 (0%)	2/814 (0.25%)
Pyrexia † A	0/148 (0%)	1/153 (0.65%)	1/814 (0.12%)
Hepatobiliary disorders			
Bile duct stone † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Cholelithiasis † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Cytolytic hepatitis † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Hepatitis † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Immune system disorders			
Drug hypersensitivity † A	0/148 (0%)	1/153 (0.65%)	0/814 (0%)
Infections and infestations			
Abdominal abscess † A	0/148 (0%)	2/153 (1.31%)	5/814 (0.61%)
Abscess intestinal † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Acute sinusitis † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Anal abscess † A	1/148 (0.68%)	0/153 (0%)	16/814 (1.97%)
Appendicitis † A	0/148 (0%)	0/153 (0%)	2/814 (0.25%)
Arthritis bacterial † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Bacteraemia † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Bacterial sepsis † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Bronchopneumonia † A	1/148 (0.68%)	0/153 (0%)	0/814 (0%)
Cellulitis † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Clostridium difficile colitis † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Device related infection † A	0/148 (0%)	1/153 (0.65%)	1/814 (0.12%)
Device related sepsis † A	1/148 (0.68%)	0/153 (0%)	0/814 (0%)
Diarrhoea infectious † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Furuncle † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Gastroenteritis † A	0/148 (0%)	1/153 (0.65%)	2/814 (0.25%)
Gastroenteritis viral † A	0/148 (0%)	0/153 (0%)	2/814 (0.25%)
Gastrointestinal infection † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Influenza † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Latent tuberculosis † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Lung infection † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Pelvic abscess † A	0/148 (0%)	1/153 (0.65%)	0/814 (0%)
Perirectal abscess † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Pneumonia † A	0/148 (0%)	0/153 (0%)	2/814 (0.25%)
Psoas abscess † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Rectal abscess † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Sepsis † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Septic shock † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Sinusitis † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Staphylococcal bacteraemia † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Upper respiratory tract infection † A	0/148 (0%)	1/153 (0.65%)	0/814 (0%)
Ureter abscess † A	1/148 (0.68%)	0/153 (0%)	0/814 (0%)
Wound infection † A	0/148 (0%)	1/153 (0.65%)	0/814 (0%)
Injury, poisoning and procedural complications			
Anastomotic complication † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Infusion related reaction † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Intentional overdose † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Intestinal anastomosis complication † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Meniscus lesion † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Pneumothorax traumatic † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Investigations			
Clostridium test positive † A	1/148 (0.68%)	0/153 (0%)	0/814 (0%)
Weight decreased † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Metabolism and nutrition disorders			
Cachexia † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Dehydration † A	0/148 (0%)	0/153 (0%)	3/814 (0.37%)

† A

Hypoalbuminaemia	0/148 (0%)	0/153 (0%)	2/814 (0.25%)
Hypokalaemia † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Iron deficiency † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Malnutrition † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Musculoskeletal and connective tissue disorders			
Arthralgia † A	1/148 (0.68%)	0/153 (0%)	0/814 (0%)
Back pain † A	0/148 (0%)	1/153 (0.65%)	0/814 (0%)
Sacroiliitis † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Synovitis † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Carcinoid tumour of the appendix † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Squamous cell carcinoma † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Nervous system disorders			
Cognitive disorder † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Headache † A	0/148 (0%)	1/153 (0.65%)	0/814 (0%)
Peripheral sensory neuropathy † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Transient ischaemic attack † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous † A	1/148 (0.68%)	0/153 (0%)	0/814 (0%)
Psychiatric disorders			
Affective disorder † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Anxiety † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Depression † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Somatoform disorder † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Stress † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Suicide attempt † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Renal and urinary disorders			
Calculus ureteric † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Nephrolithiasis † A	0/148 (0%)	0/153 (0%)	4/814 (0.49%)
Renal colic † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Renal failure acute † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Renal mass † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Ureteric obstruction † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Reproductive system and breast disorders			
Female genital tract fistula † A	1/148 (0.68%)	0/153 (0%)	1/814 (0.12%)
Menorrhagia † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Metrorrhagia † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Respiratory, thoracic and mediastinal disorders			
Dyspnoea † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Pulmonary embolism † A	0/148 (0%)	0/153 (0%)	2/814 (0.25%)
Skin and subcutaneous tissue disorders			
Skin mass † A	0/148 (0%)	1/153 (0.65%)	0/814 (0%)
Toxic epidermal necrolysis [1] † A	0/148 (0%)	1/153 (0.65%)	0/814 (0%)
Vascular disorders			
Circulatory collapse † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Deep vein thrombosis † A	0/148 (0%)	1/153 (0.65%)	1/814 (0.12%)
Hypertension † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)
Varicose vein † A	0/148 (0%)	0/153 (0%)	1/814 (0.12%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (14.0)

[1] This event occurred while the participant was receiving placebo.

Other (Not Including Serious) Adverse Events

Frequency Threshold for Reporting Other Adverse Events 5%

	Placebo Affected / at Risk (%)	**VDZ/PBO** Affected / at Risk (%)	**VDZ/VDZ** Affected / at Risk (%)
Total	96/148 (64.86%)	96/153 (62.75%)	476/814 (58.48%)
Blood and lymphatic system disorders			
Anaemia † A	9/148 (6.08%)	5/153 (3.27%)	31/814 (3.81%)
Gastrointestinal disorders			
Abdominal pain † A	21/148 (14.19%)	18/153 (11.76%)	79/814 (9.71%)
Abdominal pain upper † A	4/148 (2.7%)	8/153 (5.23%)	20/814 (2.46%)
Crohn's disease † A	28/148 (18.92%)	23/153 (15.03%)	84/814 (10.32%)
Diarrhoea † A	5/148 (3.38%)	12/153 (7.84%)	31/814 (3.81%)
Nausea † A	12/148 (8.11%)	18/153 (11.76%)	88/814 (10.81%)
Vomiting † A	10/148 (6.76%)	13/153 (8.5%)	48/814 (5.9%)
General disorders			
Fatigue † A	5/148 (3.38%)	9/153 (5.88%)	53/814 (6.51%)
Pyrexia † A	17/148 (11.49%)	22/153 (14.38%)	102/814 (12.53%)
Infections and infestations			
Nasopharyngitis † A	10/148 (6.76%)	14/153 (9.15%)	100/814 (12.29%)
Upper respiratory tract infection † A	11/148 (7.43%)	5/153 (3.27%)	54/814 (6.63%)

Musculoskeletal and connective tissue disorders			
Arthralgia † A	19/148 (12.84%)	21/153 (13.73%)	110/814 (13.51%)
Arthritis † A	9/148 (6.08%)	2/153 (1.31%)	23/814 (2.83%)
Nervous system disorders			
Headache † A	19/148 (12.84%)	28/153 (18.3%)	97/814 (11.92%)

† Indicates events were collected by systematic assessment.
A Term from vocabulary, MedDRA (14.0)

Limitations and Caveats

[Not Specified]

More Information

Certain Agreements

Principal Investigators are NOT employed by the organization sponsoring the study.

There IS an agreement between the Principal Investigator and the Sponsor (or its agents) that restricts the PI's rights to discuss or publish trial results after the trial is completed.

The first study related publication will be a multi-center publication submitted within 24 months after conclusion or termination of a study at all sites. After such multi site publication, all proposed site publications and presentations will be submitted to sponsor for review 60 days in advance of publication. Site will remove Sponsor confidential information unrelated to study results. Sponsor can delay a proposed publication for another 60 days to preserve intellectual property.

Results Point of Contact

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