Clinical trial results:
Golimumab (GLM) dose Optimisation to Adequate Levels to Achieve Response in Colitis. (GOAL-ARC)

Summary

EudraCT number	2015-004724-62
Trial protocol	IE
Global end of trial date	10 July 2023

Results information

Result version number	v1 (current)
This version publication date	02 November 2024
First version publication date	02 November 2024

Trial information

Trial identification

Sponsor protocol code	UCDCRC/15/007

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02687724
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College Dublin
Sponsor organisation address	Catherine McAuley Centre, Nelson Street, Dublin 7, Dublin 7, Ireland, D07 A8NN
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 September 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 July 2023
Global end of trial reached?	Yes
Global end of trial date	10 July 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To ascertain if use of intensive monitoring of fecal calprotectin (FCP) and drug levels of Golimumab (GLM) (during maintenance) to guide dose intensification improves rates of Patient continuous clinical response (pCCR) and reduces disease activity in UC, relative to standard dosing of GLM according to the Summary of product characteristics (SmPC)

Protection of trial subjects:

Ethics approval was obtained prior to commencement of the trial. Ethical approval was obtained from each participating site before site initiation.This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki,in accordance with Good Clinical Practice (GCP), as defined by the International Conference on Harmonisation (ICH) and in accordance with the ethical principles underlying European Union Directive 2001/20/EC and 2005/28/EC. Written informed consent for enrollment of each study subject was obtained as per local requirements and as approved by the ethics committee for the site.

Background therapy:

The intervention (intensive monitoring of fecal calprotectin (FCP) and drug levels of Golimumab (GLM), when commenced immediately post induction, to guide dose intensification is compared to standard dosing of GLM according to the Summary of product characteristics (SmPC)

Evidence for comparator: -

Actual start date of recruitment	01 February 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Ireland: 97
Worldwide total number of subjects	97
EEA total number of subjects	97

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)	94
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Trial subjects are patients aged 18 and over with moderately-severely active ulcerative colitis who have failed/ had inadequate disease control or are intolerant of 5-ASA, steroid and immunosuppressant treatment, and/or are secondary are secondary non-responders or intolerant to a prior anti-TNF agent other than GLM

Pre-assignment

Screening details:

Patients will be identified at routine outpatient appointments or at time of endoscopy for investigation of inflammatory bowel disease. A sigmoidoscopy/colonoscopy will assess disease activity and confirm a Mayo score of 6 or above and endoscopic subscore 2 or above confirming moderate-severe UC activity (within 12 weeks of first GLM injection)

Period 1

Period 1 title	Baseline period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention arm

Arm description:

Patients will receive standard loading dose of Golimumab (GLM) of 200mg at week 0 and 100mg at week 2. As with the control arm (SmPC), patients will report their modified partial mayo and Short health scale (SHS) scores every 4 weeks (the window for this will be +/- one week) in a diary and provide it to the investigator site. In addition, fecal calprotectin (FCP), GLM drug level (DL) and Anti-Drug Antibody (ADA) shall be measured every four weeks. In response to DL and FCP levels the dose of GLM shall be escalated or reduced according to protocol specified dosing optimisation algorithm, available in the published protocol. doi: 10.1136/bmjgast-2017-000174.
One subject is excluded from the Full Analysis Set (FAS) because they did not receive any study drug. Another was determined to be ineligible post randomisation and is therefore excluded from the FAS. 51 subjects were randomised to this arm but only 49 are included in efficacy analysis (FAS).

Arm type	Experimental
Investigational medicinal product name	Golimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Loading dosage at WK 0 & 2 as per protocol (200mgs week 0 and 100mgs at week 2). Following loading dose- Drug levels and FCP dictate dosage given (see published protocol doi: 10.1136/bmjgast-2017-000174)

Arm title	SmPC arm

Arm description:

Patients will receive standard loading dose of Golimumab (GLM) of 200mg at week 0 and 100mg at week 2. Patients will report their modified partial mayo and Short Health Scale (SHS) score every 4 weeks (the window for this will be +/- one week) in a diary and provide it to the investigator site. In addition, fecal calprotecting (FCP), GLM drug level (DL) and Anti-Drug Antibody (ADA) shall be measured every four weeks. In response to DL and FCP levels the dose of GLM shall be escalated or reduced according to a pre-defined algorithm. See published protocol for further information doi: 10.1136/bmjgast-2017-000174

Arm type	Active comparator

Investigational medicinal product name	Golimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Loading dosage at WK 0 & 2 as per protocol (200mgs week 0 and 100mgs at week 2). As per SmPC-weight based dosing >80kgs 100mgs every 4 weeks <80kgs 50mgs every 4 weeks. Golimumab is solution for injection supplied in a single use pre-filled pen called SmartJect.

Number of subjects in period 1[1]	Intervention arm	SmPC arm
Started	49	46
Completed	25	20
Not completed	24	26
Physician decision	2	2
Adverse event, non-fatal	1	1
Other	2	-
Pregnancy	1	-
Disease worsening	18	22
Lack of compliance	-	1

Notes:

[1] - 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: A total of 97 subjects were enrolled. One subject randomised to the intervention arm did not meet eligibility criteria and was discontinued. This subject did receive a limited amount of study drug and hence is included in the safety set (SS) but is excluded from the Full Analysis Set (FAS). Another subject did not receive any dose of study drug and hence is excluded both from the FAS and SS. Two of 97 enrolled subjects are therefore excluded from the Baseline period results, based on the FAS.

Baseline characteristics

Reporting groups	
Reporting group title	Intervention arm
Reporting group description:	
Patients will receive standard loading dose of Golimumab (GLM) of 200mg at week 0 and 100mg at week 2. As with the control arm (SmPC), patients will report their modified partial mayo and Short health scale (SHS) scores every 4 weeks (the window for this will be +/- one week) in a diary and provide it to the investigator site. In addition, fecal calprotectin (FCP), GLM drug level (DL) and Anti-Drug Antibody (ADA) shall be measured every four weeks. In response to DL and FCP levels the dose of GLM shall be escalated or reduced according to protocol specified dosing optimisation algorithm, available in the published protocol. doi: 10.1136/bmjgast-2017-000174. One subject is excluded from the Full Analysis Set (FAS) because they did not receive any study drug. Another was determined to be ineligible post randomisation and is therefore excluded from the FAS. 51 subjects were randomised to this arm but only 49 are included in efficacy analysis (FAS).	
Reporting group title	SmPC arm
Reporting group description:	
Patients will receive standard loading dose of Golimumab (GLM) of 200mg at week 0 and 100mg at week 2. Patients will report their modified partial mayo and Short Health Scale (SHS) score every 4 weeks (the window for this will be +/- one week) in a diary and provide it to the investigator site. In addition, fecal calprotecting (FCP), GLM drug level (DL) and Anti-Drug Antibody (ADA) shall be measured every four weeks. In response to DL and FCP levels the dose of GLM shall be escalated or reduced according to a pre-defined algorithm. See published protocol for further information doi: 10.1136/bmjgast-2017-000174	

Reporting group values	Intervention arm	SmPC arm	Total
Number of subjects	49	46	95
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	38.7	38.6	
standard deviation	± 11.4	± 11.8	-
Gender categorical Units: Subjects			
Female	19	22	41
Male	30	24	54
Ethnicity Units: Subjects			
White	47	46	93
Black or Black Irish	0	0	0
Asian or Asian Irish	0	0	0
Other (including mixed background)	2	0	2

Prior TNF-alpha inhibitor Units: Subjects			
Yes	11	6	17
No	38	40	78
Prior immunomodulator Units: Subjects			
Yes	14	11	25
No	35	35	70
Prior steroids Units: Subjects			
Yes	31	38	69
No	18	8	26
Prior anti-integrin therapy Units: Subjects			
Yes	3	0	3
No	46	46	92
Ever smoked? Units: Subjects			
Yes	29	22	51
No	20	24	44
Disease extent Units: Subjects			
E1: Ulcerative proctitis	4	7	11
E2: L sided UC/ distal UC	28	24	52
E3: Extensive UC	17	15	32
Findings on endoscopy Units: Subjects			
Normal	0	0	0
Mild disease	0	0	0
Moderate disease	38	35	73
Severe disease	11	11	22
BMI Units: kg/m2			
median	25	25.3	
inter-quartile range (Q1-Q3)	23 to 28.9	22.3 to 27.6	-
Age at symptom onset Units: Years			
arithmetic mean	30.4	29.3	
standard deviation	± 11	± 11.9	-
Total Mayo Score at screening Units: Points			
median	8	8.5	
inter-quartile range (Q1-Q3)	7 to 9	7 to 9	-
Partial Mayo Score at screening Units: Points			
median	6	6	
inter-quartile range (Q1-Q3)	5 to 7	5 to 7	-
Modified Partial Mayo Score at baseline Units: Points			
median	4	4	
inter-quartile range (Q1-Q3)	3 to 5	3 to 5	-

Age at diagnosis Units: Years			
arithmetic mean	30.7	30.2	
standard deviation	± 11.5	± 11.7	-

End points

End points reporting groups

Reporting group title	Intervention arm

Reporting group description:

Patients will receive standard loading dose of Golimumab (GLM) of 200mg at week 0 and 100mg at week 2. As with the control arm (SmPC), patients will report their modified partial mayo and Short health scale (SHS) scores every 4 weeks (the window for this will be +/- one week) in a diary and provide it to the investigator site. In addition, fecal calprotectin (FCP), GLM drug level (DL) and Anti-Drug Antibody (ADA) shall be measured every four weeks. In response to DL and FCP levels the dose of GLM shall be escalated or reduced according to protocol specified dosing optimisation algorithm, available in the published protocol. doi: 10.1136/bmjgast-2017-000174.
One subject is excluded from the Full Analysis Set (FAS) because they did not receive any study drug. Another was determined to be ineligible post randomisation and is therefore excluded from the FAS. 51 subjects were randomised to this arm but only 49 are included in efficacy analysis (FAS).

Reporting group title	SmPC arm

Reporting group description:

Patients will receive standard loading dose of Golimumab (GLM) of 200mg at week 0 and 100mg at week 2. Patients will report their modified partial mayo and Short Health Scale (SHS) score every 4 weeks (the window for this will be +/- one week) in a diary and provide it to the investigator site. In addition, fecal calprotecting (FCP), GLM drug level (DL) and Anti-Drug Antibody (ADA) shall be measured every four weeks. In response to DL and FCP levels the dose of GLM shall be escalated or reduced according to a pre-defined algorithm. See published protocol for further information doi: 10.1136/bmjgast-2017-000174

Primary: pCCR

End point title	pCCR

End point description:

Patient Continuous Clinical Response (pCCR) at week 46, defined as the absence of clinical flare (an increase in modified partial Mayo score of 2 points value with accompanying requirement for treatment intervention) from WK 14 through to WK 46. An increase in MPMS of 2 points or more will be determined if such an increase happens from any visit from week 14 onwards to any subsequent visit. Primary analysis is conducted on the Full Analysis Set using a conservative non-responder imputation approach to handle missing data.

- Subjects missing week 14 or 46 data are categorized as non-responders, including those discontinued due to disease worsening
- Subjects who do not complete GLM treatment per protocol are considered non-responders
- Since data on MPMS across all visits is used in determination of pCCR, only data actually collected will be used i.e. missing data between weeks 14 and 46 will be ignored

Descriptive data are reported below are also based on this categorization

End point type	Primary

End point timeframe:

The primary endpoint is evaluated from week 14 to week 46.

End point values	Intervention arm	SmPC arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	46		
Units: Subjects				
Yes	22	17		
No	27	29		

Statistical analyses

Statistical analysis title	Primary analysis

Statistical analysis description:

Analysis is conducted on the Full Analysis Set, including randomised patients having the studied disease, having taken at least one dose of study treatment after inclusion and with at least one evaluation of the primary criteria. This primary analysis is conducted using non-responder imputation, where those with missing data at weeks 14 or 46 and those who don't complete per protocol GLM treatment are considered non-responders.

Comparison groups	SmPC arm v Intervention arm
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	> 0.281 [2]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	7.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.7
upper limit	26.9

Notes:

[1] - For estimating a difference in proportions, Agresti-Caffo confidence intervals will be calculated.

[2] - p-value shown is for a one-sided test, as the sample size calculation was based on a one-sided test. The p-value for a two-sided test would be 0.562

Statistical analysis title	Sensitivity analysis 1

Statistical analysis description:

Sensitivity analysis 1 involves a variation in how subjects are categorized as achieving the primary endpoint or not. Here, subjects who do not meet criteria for Week 14 clinical response will be classified as failing to meet pCCR. This analysis will determine the impact on trial results of any subjectivity in the decision to allow subjects to continue past Week 14. Analysis are conducted in the same manner as for the primary analysis.

Comparison groups	Intervention arm v SmPC arm
Number of subjects included in analysis	95
Analysis specification	Post-hoc
Analysis type	superiority[3]
P-value	= 0.849
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.2
upper limit	22.8

Notes:

[3] - Here, 16/46 subjects in the SmPC (control) arm met the primary endpoint while 19/49 subjects in the intervention arm met the primary endpoint.

Statistical analysis title	Sensitivity analysis 2

Statistical analysis description:

This analysis is based on a logistic regression model of the primary endpoint (calculated using non-responder imputation) with adjustment for covariates including disease duration, ever smoked, age, gender, BMI, total mayo score at screening, prior use of anti-TNFa therapy and prior use of immunomodulators. The unadjusted odds ratio (model without predictors) is 1.39 (95% CI: 0.61, 3.16) while shown below is the adjusted odds ratio

Comparison groups	Intervention arm v SmPC arm
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Odds ratio (OR)
Point estimate	1.29
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	3.31

Statistical analysis title	Subgroup analysis (FAS-M)

Statistical analysis description:

This analysis is an exploratory subgroup analysis carried out on subjects in the FAS-M analysis set. These are subjects who met the criteria for Week 14 Clinical Response (using the definition used to classify subjects in the main analysis of Week 14 Clinical Response). Analysis includes 26 subjects in the SmPC arm and 27 subjects in the Intervention arm.

Comparison groups	Intervention arm v SmPC arm
Number of subjects included in analysis	95
Analysis specification	Post-hoc
Analysis type	superiority[4]
P-value	= 0.562 [5]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	8.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-16.5
upper limit	33

Notes:

[4] - Of 26 subjects who met the definition of Week 14 Cinical Response in the SmPC arm, 16/26 subsequently met the definition of pCCR. Of 27 subjects who met the definition of Week 14 Clinical Response, 19 met the definition of pCCR.

[5] - Two-sided

Secondary: Week 14 Clinical Response

End point title	Week 14 Clinical Response

End point description:

Week 14 Clinical Response is defined as

- A decrease from BL in partial Mayo score by ≥30% or a decrease of 3 points.

Or

- A decrease from BL in modified partial Mayo of 2 points or a decrease of ≥30% from baseline.

The Partial Mayo Score (PMS) is only collected at the screening visit and hence the value collected at screening is the baseline for PMS. The Modified Partial Mayo Score is collected both at screening and baseline. Thus, the value collected at baseline be used as the reference value in determination of Week 14 Clinical Response. However, the screening value will be used as the reference value where a value is not recorded at baseline.

- In the primary analysis of Week 14 Clinical Response, a non-responder imputation (NRI) approach will be taken to handle missing data at Week 14. Subjects missing data on either the PMS or MPMS scores will be deemed non-responders at Week 14, regardless of the reason for missingness.

End point type	Secondary
End point timeframe:	
Baseline to Week 14	

End point values	Intervention arm	SmPC arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	46		
Units: Subjects				
Yes	29	31		
No	10	6		
Missing	10	9		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

The effect of the intervention on Week 14 Clinical Response will be estimated as a difference in proportions with a 95% confidence interval. Two-sided, two-proportion Z test with continuity correction will test for a difference in proportions between treatment arms. A non-responder imputation (NRI) approach will be taken to handle missing data at Week 14. Subjects discontinued from GLM treatment by week 14 and subjects missing data on either the PMS or MPMS scores will be deemed non-responders

Comparison groups	Intervention arm v SmPC arm
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.946 [6]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-20.9
upper limit	18.2

Notes:

[6] - The non-responder imputation approach described above results in 11/46 subjects in the SmPC arm and 15/49 subjects in the Intervention arm meeting the definition of Week 14 Clinical Response

Secondary: Mucosal Healing at Week 46

End point title	Mucosal Healing at Week 46

End point description:

End point type	Secondary

End point timeframe:

Defined as a Mayo endoscopic subscore of 0 or 1 at Week 46.

End point values	Intervention arm	SmPC arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	46		
Units: Subjects				
Yes	17	17		
No	6	3		
Missing	26	26		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

Non-responder imputation (NRI) is used to handle missing data at Week 46. Subjects missing data on the endoscopic subscore of the Mayo Score at Week 46 will be deemed NOT to meet the endpoint of mucosal healing at week 46, regardless of the reason for missingness. Furthermore, subjects who discontinued per protocol GLM treatment will be considered as not meeting this endpoint. With this assumption, 17/49 in the intervention group and 14/46 subjects in the SmPC group meet the endpoint

Comparison groups	Intervention arm v SmPC arm
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.823
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	4.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.5
upper limit	22.6

Secondary: Moderate-Severe UC (Total Mayo Score >=6) at Week 46

End point title	Moderate-Severe UC (Total Mayo Score >=6) at Week 46

End point description:

Subjects with Total Mayo Score > 5 at week 46 will be recorded as meeting this endpoint, while those with Total Mayo Score <=5 will be considered as not meeting the endpoint.

End point type	Secondary
End point timeframe:	
Week 46	

End point values	Intervention arm	SmPC arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	46		
Units: Subjects				
Yes	2	1		
No	20	19		
Missing	27	26		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis
Statistical analysis description:	
A non-responder imputation (NRI) approach is taken to handle missing data at Week 46. Subjects missing data on Total Mayo Score at Week 46 will be deemed to meet the endpoint of moderate-severe UC, regardless of the reason for missingness. Subjects discontinued from per protocol GLM treatment will (conservatively) be assumed to meet the endpoint. These assumptions result in 30/46 (65.2%) of subjects in the SmPC arm and 29/49 (59.2%) of subjects in the intervention arm meeting the endpoint	
Comparison groups	Intervention arm v SmPC arm
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.693
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	-6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.9
upper limit	13.4

Secondary: Clinical remission at week 46

End point title	Clinical remission at week 46
End point description:	
Clinical Remission at Week 46 is defined as a Total Mayo Score <= 2 pts with no individual subscore >1.	
End point type	Secondary
End point timeframe:	
Week 46	

End point values	Intervention arm	SmPC arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	46		
Units: Subjects				
Yes	15	14		
No	7	6		
Missing	27	26		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

A non-responder imputation (NRI) approach will be taken to handle missing data at Week 46. Subjects missing data on Total Mayo Score or on any of its subscores at Week 46 will be deemed as not achieving Clinical Remission, regardless of the reason for missingness. Furthermore, subjects with data on Total Mayo Score but discontinued from GLM treatment will be categorized as failing to meet this endpoint.

Comparison groups	Intervention arm v SmPC arm
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.614 [7]
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.3
upper limit	24

Notes:

[7] - With non-responder imputation, 11/46 subjects in the control arm and 15/49 subjects in the intervention arm met this endpoint of Week 46 Clinical Remission

Secondary: 6.5 Corticosteroid free remission Week 46

End point title	6.5 Corticosteroid free remission Week 46

End point description:

Corticosteroid free remission at Week 46 is defined as a Total Mayo Score <= 2 pts with no individual subscore >1 with no concomitant steroids. Note that all subjects who met the definition of Clinical Remission at Week 46 were off concomitant steroids - hence results are the same as for Clinical Remission at Week 46.

End point type	Secondary

End point timeframe:

Week 46

End point values	Intervention arm	SmPC arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49	46		
Units: Subjects				
Yes	15	14		
No	7	6		
Missing	27	26		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

A non-responder imputation (NRI) approach will be taken to handle missing data at Week 46. Subjects missing data on Total Mayo Score or on any of its subscores at Week 46 will be deemed as not achieving Clinical Remission, regardless of the reason for missingness. Furthermore, subjects with data on Total Mayo Score but discontinued from per protocol GLM treatment will be categorized as failing to meet this endpoint.

Comparison groups	Intervention arm v SmPC arm
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.614
Method	Chi-squared corrected
Parameter estimate	Risk difference (RD)
Point estimate	6.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.3
upper limit	24

Secondary: Dublin Score at week 46

End point title	Dublin Score at week 46

End point description:

A Dublin score is calculated as a product of the Endoscopic Mayo Score and the Extent Score (E1-3) of the Montreal Classification of Disease. Higher scores indicate more severe disease. There were 18 complete cases in the intervention group, with a median change in Dublin score of -0.3 (IQR: -4, -0.5) and 15 complete cases in the SmPC arm with a median change in Dublin score of -2.0 (IQR: -4,-1). For the treatment group comparison below, baseline values were carried forward to replace missing values on change from screening to week 46 in Dublin score.

End point type	Secondary

End point timeframe:

Change from screening to Week 46

End point values	Intervention arm	SmPC arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49[8]	46[9]		
Units: Change from baseline				
median (inter-quartile range (Q1-Q3))	0 (-2 to 0)	0 (-1 to 0)		

Notes:

[8] - 31 subjects missing a value at week 46. Baseline values are carried forward to impute missing values

[9] - 31 subjects missing a value at week 46. Baseline values are carried forward to impute missing values

Statistical analyses

Statistical analysis title	Secondary endpoint analysis

Statistical analysis description:

For the analysis of this endpoint, the change in Dublin Score from screening to week 46 will be calculated and compared between treatment groups. For subjects with missing Dublin Score at week 46, a last observation carried forward approach will be taken, whereby the subject's Dublin score will be assumed to be equal to the value recorded at screening. Analysis includes a Mann Whitney U test for a difference in the change scores (calculated with LOCF) between treatment arm.

Comparison groups	Intervention arm v SmPC arm
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.835
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation to end of 46 week follow-up

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.1

Reporting groups

Reporting group title	Intervention group (Safety Set)

Reporting group description:

Includes all subjects randomised to the intervention arm who received any study drug. One of 51 subjects randomised to the Intervention Arm did not receive study drug and was hence excluded from the Safety Set.

Reporting group title	SmPC arm (Safety Set)

Reporting group description:

Includes all subjects randomised to the SmPC (Control) arm who received any dose of study drug. All 46 subjects allocated to this arm received study drug and hence are included in the Safety Set.

Serious adverse events	Intervention group (Safety Set)	SmPC arm (Safety Set)	
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 50 (22.00%)	9 / 46 (19.57%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fall	Additional description: 10016173 Fall		
alternative dictionary used: MedDRA 22			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion related reaction	Additional description: 10051792 Infusion related reaction		
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombophlebitis	Additional description: 10043570 Thrombophlebitis		
alternative dictionary used: MedDRA 21			

subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Fibrilation	Additional description: 10003658 Atrial fibrillation		
alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Peroneal nerve palsy	Additional description: 10034701 Peroneal nerve palsy. Right foot drop.		
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ulcerative	Additional description: 10009900 Colitis ulcerative		
alternative dictionary used: MedDRA 21			
subjects affected / exposed	7 / 50 (14.00%)	5 / 46 (10.87%)	
occurrences causally related to treatment / all	0 / 7	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon dysplasia	Additional description: 10071161 Colon dysplasia		
alternative dictionary used: MedDRA 25.1			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Lower respiratory tract infection	Additional description: 10024968 Lower respiratory tract infection		
alternative dictionary used: MedDRA 21			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Substance-induced psychotic disorder	Additional description: 10072388 Substance-induced psychotic disorder		

alternative dictionary used: MedDRA 21			
subjects affected / exposed	1 / 50 (2.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Wound infection	Additional description: 10048038 Wound infection		
alternative dictionary used: MedDRA 21			
subjects affected / exposed	0 / 50 (0.00%)	1 / 46 (2.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess	Additional description: 10052814 Perirectal abscess		
alternative dictionary used: MedDRA 20.1			
subjects affected / exposed	1 / 50 (2.00%)	0 / 46 (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	Intervention group (Safety Set)	SmPC arm (Safety Set)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 50 (78.00%)	33 / 46 (71.74%)	
Nervous system disorders			
10019211 Headache			
subjects affected / exposed	1 / 50 (2.00%)	3 / 46 (6.52%)	
occurrences (all)	1	4	
General disorders and administration site conditions			
10022004 Influenza like illness			
subjects affected / exposed	2 / 50 (4.00%)	3 / 46 (6.52%)	
occurrences (all)	2	7	
10016256 Fatigue			
subjects affected / exposed	5 / 50 (10.00%)	1 / 46 (2.17%)	
occurrences (all)	5	1	
Gastrointestinal disorders			

Colitis ulcerative	Additional description: 10009900 Colitis ulcerative		
subjects affected / exposed	14 / 50 (28.00%)	18 / 46 (39.13%)	
occurrences (all)	15	23	
10018836 Haematochezia			
subjects affected / exposed	2 / 50 (4.00%)	3 / 46 (6.52%)	
occurrences (all)	7	6	
10012735 Diarrhoea			
subjects affected / exposed	3 / 50 (6.00%)	0 / 46 (0.00%)	
occurrences (all)	4	0	
10000081 Abdominal pain			
subjects affected / exposed	1 / 50 (2.00%)	2 / 46 (4.35%)	
occurrences (all)	2	3	
Respiratory, thoracic and mediastinal disorders			
10011224 Cough			
subjects affected / exposed	2 / 50 (4.00%)	1 / 46 (2.17%)	
occurrences (all)	3	1	
10068319 Oropharyngeal pain			
subjects affected / exposed	2 / 50 (4.00%)	2 / 46 (4.35%)	
occurrences (all)	3	2	
Skin and subcutaneous tissue disorders			
10013786 Dry skin			
subjects affected / exposed	3 / 50 (6.00%)	1 / 46 (2.17%)	
occurrences (all)	5	1	
10037844 Rash			
subjects affected / exposed	2 / 50 (4.00%)	4 / 46 (8.70%)	
occurrences (all)	4	4	
10000496 Acne			
subjects affected / exposed	3 / 50 (6.00%)	0 / 46 (0.00%)	
occurrences (all)	3	0	
Musculoskeletal and connective tissue disorders			
10003239 Arthralgia			
subjects affected / exposed	2 / 50 (4.00%)	0 / 46 (0.00%)	
occurrences (all)	4	0	
10033425 Pain in extremity			
subjects affected / exposed	1 / 50 (2.00%)	1 / 46 (2.17%)	
occurrences (all)	3	1	

Infections and infestations			
10024968 Lower respiratory tract infection			
subjects affected / exposed	7 / 50 (14.00%)	4 / 46 (8.70%)	
occurrences (all)	8	5	
10084268 COVID-19			
subjects affected / exposed	4 / 50 (8.00%)	4 / 46 (8.70%)	
occurrences (all)	4	4	
10040753 Sinusitis			
subjects affected / exposed	2 / 50 (4.00%)	3 / 46 (6.52%)	
occurrences (all)	2	3	
10046306 Upper respiratory tract infection			
subjects affected / exposed	2 / 50 (4.00%)	2 / 46 (4.35%)	
occurrences (all)	2	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2021	• Protocol Version 1.1, Approved : 18/12/2015 – Original protocol • Protocol Version 2.0, Approved : 15/04/2016 – Substantial amendment to remove requirement for labelling of IMP according to GMP Annex 13 • Protocol Version 3.0, Approved : 31/03/2017 – Substantial amendment to modify inclusion criteria to permit recruitment of patients with prior anti-TNF agent exposure discontinued due to loss of response or intolerance • Protocol Version 4.0, Approved: 03/07/2018 –Ammendment to clarify definitions of treatment failure and steroids dosing • Protocol Version 5.0, Approved: 15/02/2021- Ammendment to add additional provision on the local dispensing of IMP at study sites to subject requiring dose escalation as part of the protocol

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
13 March 2020	Trial recruitment was suspended on 13/Mar/2020 due to the COVID-19 pandemic during which study personnel were redeployed and recruitment was re-initiated on 13/04/2021	13 April 2021

Notes:

Limitations and caveats

None reported