



## 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                       |
| Public contact               | Gráinne O'Reilly. Director of Research Clinical Trials., UCD, +353 17166603, grainne.oreilly1@ucd.ie |
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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              |
| <b>Arm title</b>             | 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 )

|                  |          |
|------------------|----------|
| <b>Arm title</b> | 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 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 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.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | 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:  |                  |
| <p>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.</p> <p>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).</p> |                  |
| Reporting group title   | SmPC arm         |
| Reporting group description:  |                  |
| <p>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 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 a pre-defined algorithm. See published protocol for further information doi: 10.1136/bmjgast-2017-000174</p>   |                  |

| 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<br>Units: Subjects             |            |              |    |
| Yes  | 11         | 6            | 17 |
| No   | 38         | 40           | 78 |
| Prior immunomodulator<br>Units: Subjects                 |            |              |    |
| Yes  | 14         | 11           | 25 |
| No   | 35         | 35           | 70 |
| Prior steroids<br>Units: Subjects                        |            |              |    |
| Yes  | 31         | 38           | 69 |
| No   | 18         | 8            | 26 |
| Prior anti-integrin therapy<br>Units: Subjects           |            |              |    |
| Yes  | 3          | 0            | 3  |
| No   | 46         | 46           | 92 |
| Ever smoked?<br>Units: Subjects                          |            |              |    |
| Yes  | 29         | 22           | 51 |
| No   | 20         | 24           | 44 |
| Disease extent<br>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<br>Units: Subjects                 |            |              |    |
| Normal   | 0          | 0            | 0  |
| Mild disease   | 0          | 0            | 0  |
| Moderate disease   | 38         | 35           | 73 |
| Severe disease   | 11         | 11           | 22 |
| BMI<br>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<br>Units: Years                     |            |              |    |
| arithmetic mean  | 30.4       | 29.3         | -  |
| standard deviation                                       | ± 11       | ± 11.9       | -  |
| Total Mayo Score at screening<br>Units: Points           |            |              |    |
| median   | 8          | 8.5          | -  |
| inter-quartile range (Q1-Q3)                             | 7 to 9     | 7 to 9       | -  |
| Partial Mayo Score at screening<br>Units: Points         |            |              |    |
| median   | 6          | 6            | -  |
| inter-quartile range (Q1-Q3)                             | 5 to 7     | 5 to 7       | -  |
| Modified Partial Mayo Score at baseline<br>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 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 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. <ul style="list-style-type: none"><li>Subjects missing week 14 or 46 data are categorized as non-responders, including those discontinued due to disease worsening</li><li>Subjects who do not complete GLM treatment per protocol are considered non-responders</li><li>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</li></ul> 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 <sup>[1]</sup>  |
| P-value   | > 0.281 <sup>[2]</sup>      |
| 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 <sup>[3]</sup>  |
| 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 <sup>[4]</sup>  |
| P-value   | = 0.562 <sup>[5]</sup>      |
| 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 Clinical 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  $\geq 30\%$  or a decrease of 3 points.

Or

- A decrease from BL in modified partial Mayo of 2 points or a decrease of  $\geq 30\%$  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 <sup>[6]</sup>      |
| 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 $\geq 6$ ) at Week 46

|                 |  |
|-----------------|--|
| End point title | Moderate-Severe UC (Total Mayo Score $\geq 6$ ) 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  $\leq 5$  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

|                                   |                             |
|-----------------------------------|-----------------------------|
| <b>Statistical analysis title</b> | 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

|  |                             |
|--|-----------------------------|
| <b>Statistical analysis title</b>  | 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 <sup>[7]</sup>      |
| 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 <sup>[8]</sup> | 46 <sup>[9]</sup> |  |  |
| 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 Fibrillation                             | 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:<br>MedDRA 21          |   |                |  |
| subjects affected / exposed                        | 1 / 50 (2.00%)                                      | 1 / 46 (2.17%) |  |
| occurrences causally related to<br>treatment / all | 0 / 1   | 0 / 1          |  |
| deaths causally related to<br>treatment / all      | 0 / 0   | 0 / 0          |  |
| Infections and infestations                        |   |                |  |
| Wound infection                                    | Additional description: 10048038 Wound infection    |                |  |
| alternative dictionary used:<br>MedDRA 21          |   |                |  |
| subjects affected / exposed                        | 0 / 50 (0.00%)                                      | 1 / 46 (2.17%) |  |
| occurrences causally related to<br>treatment / all | 0 / 0   | 0 / 1          |  |
| deaths causally related to<br>treatment / all      | 0 / 0   | 0 / 0          |  |
| Perirectal abscess                                 | Additional description: 10052814 Perirectal abscess |                |  |
| alternative dictionary used:<br>MedDRA 20.1        |   |                |  |
| subjects affected / exposed                        | 1 / 50 (2.00%)                                      | 0 / 46 (0.00%) |  |
| occurrences causally related to<br>treatment / all | 0 / 1   | 0 / 0          |  |
| deaths causally related to<br>treatment / all      | 0 / 0   | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 5 %

| <b>Non-serious adverse events</b>                        | Intervention group<br>(Safety Set) | SmPC arm (Safety<br>Set) |  |
|--|------------------------------------|--------------------------|--|
| Total subjects affected by non-serious<br>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<br>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<br>subjects affected / exposed<br>occurrences (all)          | Additional description: 10009900 Colitis ulcerative |                  |  |
|   | 14 / 50 (28.00%)                                    | 18 / 46 (39.13%) |  |
|   | 15  | 23               |  |
|   |   |                  |  |
| 10018836 Haematochezia<br>subjects affected / exposed<br>occurrences (all)      | 2 / 50 (4.00%)                                      | 3 / 46 (6.52%)   |  |
|   | 7   | 6                |  |
| 10012735 Diarrhoea<br>subjects affected / exposed<br>occurrences (all)          | 3 / 50 (6.00%)                                      | 0 / 46 (0.00%)   |  |
|   | 4   | 0                |  |
| 10000081 Abdominal pain<br>subjects affected / exposed<br>occurrences (all)     | 1 / 50 (2.00%)                                      | 2 / 46 (4.35%)   |  |
|   | 2   | 3                |  |
| Respiratory, thoracic and mediastinal disorders                                 |   |                  |  |
| 10011224 Cough<br>subjects affected / exposed<br>occurrences (all)              | 2 / 50 (4.00%)                                      | 1 / 46 (2.17%)   |  |
|   | 3   | 1                |  |
| 10068319 Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all) | 2 / 50 (4.00%)                                      | 2 / 46 (4.35%)   |  |
|   | 3   | 2                |  |
| Skin and subcutaneous tissue disorders  |   |                  |  |
| 10013786 Dry skin<br>subjects affected / exposed<br>occurrences (all)           | 3 / 50 (6.00%)                                      | 1 / 46 (2.17%)   |  |
|   | 5   | 1                |  |
| 10037844 Rash<br>subjects affected / exposed<br>occurrences (all)               | 2 / 50 (4.00%)                                      | 4 / 46 (8.70%)   |  |
|   | 4   | 4                |  |
| 10000496 Acne<br>subjects affected / exposed<br>occurrences (all)               | 3 / 50 (6.00%)                                      | 0 / 46 (0.00%)   |  |
|   | 3   | 0                |  |
| Musculoskeletal and connective tissue disorders                                 |   |                  |  |
| 10003239 Arthralgia<br>subjects affected / exposed<br>occurrences (all)         | 2 / 50 (4.00%)                                      | 0 / 46 (0.00%)   |  |
|   | 4   | 0                |  |
| 10033425 Pain in extremity<br>subjects affected / exposed<br>occurrences (all)  | 1 / 50 (2.00%)                                      | 1 / 46 (2.17%)   |  |
|   | 3   | 1                |  |

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

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 15 February 2021 | <ul style="list-style-type: none"><li>Protocol Version 1.1, Approved : 18/12/2015 – Original protocol</li><li>Protocol Version 2.0, Approved : 15/04/2016 – Substantial amendment to remove requirement for labelling of IMP according to GMP Annex 13</li><li>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</li><li>Protocol Version 4.0, Approved: 03/07/2018 –Amendment to clarify definitions of treatment failure and steroids dosing</li><li>Protocol Version 5.0, Approved: 15/02/2021- Amendment to add additional provision on the local dispensing of IMP at study sites to subject requiring dose escalation as part of the protocol</li></ul> |

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