



## Clinical trial results:

### A Randomised, Double-blind, Active Treatment Study to Induce Clinical Response and/or Remission with GSK1605786A in Subjects with Moderately-to-Severely Active Crohn's Disease

#### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2011-002817-12                |
| Trial protocol           | GR AT ES PT EE HU DE CZ DK BG |
| Global end of trial date | 17 October 2013               |

#### Results information

|                                |               |
|--------------------------------|---------------|
| Result version number          | v1 (current)  |
| This version publication date  | 27 April 2016 |
| First version publication date | 19 April 2015 |

#### Trial information

##### Trial identification

|                       |           |
|-----------------------|-----------|
| Sponsor protocol code | CCX114643 |
|-----------------------|-----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01536418 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |                                                            |
|------------------------------|------------------------------------------------------------|
| Sponsor organisation name    | GlaxoSmithKline                                            |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact               | GSK Response Center, GlaxoSmithKline, +1 8664357343,       |
| Scientific contact           | GSK Response Center, GlaxoSmithKline, +1 8664357343,       |

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                       | 06 January 2014 |
| Is this the analysis of the primary completion data? | No              |

|                                  |                 |
|----------------------------------|-----------------|
| Global end of trial reached?     | Yes             |
| Global end of trial date         | 17 October 2013 |
| Was the trial ended prematurely? | Yes             |

Notes:

## General information about the trial

Main objective of the trial:

To induce clinical response (CDAI decrease from baseline  $\geq 100$  points) and/or remission (CDAI  $<150$ ) following 12 weeks of treatment with one of two active doses of GSK1605786A for qualification of subjects for enrolment into a follow-on 52-week maintenance study (CCX114157).

Protection of trial subjects:

Subjects were allowed to continue use of certain background medications to manage their Crohn's disease.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 11 November 2011 |
| 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 | Netherlands: 2         |
| Country: Number of subjects enrolled | Portugal: 1            |
| Country: Number of subjects enrolled | Slovakia: 18           |
| Country: Number of subjects enrolled | Spain: 10              |
| Country: Number of subjects enrolled | United Kingdom: 7      |
| Country: Number of subjects enrolled | Austria: 12            |
| Country: Number of subjects enrolled | Belgium: 1             |
| Country: Number of subjects enrolled | Czech Republic: 1      |
| Country: Number of subjects enrolled | Denmark: 5             |
| Country: Number of subjects enrolled | Estonia: 6             |
| Country: Number of subjects enrolled | France: 5              |
| Country: Number of subjects enrolled | Germany: 4             |
| Country: Number of subjects enrolled | Greece: 3              |
| Country: Number of subjects enrolled | Hungary: 7             |
| Country: Number of subjects enrolled | Australia: 8           |
| Country: Number of subjects enrolled | Canada: 4              |
| Country: Number of subjects enrolled | Hong Kong: 8           |
| Country: Number of subjects enrolled | Israel: 23             |
| Country: Number of subjects enrolled | Japan: 3               |
| Country: Number of subjects enrolled | Korea, Republic of: 18 |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | New Zealand: 6         |
| Country: Number of subjects enrolled | Russian Federation: 16 |
| Country: Number of subjects enrolled | Switzerland: 8         |
| Country: Number of subjects enrolled | Taiwan: 1              |
| Country: Number of subjects enrolled | Ukraine: 12            |
| Country: Number of subjects enrolled | United States: 64      |
| Worldwide total number of subjects   | 253                    |
| EEA total number of subjects         | 82                     |

Notes:

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### 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)                      | 248 |
| From 65 to 84 years                       | 5   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Following the Screening period (approximately 2 weeks), eligible participants were randomized at Baseline (Week 0) to receive blinded treatment with one of two doses of GSK1605786A (500 milligrams [mg] once daily [QD] or 500 mg twice daily [BID]) for 12 weeks. A total of 253 participants were randomized and completed the study.

### Period 1

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

### Arms

|                              |                         |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes                     |
| <b>Arm title</b>             | GSK1605786A, 500 mg, QD |

Arm description:

Participants received GSK1605786A 500 milligrams (mg) once daily (QD), orally for 12 weeks

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | GSK1605786A  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

500 mg once daily, oral administration

|                  |                          |
|------------------|--------------------------|
| <b>Arm title</b> | GSK1605786A, 500 mg, BID |
|------------------|--------------------------|

Arm description:

Participants received GSK1605786A 500 mg twice daily (BID), orally for 12 weeks

|                                        |              |
|----------------------------------------|--------------|
| Arm type                               | Experimental |
| Investigational medicinal product name | GSK1605786A  |
| Investigational medicinal product code |              |
| Other name                             |              |
| Pharmaceutical forms                   | Capsule      |
| Routes of administration               | Oral use     |

Dosage and administration details:

500 mg twice daily, oral administration

| <b>Number of subjects in period 1</b> | GSK1605786A, 500 mg, QD | GSK1605786A, 500 mg, BID |
|---------------------------------------|-------------------------|--------------------------|
| Started                               | 127                     | 126                      |
| Completed                             | 58                      | 60                       |
| Not completed                         | 69                      | 66                       |
| Consent withdrawn by subject          | 5                       | 3                        |
| Physician decision                    | 1                       | 3                        |
| Adverse event, non-fatal              | 9                       | 4                        |
| Met Liver Chemistry Stopping Criteria | 1                       | -                        |
| Study Closed/Terminated               | 41                      | 37                       |
| Lack of efficacy                      | 10                      | 16                       |
| Protocol deviation                    | 2                       | 3                        |

## Baseline characteristics

### Reporting groups

|                                                                                            |                          |
|--------------------------------------------------------------------------------------------|--------------------------|
| Reporting group title                                                                      | GSK1605786A, 500 mg, QD  |
| Reporting group description:                                                               |                          |
| Participants received GSK1605786A 500 milligrams (mg) once daily (QD), orally for 12 weeks |                          |
| Reporting group title                                                                      | GSK1605786A, 500 mg, BID |
| Reporting group description:                                                               |                          |
| Participants received GSK1605786A 500 mg twice daily (BID), orally for 12 weeks            |                          |

| Reporting group values                             | GSK1605786A, 500 mg, QD | GSK1605786A, 500 mg, BID | Total |
|----------------------------------------------------|-------------------------|--------------------------|-------|
| Number of subjects                                 | 127                     | 126                      | 253   |
| Age categorical<br>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<br>Units: years                     |                         |                          |       |
| arithmetic mean                                    | 39.6                    | 38.5                     |       |
| standard deviation                                 | ± 13.11                 | ± 12.91                  | -     |
| Gender categorical<br>Units: Subjects              |                         |                          |       |
| Female                                             | 63                      | 64                       | 127   |
| Male                                               | 64                      | 62                       | 126   |
| Race, Customized<br>Units: Subjects                |                         |                          |       |
| White-Caucasian/European                           | 104                     | 105                      | 209   |
| White-Arabic/North African                         | 1                       | 4                        | 5     |
| Black                                              | 1                       | 1                        | 2     |
| Asian-East                                         | 13                      | 13                       | 26    |
| Asian-South East                                   | 2                       | 0                        | 2     |
| Asian-Japanese                                     | 2                       | 1                        | 3     |
| Native Hawaiian/Pacific Islander                   | 1                       | 0                        | 1     |
| Multiple race                                      | 2                       | 1                        | 3     |
| Missing                                            | 1                       | 1                        | 2     |

## End points

### End points reporting groups

|                                                                                            |                          |
|--------------------------------------------------------------------------------------------|--------------------------|
| Reporting group title                                                                      | GSK1605786A, 500 mg, QD  |
| Reporting group description:                                                               |                          |
| Participants received GSK1605786A 500 milligrams (mg) once daily (QD), orally for 12 weeks |                          |
| Reporting group title                                                                      | GSK1605786A, 500 mg, BID |
| Reporting group description:                                                               |                          |
| Participants received GSK1605786A 500 mg twice daily (BID), orally for 12 weeks            |                          |

### Primary: Percentage of participants achieving clinical response at Week 12

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                   |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Percentage of participants achieving clinical response at Week 12 |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                   |
| Clinical response is defined as a Crohn's disease activity index (CDAI) score decrease from a Baseline value of $\geq 100$ points. The CDAI is a scoring system to measure disease severity with scores of $\geq 220$ to $\leq 450$ describing the moderately-to-severely active population. The score is algorithmically derived from the sum of participants-reported Crohn's disease symptoms recorded over 7 days and investigator recorded assessments of the participants's condition, laboratory parameters and use of anti-diarrhoeal medication. Missing efficacy data (premature discontinuation or otherwise) were imputed using a "no effect" imputation where missing equals no response or no change in response. The Intent-to-Treat (ITT) population comprised of all participants who have satisfied the eligibility criteria and were assigned with study medication.. |                                                                   |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Primary                                                           |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                   |
| Baseline and Week 12                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                   |

| End point values                  | GSK1605786A, 500 mg, QD | GSK1605786A, 500 mg, BID |  |  |
|-----------------------------------|-------------------------|--------------------------|--|--|
| Subject group type                | Reporting group         | Reporting group          |  |  |
| Number of subjects analysed       | 127 <sup>[1]</sup>      | 126 <sup>[2]</sup>       |  |  |
| Units: Percentage of participants |                         |                          |  |  |
| number (not applicable)           | 25.2                    | 33.3                     |  |  |

Notes:

[1] - ITT Population

[2] - ITT Population

### Statistical analyses

|                                         |                                                    |
|-----------------------------------------|----------------------------------------------------|
| Statistical analysis title              | Statistical analysis 1                             |
| Comparison groups                       | GSK1605786A, 500 mg, QD v GSK1605786A, 500 mg, BID |
| Number of subjects included in analysis | 253                                                |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | other                                              |
| Parameter estimate                      | Mean difference (final values)                     |
| Point estimate                          | 8.1                                                |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -3      |
| upper limit         | 19.3    |

## Secondary: Percentage of participants achieving clinical remission at Week 8, Week 12 and at both Week 8 and Week 12

|                 |                                                                                                           |
|-----------------|-----------------------------------------------------------------------------------------------------------|
| End point title | Percentage of participants achieving clinical remission at Week 8, Week 12 and at both Week 8 and Week 12 |
|-----------------|-----------------------------------------------------------------------------------------------------------|

End point description:

Clinical remission is defined as a CDAI score of <150 points. The CDAI is a scoring system to measure disease severity with scores of  $\geq 220$  to  $\leq 450$  describing the moderately-to-severely active population. The score is algorithmically derived from the sum of participants-reported Crohn's disease symptoms recorded over 7 days and investigator recorded assessments of the participants's condition, laboratory parameters and use of anti-diarrhoeal medication. Missing efficacy data (premature discontinuation or otherwise) were imputed using a "no effect" imputation where missing equals no response or no change in response. If the Baseline value was <150, the participant was not considered to have achieved remission.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Week 8 and Week 12

| End point values                  | GSK1605786A, 500 mg, QD | GSK1605786A, 500 mg, BID |  |  |
|-----------------------------------|-------------------------|--------------------------|--|--|
| Subject group type                | Reporting group         | Reporting group          |  |  |
| Number of subjects analysed       | 127 <sup>[3]</sup>      | 126 <sup>[4]</sup>       |  |  |
| Units: Percentage of participants |                         |                          |  |  |
| number (not applicable)           |                         |                          |  |  |
| Week 8                            | 11.8                    | 14.3                     |  |  |
| Week 12                           | 11.8                    | 17.5                     |  |  |
| Both Weeks 8 and Week 12          | 7.9                     | 10.3                     |  |  |

Notes:

[3] - ITT Population

[4] - ITT Population

## Statistical analyses

|                            |                        |
|----------------------------|------------------------|
| Statistical analysis title | Statistical analysis 1 |
|----------------------------|------------------------|

Statistical analysis description:

Statistical comparison is for Week 8

|                                         |                                                    |
|-----------------------------------------|----------------------------------------------------|
| Comparison groups                       | GSK1605786A, 500 mg, QD v GSK1605786A, 500 mg, BID |
| Number of subjects included in analysis | 253                                                |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | other                                              |
| Parameter estimate                      | Mean difference (final values)                     |
| Point estimate                          | 2.5                                                |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -5.8    |
| upper limit         | 10.8    |

|                                         |                                                    |
|-----------------------------------------|----------------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis 2                             |
| Statistical analysis description:       |                                                    |
| Statistical comparison is for Week 12   |                                                    |
| Comparison groups                       | GSK1605786A, 500 mg, QD v GSK1605786A, 500 mg, BID |
| Number of subjects included in analysis | 253                                                |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | other                                              |
| Parameter estimate                      | Mean difference (final values)                     |
| Point estimate                          | 5.6                                                |
| Confidence interval                     |                                                    |
| level                                   | 95 %                                               |
| sides                                   | 2-sided                                            |
| lower limit                             | -3                                                 |
| upper limit                             | 14.3                                               |

|                                                       |                                                    |
|-------------------------------------------------------|----------------------------------------------------|
| <b>Statistical analysis title</b>                     | Statistical analysis 3                             |
| Statistical analysis description:                     |                                                    |
| Statistical comparison is for both Week 8 and Week 12 |                                                    |
| Comparison groups                                     | GSK1605786A, 500 mg, QD v GSK1605786A, 500 mg, BID |
| Number of subjects included in analysis               | 253                                                |
| Analysis specification                                | Pre-specified                                      |
| Analysis type                                         | other                                              |
| Parameter estimate                                    | Mean difference (final values)                     |
| Point estimate                                        | 2.4                                                |
| Confidence interval                                   |                                                    |
| level                                                 | 95 %                                               |
| sides                                                 | 2-sided                                            |
| lower limit                                           | -4.6                                               |
| upper limit                                           | 9.5                                                |

### **Secondary: Percentage of participants with a clinical response at Week 8 and at both Week 8 and Week 12**

|                 |                                                                                              |
|-----------------|----------------------------------------------------------------------------------------------|
| End point title | Percentage of participants with a clinical response at Week 8 and at both Week 8 and Week 12 |
|-----------------|----------------------------------------------------------------------------------------------|

End point description:

Clinical response is defined as a Crohn's disease activity index (CDAI) score decrease from a Baseline value of  $\geq 100$  points. The CDAI is a scoring system to measure disease severity with scores of  $\geq 220$  to  $\leq 450$  describing the moderately-to-severely active population. The score is algorithmically derived from the sum of participants-reported Crohn's disease symptoms recorded over 7 days and investigator

recorded assessments of the participants's condition, laboratory parameters and use of anti-diarrhoeal medication. Missing efficacy data (premature discontinuation or otherwise) were imputed using a "no effect" imputation where missing equals no response or no change in response.

|                              |           |
|------------------------------|-----------|
| End point type               | Secondary |
| End point timeframe:         |           |
| Baseline, Week 8 and Week 12 |           |

| End point values                  | GSK1605786A,<br>500 mg, QD | GSK1605786A,<br>500 mg, BID |  |  |
|-----------------------------------|----------------------------|-----------------------------|--|--|
| Subject group type                | Reporting group            | Reporting group             |  |  |
| Number of subjects analysed       | 127 <sup>[5]</sup>         | 126 <sup>[6]</sup>          |  |  |
| Units: Percentage of participants |                            |                             |  |  |
| number (not applicable)           |                            |                             |  |  |
| Week 8                            | 24.4                       | 29.4                        |  |  |
| Both Week 8 and Week 12           | 15.7                       | 24.6                        |  |  |

Notes:

[5] - ITT Population

[6] - ITT Population

## Statistical analyses

|                                         |                                                    |
|-----------------------------------------|----------------------------------------------------|
| <b>Statistical analysis title</b>       | Statistical analysis 1                             |
| Statistical analysis description:       |                                                    |
| Statistical comparison is for Week 8    |                                                    |
| Comparison groups                       | GSK1605786A, 500 mg, QD v GSK1605786A, 500 mg, BID |
| Number of subjects included in analysis | 253                                                |
| Analysis specification                  | Pre-specified                                      |
| Analysis type                           | other                                              |
| Parameter estimate                      | Mean difference (final values)                     |
| Point estimate                          | 5                                                  |
| Confidence interval                     |                                                    |
| level                                   | 95 %                                               |
| sides                                   | 2-sided                                            |
| lower limit                             | -6                                                 |
| upper limit                             | 15.9                                               |

|                                                       |                                                    |
|-------------------------------------------------------|----------------------------------------------------|
| <b>Statistical analysis title</b>                     | Statistical analysis 2                             |
| Statistical analysis description:                     |                                                    |
| Statistical comparison is for both Week 8 and Week 12 |                                                    |
| Comparison groups                                     | GSK1605786A, 500 mg, QD v GSK1605786A, 500 mg, BID |
| Number of subjects included in analysis               | 253                                                |
| Analysis specification                                | Pre-specified                                      |
| Analysis type                                         | other                                              |
| Parameter estimate                                    | Mean difference (final values)                     |
| Point estimate                                        | 8.9                                                |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | -1      |
| upper limit         | 18.7    |

### Secondary: Change from Baseline in C-reactive protein concentration at Weeks 4, 8, and 12

|                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                | Change from Baseline in C-reactive protein concentration at Weeks 4, 8, and 12 |
| End point description:<br>Blood samples were collected for the measurement of c-reactive protein at Baseline (Screening) and at Weeks 4, 8, and 12. Baseline is defined as the measurement at Screening (Day -21 to Day -1). Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline. Because the study was terminated prematurely, summary statistics were not compiled. |                                                                                |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                 | Secondary                                                                      |
| End point timeframe:<br>Baseline and Weeks 4, 8, and 12                                                                                                                                                                                                                                                                                                                                                                        |                                                                                |

| End point values            | GSK1605786A,<br>500 mg, QD | GSK1605786A,<br>500 mg, BID |  |  |
|-----------------------------|----------------------------|-----------------------------|--|--|
| Subject group type          | Reporting group            | Reporting group             |  |  |
| Number of subjects analysed | 0 <sup>[7]</sup>           | 0 <sup>[8]</sup>            |  |  |
| Units: Milligrams per liter |                            |                             |  |  |
| number (not applicable)     |                            |                             |  |  |

Notes:

[7] - ITT Population. Because the study was terminated prematurely, summary statistics were not compiled.

[8] - ITT Population. Because the study was terminated prematurely, summary statistics were not compiled.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in faecal calprotectin at Week 12

|                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                      | Change from Baseline in faecal calprotectin at Week 12 |
| End point description:<br>Stool samples were collected for the measurement faecal calprotectin level at Baseline (Screening) and Week 12. Baseline is defined as the measurement at Screening (Day -21 to Day -1). Change from Baseline was calculated as the value at the post-Baseline time point minus the value at Baseline. Because the study was terminated prematurely, summary statistics were not compiled. |                                                        |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                       | Secondary                                              |
| End point timeframe:<br>Baseline (Screening) and Week 12                                                                                                                                                                                                                                                                                                                                                             |                                                        |

|                             |                            |                             |  |  |
|-----------------------------|----------------------------|-----------------------------|--|--|
| <b>End point values</b>     | GSK1605786A,<br>500 mg, QD | GSK1605786A,<br>500 mg, BID |  |  |
| Subject group type          | Reporting group            | Reporting group             |  |  |
| Number of subjects analysed | 0 <sup>[9]</sup>           | 0 <sup>[10]</sup>           |  |  |
| Units: microgram per gram   |                            |                             |  |  |
| number (not applicable)     |                            |                             |  |  |

Notes:

[9] - ITT Population. Because the study was terminated prematurely, summary statistics were not compiled.

[10] - ITT Population. Because the study was terminated prematurely, summary statistics were not compiled.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacokinetics (PK) of GSK1605786A

|                 |                                      |
|-----------------|--------------------------------------|
| End point title | Pharmacokinetics (PK) of GSK1605786A |
|-----------------|--------------------------------------|

End point description:

The PK analyses was planned to perform to characterize the PK of the study drug GSK1605786A in the participant population. PK is defined as the concentration of drug in a participant's blood at certain time points after the drug was taken by mouth. These PK analyses was not conducted following the early termination of the study. Because the study was terminated prematurely, summary statistics were not compiled.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Screening) and Weeks 12

|                             |                            |                             |  |  |
|-----------------------------|----------------------------|-----------------------------|--|--|
| <b>End point values</b>     | GSK1605786A,<br>500 mg, QD | GSK1605786A,<br>500 mg, BID |  |  |
| Subject group type          | Reporting group            | Reporting group             |  |  |
| Number of subjects analysed | 0 <sup>[11]</sup>          | 0 <sup>[12]</sup>           |  |  |
| Units: microgram per gram   |                            |                             |  |  |
| number (not applicable)     |                            |                             |  |  |

Notes:

[11] - ITT Population. Because the study was terminated prematurely, summary statistics were not compiled.

[12] - ITT Population. Because the study was terminated prematurely, summary statistics were not compiled.

### Statistical analyses

No statistical analyses for this end point

### Secondary: Pharmacogenetic analyses

|                 |                          |
|-----------------|--------------------------|
| End point title | Pharmacogenetic analyses |
|-----------------|--------------------------|

End point description:

Sample for the pharmacogenetic analyses was collected during Treatment Phase visit. The pharmacogenetic analyses was planned to perform to investigate the relationship between the genetic markers with the safety and efficacy response to GSK1605786A. These pharmacogenetic analyses was not conducted following the early termination of the study. Because the study was terminated prematurely, summary statistics were not compiled.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

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End point timeframe:

Post randomization any time during early two weeks

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| <b>End point values</b>                     | GSK1605786A,<br>500 mg, QD | GSK1605786A,<br>500 mg, BID |  |  |
|---------------------------------------------|----------------------------|-----------------------------|--|--|
| Subject group type                          | Reporting group            | Reporting group             |  |  |
| Number of subjects analysed                 | 0 <sup>[13]</sup>          | 0 <sup>[14]</sup>           |  |  |
| Units: presence or absence of certain genes |                            |                             |  |  |
| number (not applicable)                     |                            |                             |  |  |

Notes:

[13] - ITT Population. Because the study was terminated prematurely, summary statistics were not compiled.

[14] - ITT Population. Because the study was terminated prematurely, summary statistics were not compiled.

### Statistical analyses

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

On-treatment adverse events (AEs) and serious adverse events (SAEs) are defined as events occurring from and until Week 16 for those participants not entering the maintenance study, CCX114157, on completion of Week 12, or until the final follow up contact

Adverse event reporting additional description:

SAEs and non-serious AEs were collected in participants of the Safety Population, comprised of all participants in the ITT population except those who did not received at least one dose of treatment;

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

### Reporting groups

|                       |                         |
|-----------------------|-------------------------|
| Reporting group title | GSK1605786A, 500 mg, QD |
|-----------------------|-------------------------|

Reporting group description:

Participants received GSK1605786A 500 milligrams (mg) once daily (QD), orally for 12 weeks

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | GSK1605786A, 500 mg, BID |
|-----------------------|--------------------------|

Reporting group description:

Participants received GSK1605786A 500 mg twice daily (BID), orally for 12 weeks

| <b>Serious adverse events</b>                                       | GSK1605786A, 500 mg, QD | GSK1605786A, 500 mg, BID |  |
|---------------------------------------------------------------------|-------------------------|--------------------------|--|
| Total subjects affected by serious adverse events                   |                         |                          |  |
| subjects affected / exposed                                         | 8 / 127 (6.30%)         | 7 / 126 (5.56%)          |  |
| number of deaths (all causes)                                       | 0                       | 0                        |  |
| number of deaths resulting from adverse events                      |                         |                          |  |
| Investigations                                                      |                         |                          |  |
| Hepatic enzyme increased                                            |                         |                          |  |
| subjects affected / exposed                                         | 1 / 127 (0.79%)         | 0 / 126 (0.00%)          |  |
| occurrences causally related to treatment / all                     | 0 / 1                   | 0 / 0                    |  |
| deaths causally related to treatment / all                          | 0 / 0                   | 0 / 0                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                         |                          |  |
| Invasive ductal breast carcinoma                                    |                         |                          |  |
| subjects affected / exposed                                         | 1 / 127 (0.79%)         | 0 / 126 (0.00%)          |  |
| occurrences causally related to treatment / all                     | 0 / 1                   | 0 / 0                    |  |
| deaths causally related to treatment / all                          | 0 / 0                   | 0 / 0                    |  |
| Cardiac disorders                                                   |                         |                          |  |
| Acute myocardial infarction                                         |                         |                          |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 127 (0.79%) | 0 / 126 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 0 / 126 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%) | 1 / 126 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Anaemia                                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 0 / 126 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Crohn's disease                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 1 / 126 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal ulcer                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 127 (0.79%) | 0 / 126 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Musculoskeletal chest pain                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%) | 1 / 126 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myalgia                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 127 (0.00%) | 1 / 126 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                                                                                                                                             |                                           |                                           |  |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|-------------------------------------------|--|
| Infections and infestations<br>Anal abscess<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all | <br><br>1 / 127 (0.79%)<br>0 / 1<br>0 / 0 | <br><br>0 / 126 (0.00%)<br>0 / 0<br>0 / 0 |  |
| Bronchitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                  | <br>0 / 127 (0.00%)<br>0 / 0<br>0 / 0     | <br>1 / 126 (0.79%)<br>0 / 1<br>0 / 0     |  |
| Cellulitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                  | <br>0 / 127 (0.00%)<br>0 / 0<br>0 / 0     | <br>1 / 126 (0.79%)<br>0 / 1<br>0 / 0     |  |
| Tonsillitis<br>subjects affected / exposed<br>occurrences causally related to treatment / all<br>deaths causally related to treatment / all                                 | <br>0 / 127 (0.00%)<br>0 / 0<br>0 / 0     | <br>1 / 126 (0.79%)<br>0 / 1<br>0 / 0     |  |

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

| <b>Non-serious adverse events</b>                     | GSK1605786A, 500 mg, QD | GSK1605786A, 500 mg, BID |  |
|-------------------------------------------------------|-------------------------|--------------------------|--|
| Total subjects affected by non-serious adverse events |                         |                          |  |
| subjects affected / exposed                           | 81 / 127 (63.78%)       | 80 / 126 (63.49%)        |  |
| Nervous system disorders                              |                         |                          |  |
| Headache                                              |                         |                          |  |
| subjects affected / exposed                           | 10 / 127 (7.87%)        | 14 / 126 (11.11%)        |  |
| occurrences (all)                                     | 17                      | 20                       |  |
| General disorders and administration site conditions  |                         |                          |  |
| Pyrexia                                               |                         |                          |  |
| subjects affected / exposed                           | 8 / 127 (6.30%)         | 3 / 126 (2.38%)          |  |
| occurrences (all)                                     | 9                       | 3                        |  |
| Gastrointestinal disorders                            |                         |                          |  |
| Abdominal pain                                        |                         |                          |  |
| subjects affected / exposed                           | 13 / 127 (10.24%)       | 12 / 126 (9.52%)         |  |
| occurrences (all)                                     | 13                      | 17                       |  |

|                             |                 |                  |  |
|-----------------------------|-----------------|------------------|--|
| Dyspepsia                   |                 |                  |  |
| subjects affected / exposed | 6 / 127 (4.72%) | 10 / 126 (7.94%) |  |
| occurrences (all)           | 6               | 12               |  |
| Crohn's disease             |                 |                  |  |
| subjects affected / exposed | 7 / 127 (5.51%) | 7 / 126 (5.56%)  |  |
| occurrences (all)           | 8               | 7                |  |
| Nausea                      |                 |                  |  |
| subjects affected / exposed | 9 / 127 (7.09%) | 5 / 126 (3.97%)  |  |
| occurrences (all)           | 9               | 6                |  |
| Infections and infestations |                 |                  |  |
| Nasopharyngitis             |                 |                  |  |
| subjects affected / exposed | 8 / 127 (6.30%) | 5 / 126 (3.97%)  |  |
| occurrences (all)           | 9               | 6                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 20 February 2013 | <p>Clarify that CCX114643 is not positioned as a pivotal study, but is a feeder study for the pivotal maintenance trial, CCX114157 as this study was not designed to provide pivotal evidence of induction efficacy to support a registration package. This study was included as a component of the Phase III clinical program, positioned as a feeder study to qualify subjects for the maintenance study, CCX114157, and additional clarity was provided in the modified wording. Amend description of eligible patients to clarify that subjects must have had Crohn's disease for at least 4 months duration, rather than a diagnosis for greater than 4 months as the protocol was designed to include patients who have had Crohn's disease for greater than 4 months duration. Clarify that the management of the approximate 50% limitation of inclusion of subjects who received prior treatment with an anti-TNF agent and discontinued due to loss or lack of efficacy was implemented by the GSK study team to ensure that all eligible subjects who enter screening were able to be randomised. Amend duration of subject participation from a minimum of 15 weeks and a maximum of 19 weeks to a minimum duration of approximately 14 weeks and a maximum duration of 21 weeks to reflect the shortening of the screening period to approximately 2 weeks, consistent with the most common period of time for subjects to complete the screening assessments. The maximum duration reflects the duration of participation required if both a 5-week screening period and a 4-week follow up post completion of treatment were required. Clarify that fistula remission is being assessed as closure of all fistula that were open at baseline , as fistula that are draining are open and the wording was modified for consistency with the approach for data collection and the wording in the eCRF. Clarify that treatment allocation will only be grouped by subjects who have ever received anti-TNF therapy or not and not by current use of corticosteroids.</p> |
| 20 February 2013 | <p>Include confirmation of active disease by ileocolonoscopy within 3 months prior to screening with documentation confirming the presence of a minimum of 3 nonanastomotic ulcerations (each &gt;5 mm in diameter) consistent with Crohn's disease, as patients may have active Crohn's disease in the absence of elevations in the inflammatory biomarkers, CRP or faecal calprotectin. Clarify that the determination of inadequate response and/or intolerance/adverse event for discontinuation of corticosteroids or immunosuppressants will be based on investigator judgment, as this determination is most appropriately based on the expert opinion of the investigator. Amend requirement for subjects to complete at least 8 consecutive days of Crohn's disease symptom recording using the IVRS prior to the Randomisation Visit, as the CDAI score is based on 7 days of patient symptoms and the IVRS did not require 8 days of patient-recorded information to confirm the CDAI score and eligibility for randomization. Clarify acceptable methods for confirmation of male partner sterilisation prior to the female subject's entry into the study, as male partner sterilisation prior to the female subject's entry into the study could be confirmed by interview with the subject or substantiated by other methods as deemed necessary by the investigator. Clarify that only fistula with abscesses and fistula likely to require surgery are exclusionary. Clarify that short bowel syndrome or chronic diarrhoea related to malabsorption and/or multiple bowel re-sections for Crohn's disease are exclusionary. Updated prohibited medications: Use of any biologic for the treatment of Crohn's disease, including investigational agents is prohibited, with natalizumab, vedolizumab, ustekinumab specifically named; use of intravenous antibiotics for the treatment of Crohn's disease is no longer prohibited; stable use of enteral feeding or short term enteral or parenteral nutritional supplementation is no longer prohibited.</p>        |

|                  |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 20 February 2013 | <p>The start of long-term enteral feeding within 4 weeks prior to screening is not allowed based on the following rationale: Use of all biologics, including investigational agents, was exclusionary due to their potential to impact the ability to more fully characterize the efficacy and safety profile of GSK1605786A. Immunosuppressants considered to be investigational agents may have received approval during the conduct of this study. Additional wording was included to clarify that use of any immunosuppressant not specifically designated as a permitted medication is prohibited. Intravenous antibiotics are not commonly used to treat Crohn's disease symptoms but may be used to treat certain gastrointestinal complications such as abscesses. Due to the limited potential to impact the efficacy profile of GSK1605786A and the potential need for treatment of Crohn's disease-related abscesses or other complications, it was appropriate to allow the use of these medications. The stable use of enteral feeding is consistent with allowance of other Crohn's disease medications at stable doses, with minimal potential to impact the safety and efficacy profile of GSK1605786A. Clarify re-screening of subjects who test positive for C difficile and receive antibiotic treatment to specify that subjects may be re-screened when they have completed treatment for C difficile and the investigator has determined that the infection has resolved. Clarify that confirmation of positive hepatitis B and hepatitis C test results and confirmation of positive QuantiFERON TB Gold test results was allowed. Clarify description of the study hypotheses in a manner consistent with the study objectives. Identify additional populations for analysis (biomarker, quality of life, and PK), and refine the definition of the Safety population. Include additional language clarifying the interpretation, significance, and multiplicity adjustment for presentation of p-values.</p> |
| 20 February 2013 | <p>Include description of the interim analysis for the IDMC. Include definition of the term baseline for analysis purposes.</p> <p>Include the Week 12 timepoint for the analysis endpoints.</p> <p>Correct the description of the response and remission endpoints, describe the logistic regression model in more detail, refine the definition of clinical response and remission, remove the Fisher's Exact test analysis.</p> <p>Add the analysis of CDAI 70-point decrease and clarify the description of the analysis of fistula remission.</p> <p>Correct and clarify the algorithm used to assign exposure in the case of missing data.</p> <p>Describe subgroup analyses of safety to be performed.</p> <p>Denote the separate analyses of machine and manually collected ECG data.</p> <p>Correct description of SF36 v2 raw item and summary scores.</p> <p>Include analysis of a log transformation of the biomarker data and clarify the description of the timepoint.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date           | Interruption                                                                                                                       | Restart date |
|----------------|------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 23 August 2013 | <p>Discontinue investigational product and discontinue enrollment of new subjects.</p> <p>4 September 2013 - Study termination</p> | -            |

Notes:

## Limitations and caveats

None reported