



## Clinical trial results:

**A multi-center, double-blind, randomized, placebo-controlled, dose-finding study in patients with active rheumatoid arthritis incompletely controlled on stable MTX doses to investigate efficacy and safety of SC BT061**

### Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2010-018485-24  |
| Trial protocol           | CZ ES DE HU LV  |
| Global end of trial date | 16 October 2013 |

### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 25 December 2021 |
| First version publication date | 25 December 2021 |

### Trial information

#### Trial identification

|                       |     |
|-----------------------|-----|
| Sponsor protocol code | 979 |
|-----------------------|-----|

#### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01481493 |
| WHO universal trial number (UTN)   | -           |

Notes:

### Sponsors

|                              |                                                                          |
|------------------------------|--------------------------------------------------------------------------|
| Sponsor organisation name    | Biotest AG                                                               |
| Sponsor organisation address | Landsteinerstr. 5, Dreieich, Germany, 63303                              |
| Public contact               | Daniela Zipp, Biotest AG, +49 6103 801 255 ,<br>daniela.zipp@biotest.com |
| Scientific contact           | Daniela Zipp, Biotest AG, +49 6103 801 255 ,<br>daniela.zipp@biotest.com |

Notes:

### Paediatric regulatory details

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

Notes:

## Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 16 October 2014 |
| Is this the analysis of the primary completion data? | Yes             |
| Primary completion date                              | 05 August 2013  |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 16 October 2013 |
| Was the trial ended prematurely?                     | Yes             |

Notes:

## General information about the trial

Main objective of the trial:

Is to investigate dose-response information on efficacy.

Primary efficacy variable is ACR20 (at Week 13).

Protection of trial subjects:

The patient had to give written consent to participate in the trial by signing and dating the informed consent form (ICF) before screening. Any new and relevant information that evolved during the course of the trial concerning the investigational medicinal product (IMP), alternative treatments, or the risk/benefit ratio was communicated to the patient.

After SC administration the patient was asked to stay at the investigational site for at least 2 hours to cover the potential risk of a type I hypersensitivity reaction. Therefore, intensive care measures had to be available. Patients should be informed that such reactions are possible and prompt medical attention should be sought if allergic reactions occur.

After administration of the last dose of the IMP patients were observed for a 12-week follow-up period on a regular outpatient basis. All these patients had in addition a safety follow-up visit at Week 24. Treatment is discontinued if at least one of the following three criteria are met for two consecutive weekly assessments.

- CD3CD4 cell count  $\leq 200$  cells/ $\mu$ l or
- CD3CD4 cell count  $< 50\%$  of individual baseline count or
- Total lymphocyte count  $< 50\%$  of individual baseline count

The treatment will be discontinued for male patients in case:

- TSH, follicle-stimulating hormone (FSH), luteinizing hormone (LH) or testosterone levels are outside the normal range and
- The investigator assesses these changes as compared to baseline as clinically relevant for 2 consecutive measurements.

Other reasons for treatment discontinuation are:

- Prolonged lymphopenia at two consecutive weekly visits
- Lymphopenia is defined as  $< 1000$  lymphocytes /  $\mu$ l ( $< 1.000 * 10^9$  lymphocytes / l) in a whole blood specimen.
- Anaphylactic or other serious allergic reaction

Patients withdrawn from treatment should be followed up for at least 2 additional weeks and should . In case of an AE, the withdrawn patient should be followed up until the AE is resolved or in a steady state.

Background therapy: -

Evidence for comparator: -

|                                                           |                  |
|-----------------------------------------------------------|------------------|
| Actual start date of recruitment                          | 21 December 2010 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | No               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |          |
|--------------------------------------|----------|
| Country: Number of subjects enrolled | Spain: 1 |
|--------------------------------------|----------|

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Czech Republic: 49 |
| Country: Number of subjects enrolled | Germany: 8         |
| Country: Number of subjects enrolled | Hungary: 2         |
| Country: Number of subjects enrolled | Italy: 2           |
| Country: Number of subjects enrolled | Latvia: 10         |
| Country: Number of subjects enrolled | Poland: 56         |
| Worldwide total number of subjects   | 128                |
| EEA total number of subjects         | 128                |

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)                      | 101 |
| From 65 to 84 years                       | 27  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

The Screening period was up to 6 weeks for each subject.

The screening started on 21-DEC-2010 and ended on 04-FEB-2013 (2 year and 2 months). The active sites were in Czech Republic, Germany, Spain, Italy, Poland, Hungary and Latvia.

In total, 128 patients was randomized onto the study. Of which 127 patients received study treatment.

### Pre-assignment

Screening details:

Main inclusion criteria: Adult patients (18–75 years, both gender) with active RA (duration of  $\geq$  12months) with functional class I-III incompletely controlled on methotrexate (MTX), with a history of at least one traditional disease modifying antirheumatic drug (DMARD) with an inadequate response despite  $\geq$  3 months of treatment and who signed ICF.

### Period 1

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| Period 1 title               | Controlled Treatment Period (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 |

Blinding implementation details:

All study staff at the investigational site and study personnel at the sponsor / clinical research organization(s) involved in the conduct of the study remained blinded until study unblinding. Plasma concentrations of BT061 was determined at Biotest only after the blinded data review meeting (BDRM). The independent statistician, independent laboratory specialists and the IDRB members had access to such data before the BDRM. Unblinded personnel were not involved in any analysis.

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Placebo group ( Group D) received weekly subcutaneous placebo for 12 weeks.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Placebo                |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

2 ml placebo (0 mg/ml BT061) (2 vials) was administered subcutaneously weekly for a 12-week period (in total 12 applications).

The IMP (placebo) was administered by the investigator or designated study staff according to the randomized assigned treatment group.

1 ml of each vial is injected at two different abdominal SC sites. Both SC doses of 1 ml volume each are administered undiluted and slowly in the region of the anterior abdomen into an area of intact skin. 1 ml of each vial is injected at two different abdominal SC sites. Both SC doses of 1 ml volume each are administered undiluted and slowly in the region of the anterior abdomen into an area of intact skin.

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | BT061 25 mg |
|------------------|-------------|

Arm description:

BT061 25 mg Group received weekly subcutaneous 25 mg BT061 for 12 weeks.

|          |              |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

|                                        |                        |
|----------------------------------------|------------------------|
| Investigational medicinal product name | BT061 25 mg            |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

**Dosage and administration details:**

25 mg BT061 in 2 ml (1 ml 25mg/ml BT061 + 1 ml placebo 0 mg/ml BT061) was administered subcutaneously weekly for a 12-week period (in total 12 applications).

The IMP (BT061) was administered by the investigator or designated study staff according to the randomized assigned treatment group.

1 ml of each vial is injected at two different abdominal SC sites. Both SC doses of 1 ml volume each are administered undiluted and slowly in the region of the anterior abdomen into an area of intact skin.

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | BT061 50 mg |
|------------------|-------------|

**Arm description:**

BT061 50 mg group received weekly subcutaneous 50 mg BT061 for 12 weeks.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | BT061 50 mg            |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

**Dosage and administration details:**

50 mg BT061 in 2 ml (1 ml 50 mg/ml BT061 + 1 ml placebo 0 mg/ml BT061) was administered subcutaneously weekly for a 12-week period (in total 12 applications).

The IMP (BT061) was administered by the investigator or designated study staff according to the randomized assigned treatment group.

1 ml of each vial is injected at two different abdominal SC sites. Both SC doses of 1 ml volume each are administered undiluted and slowly in the region of the anterior abdomen into an area of intact skin.

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | BT061 75 mg |
|------------------|-------------|

**Arm description:**

BT061 75 mg group received weekly subcutaneous 75 mg BT061 for 12 weeks.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | BT061 75 mg            |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

**Dosage and administration details:**

75 mg BT061 in 2 ml (1 ml 25 mg/ml BT061 + 1 ml 50 mg/ml BT061) was administered subcutaneously weekly for a 12-week period (in total 12 applications).

The IMP (BT061) was administered by the investigator or designated study staff according to the randomized assigned treatment group.

1 ml of each vial is injected at two different abdominal SC sites. Both SC doses of 1 ml volume each are administered undiluted and slowly in the region of the anterior abdomen into an area of intact skin.

| <b>Number of subjects in period 1<sup>[1]</sup></b> | Placebo | BT061 25 mg | BT061 50 mg |
|-----------------------------------------------------|---------|-------------|-------------|
| Started                                             | 32      | 32          | 32          |
| Completed                                           | 28      | 30          | 27          |
| Not completed                                       | 4       | 2           | 5           |
| Consent withdrawn by subject                        | -       | -           | 1           |

|                                             |   |   |   |
|---------------------------------------------|---|---|---|
| positive CMV IgM test                       | - | - | - |
| patient absence                             | 1 | - | - |
| Adverse event, non-fatal                    | - | - | 2 |
| patient decision to withdraw from treatment | - | - | 1 |
| positive EBV IgM test                       | - | 1 | - |
| positive quantiferon test                   | 1 | - | 1 |
| Protocol deviation                          | 2 | 1 | - |
| Lack of efficacy                            | - | - | - |

| <b>Number of subjects in period 1<sup>[1]</sup></b> | BT061 75 mg |
|-----------------------------------------------------|-------------|
| Started                                             | 31          |
| Completed                                           | 27          |
| Not completed                                       | 4           |
| Consent withdrawn by subject                        | 2           |
| positive CMV IgM test                               | 1           |
| patient absence                                     | -           |
| Adverse event, non-fatal                            | -           |
| patient decision to withdraw from treatment         | -           |
| positive EBV IgM test                               | -           |
| positive quantiferon test                           | -           |
| Protocol deviation                                  | -           |
| Lack of efficacy                                    | 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 128 patients were randomized of which 127 patients were treated and included in the APTAS. For patient I0302 (75 mg BT061) the randomization did not lead to treatment due to a system error. Patient I0302 was screened on 16-APR-2012 and, according to the protocol, the Screening period was 6 weeks. On 28 MAY 2012 the 6-week Screening period was exceeded. The sub-investigator tried to randomize the patient on IWRS on time, but she could not because of a problem with IMP in IWRS.

## Baseline characteristics

### Reporting groups

|                                                                                                             |             |
|-------------------------------------------------------------------------------------------------------------|-------------|
| Reporting group title                                                                                       | Placebo     |
| Reporting group description:<br>Placebo group ( Group D) received weekly subcutaneous placebo for 12 weeks. |             |
| Reporting group title                                                                                       | BT061 25 mg |
| Reporting group description:<br>BT061 25 mg Group received weekly subcutaneous 25 mg BT061 for 12 weeks.    |             |
| Reporting group title                                                                                       | BT061 50 mg |
| Reporting group description:<br>BT061 50 mg group received weekly subcutaneous 50 mg BT061 for 12 weeks.    |             |
| Reporting group title                                                                                       | BT061 75 mg |
| Reporting group description:<br>BT061 75 mg group received weekly subcutaneous 75 mg BT061 for 12 weeks.    |             |

| Reporting group values                | Placebo  | BT061 25 mg | BT061 50 mg |
|---------------------------------------|----------|-------------|-------------|
| Number of subjects                    | 32       | 32          | 32          |
| Age categorical<br>Units: Subjects    |          |             |             |
| Adults (18- <40 years)                | 2        | 4           | 5           |
| Adults (40-65 years)                  | 23       | 21          | 20          |
| Adults (>65 - 77 years)               | 7        | 7           | 7           |
| Age continuous<br>Units: years        |          |             |             |
| median                                | 58       | 54          | 56.5        |
| full range (min-max)                  | 33 to 75 | 26 to 71    | 25 to 76    |
| Gender categorical<br>Units: Subjects |          |             |             |
| Female                                | 25       | 28          | 29          |
| Male                                  | 7        | 4           | 3           |

| Reporting group values                | BT061 75 mg | Total |  |
|---------------------------------------|-------------|-------|--|
| Number of subjects                    | 31          | 127   |  |
| Age categorical<br>Units: Subjects    |             |       |  |
| Adults (18- <40 years)                | 4           | 15    |  |
| Adults (40-65 years)                  | 24          | 88    |  |
| Adults (>65 - 77 years)               | 3           | 24    |  |
| Age continuous<br>Units: years        |             |       |  |
| median                                | 54          | -     |  |
| full range (min-max)                  | 26 to 74    | -     |  |
| Gender categorical<br>Units: Subjects |             |       |  |
| Female                                | 25          | 107   |  |
| Male                                  | 6           | 20    |  |

## Subject analysis sets

|                            |                                   |
|----------------------------|-----------------------------------|
| Subject analysis set title | All patients treated analysis set |
| Subject analysis set type  | Safety analysis                   |

Subject analysis set description:

All patients who received at least a single dose of study medication (IMP).

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | Full analysis set  |
| Subject analysis set type  | Intention-to-treat |

Subject analysis set description:

All patients who received at least one dose of IMP and have at least one postbaseline assessment with respect to the efficacy parameters.

|                            |                                |
|----------------------------|--------------------------------|
| Subject analysis set title | Per-protocol (PP) analysis set |
| Subject analysis set type  | Per protocol                   |

Subject analysis set description:

All patients of the full analysis set without any major protocol violations as defined during the blinded data review meeting. Patients with major protocol deviations or incomplete documentation of relevant data will be excluded from the PP analysis.

Patients who miss more than two doses of the IMP do not qualify for the perprotocol analysis set. In any case patients must have received the last two IMP injections of Week 11 and Week 12 to qualify for the PP set.

|                            |                    |
|----------------------------|--------------------|
| Subject analysis set title | PK analysis set    |
| Subject analysis set type  | Sub-group analysis |

Subject analysis set description:

Patients will be considered evaluable for PK analysis if they received at least one dose of BT061, and if they have at least one post-treatment plasma concentration measure of BT061.

| Reporting group values                                           | All patients treated analysis set | Full analysis set | Per-protocol (PP) analysis set |
|------------------------------------------------------------------|-----------------------------------|-------------------|--------------------------------|
| Number of subjects                                               | 127                               | 127               | 89                             |
| Age categorical<br>Units: Subjects                               |                                   |                   |                                |
| Adults (18- <40 years)                                           | 15                                |                   |                                |
| Adults (40-65 years)                                             | 88                                |                   |                                |
| Adults (>65 - 77 years)                                          | 24                                |                   |                                |
| Age continuous<br>Units: years<br>median<br>full range (min-max) |                                   |                   |                                |
| Gender categorical<br>Units: Subjects                            |                                   |                   |                                |
| Female                                                           | 107                               |                   |                                |
| Male                                                             | 20                                |                   |                                |

| Reporting group values                                           | PK analysis set |  |  |
|------------------------------------------------------------------|-----------------|--|--|
| Number of subjects                                               | 127             |  |  |
| Age categorical<br>Units: Subjects                               |                 |  |  |
| Adults (18- <40 years)                                           |                 |  |  |
| Adults (40-65 years)                                             |                 |  |  |
| Adults (>65 - 77 years)                                          |                 |  |  |
| Age continuous<br>Units: years<br>median<br>full range (min-max) |                 |  |  |



|                    |  |  |  |
|--------------------|--|--|--|
| Gender categorical |  |  |  |
| Units: Subjects    |  |  |  |
| Female             |  |  |  |
| Male               |  |  |  |

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## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | Placebo                           |
| Reporting group description:<br>Placebo group ( Group D) received weekly subcutaneous placebo for 12 weeks.                                                                                                                                                                                                                                                                                                                                                                                                                |                                   |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | BT061 25 mg                       |
| Reporting group description:<br>BT061 25 mg Group received weekly subcutaneous 25 mg BT061 for 12 weeks.                                                                                                                                                                                                                                                                                                                                                                                                                   |                                   |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | BT061 50 mg                       |
| Reporting group description:<br>BT061 50 mg group received weekly subcutaneous 50 mg BT061 for 12 weeks.                                                                                                                                                                                                                                                                                                                                                                                                                   |                                   |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | BT061 75 mg                       |
| Reporting group description:<br>BT061 75 mg group received weekly subcutaneous 75 mg BT061 for 12 weeks.                                                                                                                                                                                                                                                                                                                                                                                                                   |                                   |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | All patients treated analysis set |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Safety analysis                   |
| Subject analysis set description:<br>All patients who received at least a single dose of study medication (IMP).                                                                                                                                                                                                                                                                                                                                                                                                           |                                   |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Full analysis set                 |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Intention-to-treat                |
| Subject analysis set description:<br>All patients who received at least one dose of IMP and have at least one postbaseline assessment with respect to the efficacy parameters.                                                                                                                                                                                                                                                                                                                                             |                                   |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Per-protocol (PP) analysis set    |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Per protocol                      |
| Subject analysis set description:<br>All patients of the full analysis set without any major protocol violations as defined during the blinded data review meeting. Patients with major protocol deviations or incomplete documentation of relevant data will be excluded from the PP analysis.<br>Patients who miss more than two doses of the IMP do not qualify for the perprotocol analysis set. In any case patients must have received the last two IMP injections of Week 11 and Week 12 to qualify for the PP set. |                                   |
| Subject analysis set title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | PK analysis set                   |
| Subject analysis set type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Sub-group analysis                |
| Subject analysis set description:<br>Patients will be considered evaluable for PK analysis if they received at least one dose of BT061, and if they have at least one post-treatment plasma concentration measure of BT061.                                                                                                                                                                                                                                                                                                |                                   |

### Primary: ACR20 response at Week 13

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                           |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | ACR20 response at Week 13 |
| End point description:<br><br>The primary objective of this study was to investigate dose-response information on efficacy using the ACR20 response criteria after 12 weeks of treatment at study Week 13 (one week after end of treatment). The impact of the IMP on rheumatoid arthritis (RA) disease activity was evaluated by the difference between pre-treatment (baseline) disease activity and one week post-treatment (Week 13) disease activity.<br><br>An ACR20 response was defined as at least 20% improvement in both the tender joint count and the swollen joint count and at least 20% improvement in 3 of the 5 other core set measures including CRP and/or ESR, Investigator assessment of disease activity, Patient assessment of disease activity, Patient assessment of pain, Health Assessment Questionnaire (HAQ). |                           |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Primary                   |

End point timeframe:

From baseline to study week 13 ( one week after 12 weeks of treatment)

| End point values            | Placebo         | BT061 25 mg     | BT061 50 mg     | BT061 75 mg     |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32              | 32              | 32              | 31              |
| Units: subjects             |                 |                 |                 |                 |
| Response                    | 14              | 18              | 18              | 15              |
| No response                 | 18              | 14              | 14              | 16              |

| End point values            | All patients treated analysis set |  |  |  |
|-----------------------------|-----------------------------------|--|--|--|
| Subject group type          | Subject analysis set              |  |  |  |
| Number of subjects analysed | 127                               |  |  |  |
| Units: subjects             |                                   |  |  |  |
| Response                    | 65                                |  |  |  |
| No response                 | 62                                |  |  |  |

## Statistical analyses

| Statistical analysis title | BT061 25 mg versus placebo |
|----------------------------|----------------------------|
|----------------------------|----------------------------|

Statistical analysis description:

The primary analysis is the final analysis of the 2 groups (BT061 25 mg and placebo) of ACR20 response at Week 13 (using last observation carried forward (LOCF)) which was analysed using logistic regression adjusted for centre effect. The adjusted odds ratio (OR) with 95% confidence interval (CI) and the Wald p-value were calculated for the selected active treatment group against the placebo group together with the significance of the centre effect.

|                                         |                       |
|-----------------------------------------|-----------------------|
| Comparison groups                       | BT061 25 mg v Placebo |
| Number of subjects included in analysis | 64                    |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | > 0.05 <sup>[1]</sup> |
| Method                                  | Regression, Logistic  |
| Parameter estimate                      | Odds ratio (OR)       |
| Point estimate                          | 1.65                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 0.62                  |
| upper limit                             | 4.44                  |

Notes:

[1] - Wald X2 p-value = 0.3186 and Fisher 2-sided p-value = 0.4536. There was no statistically significant difference in ACR20 response rate versus placebo group.

| Statistical analysis title | BT061 50 mg versus placebo |
|----------------------------|----------------------------|
|----------------------------|----------------------------|

**Statistical analysis description:**

The primary analysis is the final analysis of the 2 groups (BT061 50 mg and placebo) of ACR20 response at Week 13 (using last observation carried forward (LOCF)) which was analysed using logistic regression adjusted for centre effect. The adjusted odds ratio (OR) with 95% confidence interval (CI) and the Wald p-value were calculated for the selected active treatment group against the placebo group together with the significance of the centre effect.

|                                         |                       |
|-----------------------------------------|-----------------------|
| Comparison groups                       | BT061 50 mg v Placebo |
| Number of subjects included in analysis | 64                    |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | > 0.05 [2]            |
| Method                                  | Regression, Logistic  |
| Parameter estimate                      | Odds ratio (OR)       |
| Point estimate                          | 1.65                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 0.62                  |
| upper limit                             | 4.44                  |

**Notes:**

[2] - Wald X2 p-value = 0.3186 and Fisher 2-sided p-value = 0.4536. There was no statistically significant difference in ACR20 response rate versus placebo group.

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | BT061 75 mg versus placebo |
|-----------------------------------|----------------------------|

**Statistical analysis description:**

The primary analysis is the final analysis of the 2 groups (BT061 75 mg and placebo) of ACR20 response at Week 13 (using last observation carried forward (LOCF)) which was analysed using logistic regression adjusted for centre effect. The adjusted odds ratio (OR) with 95% confidence interval (CI) and the Wald p-value were calculated for the selected active treatment group against the placebo group together with the significance of the centre effect.

|                                         |                       |
|-----------------------------------------|-----------------------|
| Comparison groups                       | BT061 75 mg v Placebo |
| Number of subjects included in analysis | 63                    |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | > 0.05 [3]            |
| Method                                  | Regression, Logistic  |
| Parameter estimate                      | Odds ratio (OR)       |
| Point estimate                          | 1.21                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 0.45                  |
| upper limit                             | 3.25                  |

**Notes:**

[3] - Wald X2 p-value = 0.7121 and Fisher 2-sided p-value = 0.8025. There was no statistically significant difference in ACR20 response rate versus placebo group.

**Secondary: ACR50 Response**

|                 |                |
|-----------------|----------------|
| End point title | ACR50 Response |
|-----------------|----------------|

**End point description:**

ACR50 response was derived using last observation carried forward and Non-responder Imputation.

An ACR50 response was defined as at least 50% improvement in both the tender joint count and the swollen joint count and at least 50% improvement in 3 of the 5 other core set measures including CRP and/or ESR, Investigator assessment of disease activity, Patient assessment of disease activity, Patient assessment of pain, Health Assessment Questionnaire (HAQ).

|                                |           |
|--------------------------------|-----------|
| End point type                 | Secondary |
| End point timeframe:           |           |
| From baseline to study Week 13 |           |

| End point values            | Placebo         | BT061 25 mg     | BT061 50 mg     | BT061 75 mg     |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32              | 32              | 32              | 31              |
| Units: subjects             |                 |                 |                 |                 |
| Response                    | 4               | 7               | 4               | 11              |
| No response                 | 28              | 25              | 28              | 20              |

| End point values            | All patients treated analysis set |  |  |  |
|-----------------------------|-----------------------------------|--|--|--|
| Subject group type          | Subject analysis set              |  |  |  |
| Number of subjects analysed | 127                               |  |  |  |
| Units: subjects             |                                   |  |  |  |
| Response                    | 26                                |  |  |  |
| No response                 | 101                               |  |  |  |

## Statistical analyses

| Statistical analysis title | BT061 25 mg versus placebo |
|----------------------------|----------------------------|
|----------------------------|----------------------------|

Statistical analysis description:

The final analysis of the 2 groups (BT061 25 mg and placebo) of ACR50 response at Week 13 (using last observation carried forward (LOCF)) which was analysed using logistic regression adjusted for centre effect. The adjusted odds ratio (OR) with 95% confidence interval (CI) and the Wald p-value were calculated for the selected active treatment group against the placebo group together with the significance of the centre effect.

|                                         |                       |
|-----------------------------------------|-----------------------|
| Comparison groups                       | BT061 25 mg v Placebo |
| Number of subjects included in analysis | 64                    |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | > 0.05 <sup>[4]</sup> |
| Method                                  | Regression, Logistic  |
| Parameter estimate                      | Odds ratio (OR)       |
| Point estimate                          | 1.96                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 0.51                  |
| upper limit                             | 7.5                   |

Notes:

[4] - Wald X2 p-value = 0.3256 and Fisher 2-sided p-value = 0.5092. There was no statistically significant difference in ACR50 response rate versus placebo group.

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | BT061 50 mg versus placebo |
|-----------------------------------|----------------------------|

Statistical analysis description:

The primary analysis is the final analysis of the 2 groups (BT061 50 mg and placebo) of ACR20 response at Week 13 (using last observation carried forward (LOCF)) which was analysed using logistic regression adjusted for centre effect. The adjusted odds ratio (OR) with 95% confidence interval (CI) and the Wald p-value were calculated for the selected active treatment group against the placebo group together with the significance of the centre effect.

|                                         |                       |
|-----------------------------------------|-----------------------|
| Comparison groups                       | BT061 50 mg v Placebo |
| Number of subjects included in analysis | 64                    |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | > 0.05 [5]            |
| Method                                  | Regression, Logistic  |
| Parameter estimate                      | Odds ratio (OR)       |
| Point estimate                          | 1                     |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 0.23                  |
| upper limit                             | 4.4                   |

Notes:

[5] - Wald X2 p-value = 1.0000 and Fisher 2-sided p-value = 1.0000. There was no statistically significant difference in ACR50 response rate versus placebo group.

|                                   |                            |
|-----------------------------------|----------------------------|
| <b>Statistical analysis title</b> | BT061 75 mg versus placebo |
|-----------------------------------|----------------------------|

Statistical analysis description:

The primary analysis is the final analysis of the 2 groups (BT061 75 mg and placebo) of ACR20 response at Week 13 (using last observation carried forward (LOCF)) which was analysed using logistic regression adjusted for centre effect. The adjusted odds ratio (OR) with 95% confidence interval (CI) and the Wald p-value were calculated for the selected active treatment group against the placebo group together with the significance of the centre effect.

|                                         |                       |
|-----------------------------------------|-----------------------|
| Comparison groups                       | BT061 75 mg v Placebo |
| Number of subjects included in analysis | 63                    |
| Analysis specification                  | Pre-specified         |
| Analysis type                           | superiority           |
| P-value                                 | < 0.05 [6]            |
| Method                                  | Regression, Logistic  |
| Parameter estimate                      | Odds ratio (OR)       |
| Point estimate                          | 3.85                  |
| Confidence interval                     |                       |
| level                                   | 95 %                  |
| sides                                   | 2-sided               |
| lower limit                             | 1.07                  |
| upper limit                             | 13.85                 |

Notes:

[6] - Wald X2 p-value = 0.0390 and Fisher 2-sided p-value = 0.0413. There was statistically significant difference in ACR50 response rate versus placebo group.

## Secondary: ACR 70 Response

|                 |                 |
|-----------------|-----------------|
| End point title | ACR 70 Response |
|-----------------|-----------------|

End point description:

ACR70 response was derived using last observation carried forward and Non-responder Imputation. An ACR70 response was defined as at least 70% improvement in both the tender joint count and the swollen joint count and at least 70% improvement in 3 of the 5 other core set measures including CRP and/or ESR, Investigator assessment of disease activity, Patient assessment of disease activity, Patient assessment of pain, Health Assessment Questionnaire (HAQ).

|                                |           |
|--------------------------------|-----------|
| End point type                 | Secondary |
| End point timeframe:           |           |
| From baseline to study Week 13 |           |

| End point values            | Placebo         | BT061 25 mg     | BT061 50 mg     | BT061 75 mg     |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32              | 32              | 32              | 31              |
| Units: subjects             |                 |                 |                 |                 |
| Response                    | 0               | 1               | 1               | 2               |
| No response                 | 32              | 31              | 31              | 29              |

| End point values            | All patients treated analysis set |  |  |  |
|-----------------------------|-----------------------------------|--|--|--|
| Subject group type          | Subject analysis set              |  |  |  |
| Number of subjects analysed | 127                               |  |  |  |
| Units: subjects             |                                   |  |  |  |
| Response                    | 4                                 |  |  |  |
| No response                 | 123                               |  |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Hybrid ACR Scores

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                   |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Hybrid ACR Scores |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |                   |
| <p>The hybrid ACR is derived at each post-baseline visit from the 7 core set items (components: the tender joint count and the swollen joint count and other core set measures including CRP and/or ESR, Investigator assessment of disease activity, Patient assessment of disease activity, Patient assessment of pain, Health Assessment Questionnaire (HAQ)) by the following steps:</p> <ol style="list-style-type: none"><li>1. For each component:<br/>„Bound %change“ = percentage improvement (defined above) provided this is &gt;-100%;<br/>-100% otherwise (Thus, a deterioration can never go beyond -100%.)</li><li>2. „Mean %change“ = mean of the 7 „bound %change“ values classified as &lt;20, 20-&lt;50, 50-&lt;70 or 70+.</li><li>3. ACR status = „not ACR20“ or „ACR20 but not ACR50“ or „ACR50 but not ACR70“ or „ACR70“ based on the definitions of ACR20, ACR50 and ACR70.</li></ol> |                   |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | Secondary         |

End point timeframe:  
From baseline to study Week 13

| End point values              | Placebo             | BT061 25 mg         | BT061 50 mg          | BT061 75 mg           |
|-------------------------------|---------------------|---------------------|----------------------|-----------------------|
| Subject group type            | Reporting group     | Reporting group     | Reporting group      | Reporting group       |
| Number of subjects analysed   | 31                  | 32                  | 32                   | 30                    |
| Units: scores                 |                     |                     |                      |                       |
| median (full range (min-max)) | 19.99 (5.8 to 70.0) | 37.26 (6.5 to 73.0) | 30.30 (-0.1 to 72.7) | 29.91 (-62.2 to 70.0) |

### Statistical analyses

No statistical analyses for this end point

### Secondary: DAS28 scores

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |              |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | DAS28 scores |
| End point description:<br>Disease activity score for 28 joints (DAS28) combines information from swollen joints, tender joints, acute phase response, and general health into one continuous measure of RA inflammation. DAS28 criteria are a modified version of DAS, which has a reduced and non-graded joint count. It consists of a 28 tender joint count (range 0 to 28), a 28 swollen joint count (range 0 to 28), ESR, and an optional general health assessment on a VAS (range 0 to 100), which will be assessed for this study. DAS28 has a continuous scale ranging from 0 to 10. The level of disease activity is interpreted as low ( $\text{DAS28} \leq 3.2$ ), moderate ( $3.2 < \text{DAS28} \leq 5.1$ ), and high ( $\text{DAS28} > 5.1$ ). Higher DAS28 scores means worse disease activity. |              |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Secondary    |
| End point timeframe:<br>From baseline to study Week 13                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |              |

| End point values              | Placebo           | BT061 25 mg     | BT061 50 mg       | BT061 75 mg       |
|-------------------------------|-------------------|-----------------|-------------------|-------------------|
| Subject group type            | Reporting group   | Reporting group | Reporting group   | Reporting group   |
| Number of subjects analysed   | 32                | 32              | 32                | 31                |
| Units: scores                 |                   |                 |                   |                   |
| median (full range (min-max)) | 5.03 (1.8 to 7.1) | 4.25 (1.9 to 7) | 4.97 (3.1 to 6.4) | 4.91 (1.9 to 7.3) |

### Statistical analyses

No statistical analyses for this end point

### Secondary: EULAR Response

|                 |                |
|-----------------|----------------|
| End point title | EULAR Response |
|-----------------|----------------|



End point description:

The EULAR response is defined at each post-baseline visit in terms of Disease Activity Scores (DAS28) change from baseline. If the score is missing it will be derived using LOCF.

If DAS28 at endpoint  $\leq 3.2$ , the response was categorized based on improvement (reduction) in DAS28 from baseline  $>1.2$  (Good),  $> 0.6$  and  $\leq 1.2$  (Moderate) and  $\leq 0.6$  (None).

If DAS28 at endpoint  $> 3.2$  and  $\leq 5.1$ , the response was categorized based on improvement (reduction) in DAS28 from baseline  $>1.2$  (Moderate),  $> 0.6$  and  $\leq 1.2$  (Moderate) and  $\leq 0.6$  (None).

If DAS28 at endpoint  $> 5.1$ , the response was categorized based on improvement (reduction) in DAS28 from baseline  $>1.2$  (Moderate),  $> 0.6$  and  $\leq 1.2$  (None) and  $\leq 0.6$  (None).

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

End point timeframe:

From baseline to study Week 13

| End point values            | Placebo         | BT061 25 mg     | BT061 50 mg     | BT061 75 mg     |
|-----------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type          | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 32              | 32              | 32              | 31              |
| Units: subjects             |                 |                 |                 |                 |
| Good Response               | 1               | 6               | 1               | 5               |
| Moderate Response           | 18              | 20              | 20              | 20              |
| None                        | 13              | 6               | 11              | 6               |

## Statistical analyses

No statistical analyses for this end point

## Secondary: CDAI scores

|                 |             |
|-----------------|-------------|
| End point title | CDAI scores |
|-----------------|-------------|

End point description:

Clinical Disease Activity Index (CDAI) was calculated at each post-baseline visit as the sum of the number of tender joints (t28) from the 28 joints shaded on the CRF, the number of swollen joints (sw28), the disease activity (patient's global assessment) and the disease activity (physician's global assessment).

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

End point timeframe:

From baseline to study Week 13

| End point values              | Placebo             | BT061 25 mg         | BT061 50 mg         | BT061 75 mg        |
|-------------------------------|---------------------|---------------------|---------------------|--------------------|
| Subject group type            | Reporting group     | Reporting group     | Reporting group     | Reporting group    |
| Number of subjects analysed   | 32                  | 32                  | 32                  | 31                 |
| Units: scores                 |                     |                     |                     |                    |
| median (full range (min-max)) | 22.65 (4.3 to 44.3) | 13.05 (1.7 to 46.5) | 21.35 (4.7 to 40.6) | 18.4 (1.6 to 49.7) |

## Statistical analyses

No statistical analyses for this end point

### Secondary: SDAI Scores

|                                                                                                                                                                                                                                                                                                                                                             |             |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|
| End point title                                                                                                                                                                                                                                                                                                                                             | SDAI Scores |
| End point description:<br>The Simplified Disease Activity Index (SDAI) was calculated at each post-baseline visit as the sum of the Clinical Disease Activity Index (CDAI) and the C-reactive protein (CRP) (in mg/dL).<br>If any components of the SDAI are missing then the score will be missing. If the score is missing it will be derived using LOCF. |             |
| End point type                                                                                                                                                                                                                                                                                                                                              | Secondary   |
| End point timeframe:<br>From baseline to study Week 13                                                                                                                                                                                                                                                                                                      |             |

| End point values              | Placebo            | BT061 25 mg        | BT061 50 mg         | BT061 75 mg     |
|-------------------------------|--------------------|--------------------|---------------------|-----------------|
| Subject group type            | Reporting group    | Reporting group    | Reporting group     | Reporting group |
| Number of subjects analysed   | 32                 | 32                 | 32                  | 31              |
| Units: scores                 |                    |                    |                     |                 |
| median (full range (min-max)) | 23.8 (4.4 to 47.4) | 13.8 (1.8 to 46.8) | 21.95 (4.8 to 40.7) | 19 (1.7 to 56)  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Tender Joint count change from Baseline

|                                                                                                                                                                                                                                                                                                                           |                                         |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                           | Tender Joint count change from Baseline |
| End point description:<br>Single Component of ACR for RA assesses: 68 joints for tenderness.<br>Mean levels and percentage changes from baseline were plotted against weeks since start of treatment by treatment group.<br><br>Minus percentage changes from baseline means improvement and plus change means worsening. |                                         |
| End point type                                                                                                                                                                                                                                                                                                            | Secondary                               |
| End point timeframe:<br>From baseline to study Week 13                                                                                                                                                                                                                                                                    |                                         |

| End point values                     | Placebo               | BT061 25 mg           | BT061 50 mg           | BT061 75 mg           |
|--------------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Subject group type                   | Reporting group       | Reporting group       | Reporting group       | Reporting group       |
| Number of subjects analysed          | 32                    | 32                    | 32                    | 31                    |
| Units: percent change                |                       |                       |                       |                       |
| arithmetic mean (standard deviation) | -38.71 ( $\pm$ 38.48) | -56.09 ( $\pm$ 31.37) | -47.22 ( $\pm$ 25.67) | -46.16 ( $\pm$ 36.33) |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Swollen Joint Count change from Baseline

|                 |                                          |
|-----------------|------------------------------------------|
| End point title | Swollen Joint Count change from Baseline |
|-----------------|------------------------------------------|

End point description:

Single Component of ACR for RA assesses: 68 joints for swollenness.

Mean levels and percentage changes from baseline were plotted against weeks since start of treatment by treatment group.

Minus percentage changes from baseline means improvement and plus change means worsening.

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

End point timeframe:

From baseline to study Week 13

| End point values                     | Placebo          | BT061 25 mg      | BT061 50 mg      | BT061 75 mg      |
|--------------------------------------|------------------|------------------|------------------|------------------|
| Subject group type                   | Reporting group  | Reporting group  | Reporting group  | Reporting group  |
| Number of subjects analysed          | 32               | 32               | 32               | 31               |
| Units: percent change                |                  |                  |                  |                  |
| arithmetic mean (standard deviation) | -42.80 (± 34.28) | -67.90 (± 27.28) | -59.89 (± 27.56) | -60.52 (± 37.81) |

## Statistical analyses

No statistical analyses for this end point

### Secondary: C-reactive protein change from Baseline

|                 |                                         |
|-----------------|-----------------------------------------|
| End point title | C-reactive protein change from Baseline |
|-----------------|-----------------------------------------|

End point description:

Mean levels of C-reactive protein (CRP in mg/L) and percentage changes from baseline will be plotted against weeks since start of treatment by treatment group.

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

End point timeframe:

From baseline to study Week 13

| End point values                     | Placebo          | BT061 25 mg     | BT061 50 mg      | BT061 75 mg      |
|--------------------------------------|------------------|-----------------|------------------|------------------|
| Subject group type                   | Reporting group  | Reporting group | Reporting group  | Reporting group  |
| Number of subjects analysed          | 32               | 32              | 32               | 31               |
| Units: Percent change                |                  |                 |                  |                  |
| arithmetic mean (standard deviation) | 31.85 (± 179.58) | 10.33 (± 83.99) | 41.98 (± 160.30) | 37.11 (± 154.61) |

## Statistical analyses

No statistical analyses for this end point

### Secondary: ESR change from Baseline

|                                                                                                                                                                                            |                          |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| End point title                                                                                                                                                                            | ESR change from Baseline |
| End point description:<br>Erythrocyte Sedimentation Rate (ESR) Mean levels and percentage changes from baseline will be plotted against weeks since start of treatment by treatment group. |                          |
| End point type                                                                                                                                                                             | Secondary                |
| End point timeframe:<br>From baseline to study Week 13                                                                                                                                     |                          |

| End point values                     | Placebo          | BT061 25 mg      | BT061 50 mg      | BT061 75 mg      |
|--------------------------------------|------------------|------------------|------------------|------------------|
| Subject group type                   | Reporting group  | Reporting group  | Reporting group  | Reporting group  |
| Number of subjects analysed          | 32               | 32               | 32               | 31               |
| Units: percent change                |                  |                  |                  |                  |
| arithmetic mean (standard deviation) | -36.72 (± 32.23) | -43.49 (± 26.62) | -28.08 (± 40.20) | -43.46 (± 33.83) |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change of VAS for Global Disease Activity (Investigator) from Baseline

|                                                                                                                                                                                                                          |                                                                        |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                          | Change of VAS for Global Disease Activity (Investigator) from Baseline |
| End point description:<br>Mean levels and percentage changes from baseline for ACR component (VAS for global disease activity (investigator)) will be plotted against weeks since start of treatment by treatment group. |                                                                        |
| End point type                                                                                                                                                                                                           | Secondary                                                              |
| End point timeframe:<br>From baseline to study Week 13                                                                                                                                                                   |                                                                        |

| End point values                     | Placebo               | BT061 25 mg           | BT061 50 mg           | BT061 75 mg           |
|--------------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Subject group type                   | Reporting group       | Reporting group       | Reporting group       | Reporting group       |
| Number of subjects analysed          | 32                    | 32                    | 32                    | 31                    |
| Units: percent change                |                       |                       |                       |                       |
| arithmetic mean (standard deviation) | -39.49 ( $\pm$ 28.93) | -49.75 ( $\pm$ 32.84) | -40.56 ( $\pm$ 30.18) | -42.11 ( $\pm$ 31.36) |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change of VAS for Global Disease Activity (Patient) from Baseline

|                 |                                                                   |
|-----------------|-------------------------------------------------------------------|
| End point title | Change of VAS for Global Disease Activity (Patient) from Baseline |
|-----------------|-------------------------------------------------------------------|

End point description:

Mean levels and percentage changes from baseline for ACR component (VAS for global disease activity (patient)) will be plotted against weeks since start of treatment by treatment group.

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

End point timeframe:

From baseline to study Week 13

| End point values                     | Placebo               | BT061 25 mg           | BT061 50 mg           | BT061 75 mg           |
|--------------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Subject group type                   | Reporting group       | Reporting group       | Reporting group       | Reporting group       |
| Number of subjects analysed          | 32                    | 32                    | 32                    | 31                    |
| Units: percent change                |                       |                       |                       |                       |
| arithmetic mean (standard deviation) | -25.88 ( $\pm$ 27.03) | -19.09 ( $\pm$ 44.67) | -21.55 ( $\pm$ 41.28) | -31.04 ( $\pm$ 43.71) |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change of VAS for Patient's Pain from Baseline

|                 |                                                |
|-----------------|------------------------------------------------|
| End point title | Change of VAS for Patient's Pain from Baseline |
|-----------------|------------------------------------------------|

End point description:

Mean levels and percentage changes from baseline for ACR component (VAS for Patient's Pain) will be plotted against weeks since start of treatment by treatment group.

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

End point timeframe:

From baseline to study Week 13

| End point values                     | Placebo          | BT061 25 mg      | BT061 50 mg      | BT061 75 mg      |
|--------------------------------------|------------------|------------------|------------------|------------------|
| Subject group type                   | Reporting group  | Reporting group  | Reporting group  | Reporting group  |
| Number of subjects analysed          | 32               | 32               | 32               | 31               |
| Units: percent change                |                  |                  |                  |                  |
| arithmetic mean (standard deviation) | -22.48 (± 37.82) | -21.03 (± 39.60) | -25.16 (± 39.23) | -40.27 (± 30.39) |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change of Health Assessment Questionnaire from Baseline

|                                                                                                                                                                                                           |                                                         |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------|
| End point title                                                                                                                                                                                           | Change of Health Assessment Questionnaire from Baseline |
| End point description:<br>Mean levels and percentage changes from baseline for ACR component (Health Assessment Questionnaire) will be plotted against weeks since start of treatment by treatment group. |                                                         |
| End point type                                                                                                                                                                                            | Secondary                                               |
| End point timeframe:<br>From baseline to study Week 13                                                                                                                                                    |                                                         |

| End point values                     | Placebo          | BT061 25 mg     | BT061 50 mg      | BT061 75 mg      |
|--------------------------------------|------------------|-----------------|------------------|------------------|
| Subject group type                   | Reporting group  | Reporting group | Reporting group  | Reporting group  |
| Number of subjects analysed          | 32               | 32              | 32               | 31               |
| Units: percent change                |                  |                 |                  |                  |
| arithmetic mean (standard deviation) | -20.67 (± 40.62) | -0.63 (± 96.15) | -20.99 (± 32.15) | 14.27 (± 196.78) |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change of FACIT-Fatigue Questionnaire Total Score from Baseline

|                                                                                                                                                                                                                       |                                                                 |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------|
| End point title                                                                                                                                                                                                       | Change of FACIT-Fatigue Questionnaire Total Score from Baseline |
| End point description:<br>Mean levels and percent changes of Functional Assessment Of Chronic Illness Therapy (FACIT) - Fatigue Questionnaire were plotted against weeks since start of treatment by treatment group. |                                                                 |
| End point type                                                                                                                                                                                                        | Secondary                                                       |
| End point timeframe:<br>From baseline to study Week 13                                                                                                                                                                |                                                                 |

| <b>End point values</b>              | Placebo         | BT061 25 mg     | BT061 50 mg     | BT061 75 mg     |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type                   | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed          | 32              | 32              | 32              | 31              |
| Units: percent change                |                 |                 |                 |                 |
| arithmetic mean (standard deviation) | 23.57 (± 50.69) | 15.19 (± 47.91) | 25.51 (± 34.08) | 22.25 (± 39.88) |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From signed informed consent to the end of follow up (up to 30 weeks)

Adverse event reporting additional description:

Only serious nontreatment- emergent AEs that were related to study procedures have been collected. An AE that occurs from the time the patient receives his/her first dose of study drug until his/her final follow up visit, was treatment-emergent AE (TEAE). All TEAEs will be collected.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 14.0 |
|--------------------|------|

### Reporting groups

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | All Patients Treated Analysis Set |
|-----------------------|-----------------------------------|

Reporting group description:

The All Patients Treated Analysis Set (APTAS) was defined as those patients who are randomised to treatment and receive at least one dose of study medication (BT061 or placebo).

The APTAS has been used for all safety analyses. Patients who received the wrong treatment in error were analyzed as treated for safety analyses.

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects in Placebo group received sc. 2 ml placebo once weekly (0 mg BT061) for 12 weeks.

|                       |             |
|-----------------------|-------------|
| Reporting group title | BT061 25 mg |
|-----------------------|-------------|

Reporting group description:

Subjects in BT061 25 mg group received sc. 1 ml placebo plus 1 ml BT061 25mg/ml once weekly (25 mg BT061) for 12 weeks.

|                       |             |
|-----------------------|-------------|
| Reporting group title | BT061 50 mg |
|-----------------------|-------------|

Reporting group description:

Subjects in BT061 25 mg group received sc. 1 ml placebo plus 1 ml BT061 50 mg/ml once weekly (50 mg BT061) for 12 weeks.

|                       |             |
|-----------------------|-------------|
| Reporting group title | BT061 75 mg |
|-----------------------|-------------|

Reporting group description:

Subjects in BT061 75 mg group received sc. 1 ml BT061 25mg/ml plus 1 ml BT061 50mg/ml once weekly (75 mg BT061) for 12 weeks.

| Serious adverse events                            | All Patients Treated Analysis Set                                                                                               | Placebo        | BT061 25 mg    |
|---------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|----------------|----------------|
| Total subjects affected by serious adverse events |                                                                                                                                 |                |                |
| subjects affected / exposed                       | 6 / 127 (4.72%)                                                                                                                 | 2 / 32 (6.25%) | 1 / 32 (3.13%) |
| number of deaths (all causes)                     | 1                                                                                                                               | 0              | 1              |
| number of deaths resulting from adverse events    | 1                                                                                                                               | 0              | 1              |
| Vascular disorders                                |                                                                                                                                 |                |                |
| Hypertension                                      | Additional description: UNCONTROLLED HYPERTENSION: onset on study day 23, duration of 9 days and resolved. Severity was severe. |                |                |



|                                                                                                                          |                                                                                                                                              |                |                |
|--------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|----------------|----------------|
| subjects affected / exposed                                                                                              | 1 / 127 (0.79%)                                                                                                                              | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all                                                                          | 1 / 1                                                                                                                                        | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                                                                               | 0 / 0                                                                                                                                        | 0 / 0          | 0 / 0          |
| <b>Gastrointestinal disorders</b>                                                                                        |                                                                                                                                              |                |                |
| Enterocolitis                                                                                                            | Additional description: Enterocolitis: onset on study day 142, duration of 6 days and resolved; Severity was moderate.                       |                |                |
| subjects affected / exposed                                                                                              | 1 / 127 (0.79%)                                                                                                                              | 1 / 32 (3.13%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all                                                                          | 0 / 1                                                                                                                                        | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all                                                                               | 0 / 0                                                                                                                                        | 0 / 0          | 0 / 0          |
| <b>Gastritis</b>                                                                                                         |                                                                                                                                              |                |                |
| Additional description: Acute Gastritis: onset on study day 142, duration of 6 days and resolved; Severity was moderate. |                                                                                                                                              |                |                |
| subjects affected / exposed                                                                                              | 1 / 127 (0.79%)                                                                                                                              | 1 / 32 (3.13%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all                                                                          | 0 / 1                                                                                                                                        | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all                                                                               | 0 / 0                                                                                                                                        | 0 / 0          | 0 / 0          |
| <b>Musculoskeletal and connective tissue disorders</b>                                                                   |                                                                                                                                              |                |                |
| Rheumatoid arthritis                                                                                                     | Additional description: RA EXACERBATION                                                                                                      |                |                |
| subjects affected / exposed                                                                                              | 2 / 127 (1.57%)                                                                                                                              | 1 / 32 (3.13%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all                                                                          | 0 / 2                                                                                                                                        | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all                                                                               | 0 / 0                                                                                                                                        | 0 / 0          | 0 / 0          |
| <b>Infections and infestations</b>                                                                                       |                                                                                                                                              |                |                |
| EXTREMITIES GANGRENE                                                                                                     | Additional description: GANGRENE OF TOES OF THE LEFT: onset on study day 157, duration of 9 days and resulted in death. Severity was severe. |                |                |
| subjects affected / exposed                                                                                              | 1 / 127 (0.79%)                                                                                                                              | 0 / 32 (0.00%) | 1 / 32 (3.13%) |
| occurrences causally related to treatment / all                                                                          | 0 / 1                                                                                                                                        | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all                                                                               | 0 / 1                                                                                                                                        | 0 / 0          | 0 / 1          |
| PNEUMONIA                                                                                                                | Additional description: PNEUMONIA BILATERAL: onset on study day 67, duration of 13 days and resolved. Severity was moderate.                 |                |                |
| subjects affected / exposed                                                                                              | 1 / 127 (0.79%)                                                                                                                              | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences causally related to treatment / all                                                                          | 0 / 1                                                                                                                                        | 0 / 0          | 0 / 0          |
| deaths causally related to treatment / all                                                                               | 0 / 0                                                                                                                                        | 0 / 0          | 0 / 0          |

|                                                   |                                                                                                                                 |                |  |
|---------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|----------------|--|
| <b>Serious adverse events</b>                     | BT061 50 mg                                                                                                                     | BT061 75 mg    |  |
| Total subjects affected by serious adverse events |                                                                                                                                 |                |  |
| subjects affected / exposed                       | 1 / 32 (3.13%)                                                                                                                  | 2 / 31 (6.45%) |  |
| number of deaths (all causes)                     | 0                                                                                                                               | 0              |  |
| number of deaths resulting from adverse events    | 0                                                                                                                               | 0              |  |
| <b>Vascular disorders</b>                         |                                                                                                                                 |                |  |
| Hypertension                                      | Additional description: UNCONTROLLED HYPERTENSION: onset on study day 23, duration of 9 days and resolved. Severity was severe. |                |  |

|                                                                                                                              |                                                                                                                                              |                |  |
|------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|----------------|--|
| subjects affected / exposed                                                                                                  | 0 / 32 (0.00%)                                                                                                                               | 1 / 31 (3.23%) |  |
| occurrences causally related to treatment / all                                                                              | 0 / 0                                                                                                                                        | 1 / 1          |  |
| deaths causally related to treatment / all                                                                                   | 0 / 0                                                                                                                                        | 0 / 0          |  |
| <b>Gastrointestinal disorders</b>                                                                                            |                                                                                                                                              |                |  |
| Enterocolitis                                                                                                                | Additional description: Enterocolitis: onset on study day 142, duration of 6 days and resolved; Severity was moderate.                       |                |  |
| subjects affected / exposed                                                                                                  | 0 / 32 (0.00%)                                                                                                                               | 0 / 31 (0.00%) |  |
| occurrences causally related to treatment / all                                                                              | 0 / 0                                                                                                                                        | 0 / 0          |  |
| deaths causally related to treatment / all                                                                                   | 0 / 0                                                                                                                                        | 0 / 0          |  |
| <b>Gastritis</b>                                                                                                             |                                                                                                                                              |                |  |
| Additional description: Acute Gastritis: onset on study day 142, duration of 6 days and resolved; Severity was moderate.     |                                                                                                                                              |                |  |
| subjects affected / exposed                                                                                                  | 0 / 32 (0.00%)                                                                                                                               | 0 / 31 (0.00%) |  |
| occurrences causally related to treatment / all                                                                              | 0 / 0                                                                                                                                        | 0 / 0          |  |
| deaths causally related to treatment / all                                                                                   | 0 / 0                                                                                                                                        | 0 / 0          |  |
| <b>Musculoskeletal and connective tissue disorders</b>                                                                       |                                                                                                                                              |                |  |
| Rheumatoid arthritis                                                                                                         | Additional description: RA EXACERBATION                                                                                                      |                |  |
| subjects affected / exposed                                                                                                  | 0 / 32 (0.00%)                                                                                                                               | 1 / 31 (3.23%) |  |
| occurrences causally related to treatment / all                                                                              | 0 / 0                                                                                                                                        | 0 / 1          |  |
| deaths causally related to treatment / all                                                                                   | 0 / 0                                                                                                                                        | 0 / 0          |  |
| <b>Infections and infestations</b>                                                                                           |                                                                                                                                              |                |  |
| EXTREMITIES GANGRENE                                                                                                         | Additional description: GANGRENE OF TOES OF THE LEFT: onset on study day 157, duration of 9 days and resulted in death. Severity was severe. |                |  |
| subjects affected / exposed                                                                                                  | 0 / 32 (0.00%)                                                                                                                               | 0 / 31 (0.00%) |  |
| occurrences causally related to treatment / all                                                                              | 0 / 0                                                                                                                                        | 0 / 0          |  |
| deaths causally related to treatment / all                                                                                   | 0 / 0                                                                                                                                        | 0 / 0          |  |
| <b>PNEUMONIA</b>                                                                                                             |                                                                                                                                              |                |  |
| Additional description: PNEUMONIA BILATERAL: onset on study day 67, duration of 13 days and resolved. Severity was moderate. |                                                                                                                                              |                |  |
| subjects affected / exposed                                                                                                  | 1 / 32 (3.13%)                                                                                                                               | 0 / 31 (0.00%) |  |
| occurrences causally related to treatment / all                                                                              | 0 / 1                                                                                                                                        | 0 / 0          |  |
| deaths causally related to treatment / all                                                                                   | 0 / 0                                                                                                                                        | 0 / 0          |  |

Frequency threshold for reporting non-serious adverse events: 0 %

| Non-serious adverse events                            | All Patients Treated Analysis Set | Placebo          | BT061 25 mg      |
|-------------------------------------------------------|-----------------------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events |                                   |                  |                  |
| subjects affected / exposed                           | 80 / 127 (62.99%)                 | 20 / 32 (62.50%) | 16 / 32 (50.00%) |

|                                                      |                 |                |                |
|------------------------------------------------------|-----------------|----------------|----------------|
| Vascular disorders                                   |                 |                |                |
| Haematoma                                            |                 |                |                |
| subjects affected / exposed                          | 1 / 127 (0.79%) | 1 / 32 (3.13%) | 0 / 32 (0.00%) |
| occurrences (all)                                    | 1               | 1              | 0              |
| Hypertension                                         |                 |                |                |
| subjects affected / exposed                          | 1 / 127 (0.79%) | 1 / 32 (3.13%) | 0 / 32 (0.00%) |
| occurrences (all)                                    | 1               | 1              | 0              |
| Pelvic venous thrombosis                             |                 |                |                |
| subjects affected / exposed                          | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 1 / 32 (3.13%) |
| occurrences (all)                                    | 1               | 0              | 1              |
| Thrombophlebitis superficial                         |                 |                |                |
| subjects affected / exposed                          | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 1 / 32 (3.13%) |
| occurrences (all)                                    | 1               | 0              | 1              |
| General disorders and administration site conditions |                 |                |                |
| Influenza like illness                               |                 |                |                |
| subjects affected / exposed                          | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)                                    | 1               | 0              | 0              |
| Oedema peripheral                                    |                 |                |                |
| subjects affected / exposed                          | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)                                    | 1               | 0              | 0              |
| Pyrexia                                              |                 |                |                |
| subjects affected / exposed                          | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)                                    | 4               | 0              | 0              |
| Reproductive system and breast disorders             |                 |                |                |
| Spermatocele                                         |                 |                |                |
| subjects affected / exposed                          | 1 / 127 (0.79%) | 1 / 32 (3.13%) | 0 / 32 (0.00%) |
| occurrences (all)                                    | 1               | 1              | 0              |
| Varicocele                                           |                 |                |                |
| subjects affected / exposed                          | 1 / 127 (0.79%) | 1 / 32 (3.13%) | 0 / 32 (0.00%) |
| occurrences (all)                                    | 1               | 1              | 0              |
| Respiratory, thoracic and mediastinal disorders      |                 |                |                |
| Cough                                                |                 |                |                |
| subjects affected / exposed                          | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)                                    | 1               | 0              | 0              |
| Dyspnoea                                             |                 |                |                |

|                                                                                                          |                      |                     |                     |
|----------------------------------------------------------------------------------------------------------|----------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                                         | 1 / 127 (0.79%)<br>1 | 1 / 32 (3.13%)<br>1 | 0 / 32 (0.00%)<br>0 |
| Dyspnoea exertional<br>subjects affected / exposed<br>occurrences (all)                                  | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Psychiatric disorders<br>Depressed mood<br>subjects affected / exposed<br>occurrences (all)              | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 1 / 32 (3.13%)<br>1 |
| Investigations<br>Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Blood albumin decreased<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 127 (0.79%)<br>2 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Cytomegalovirus test positive<br>subjects affected / exposed<br>occurrences (all)                        | 2 / 127 (1.57%)<br>2 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Epstein-Barr virus antibody positive<br>subjects affected / exposed<br>occurrences (all)                 | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 1 / 32 (3.13%)<br>1 |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 127 (0.79%)<br>1 | 1 / 32 (3.13%)<br>1 | 0 / 32 (0.00%)<br>0 |
| Mycobacterium tuberculosis complex<br>test positiv<br>subjects affected / exposed<br>occurrences (all)   | 5 / 127 (3.94%)<br>5 | 3 / 32 (9.38%)<br>3 | 1 / 32 (3.13%)<br>1 |
| Protein total decreased<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Transaminases increased                                                                                  |                      |                     |                     |

|                                                                                      |                      |                     |                     |
|--------------------------------------------------------------------------------------|----------------------|---------------------|---------------------|
| subjects affected / exposed<br>occurrences (all)                                     | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Epstein-Barr virus test positive<br>subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Injury, poisoning and procedural complications                                       |                      |                     |                     |
| Fall                                                                                 |                      |                     |                     |
| subjects affected / exposed<br>occurrences (all)                                     | 2 / 127 (1.57%)<br>2 | 1 / 32 (3.13%)<br>1 | 0 / 32 (0.00%)<br>0 |
| Rib fracture                                                                         |                      |                     |                     |
| subjects affected / exposed<br>occurrences (all)                                     | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Traumatic haematoma                                                                  |                      |                     |                     |
| subjects affected / exposed<br>occurrences (all)                                     | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Cardiac disorders                                                                    |                      |                     |                     |
| Atrioventricular block first degree                                                  |                      |                     |                     |
| subjects affected / exposed<br>occurrences (all)                                     | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Nervous system disorders                                                             |                      |                     |                     |
| Cervicobrachial syndrome                                                             |                      |                     |                     |
| subjects affected / exposed<br>occurrences (all)                                     | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Headache                                                                             |                      |                     |                     |
| subjects affected / exposed<br>occurrences (all)                                     | 8 / 127 (6.30%)<br>9 | 3 / 32 (9.38%)<br>4 | 3 / 32 (9.38%)<br>3 |
| Blood and lymphatic system disorders                                                 |                      |                     |                     |
| Anaemia                                                                              |                      |                     |                     |
| subjects affected / exposed<br>occurrences (all)                                     | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 1 / 32 (3.13%)<br>1 |
| Leukopenia                                                                           |                      |                     |                     |
| subjects affected / exposed<br>occurrences (all)                                     | 1 / 127 (0.79%)<br>0 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Lymphadenopathy                                                                      |                      |                     |                     |
| subjects affected / exposed<br>occurrences (all)                                     | 1 / 127 (0.79%)<br>1 | 1 / 32 (3.13%)<br>1 | 0 / 32 (0.00%)<br>0 |

|                                        |                 |                |                |
|----------------------------------------|-----------------|----------------|----------------|
| Ear and labyrinth disorders            |                 |                |                |
| Vertigo                                |                 |                |                |
| subjects affected / exposed            | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)                      | 1               | 0              | 0              |
| Eye disorders                          |                 |                |                |
| Conjunctivitis                         |                 |                |                |
| subjects affected / exposed            | 1 / 127 (0.79%) | 1 / 32 (3.13%) | 0 / 32 (0.00%) |
| occurrences (all)                      | 1               | 1              | 0              |
| Sicca syndrome                         |                 |                |                |
| subjects affected / exposed            | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)                      | 1               | 0              | 0              |
| Gastrointestinal disorders             |                 |                |                |
| Abdominal pain                         |                 |                |                |
| subjects affected / exposed            | 1 / 127 (0.79%) | 1 / 32 (3.13%) | 0 / 32 (0.00%) |
| occurrences (all)                      | 1               | 1              | 0              |
| Aphthous stomatitis                    |                 |                |                |
| subjects affected / exposed            | 1 / 127 (0.79%) | 1 / 32 (3.13%) | 0 / 32 (0.00%) |
| occurrences (all)                      | 1               | 1              | 0              |
| Diarrhoea                              |                 |                |                |
| subjects affected / exposed            | 2 / 127 (1.57%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)                      | 2               | 0              | 0              |
| Dyspepsia                              |                 |                |                |
| subjects affected / exposed            | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)                      | 1               | 0              | 0              |
| Glossodynia                            |                 |                |                |
| subjects affected / exposed            | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)                      | 1               | 0              | 0              |
| Nausea                                 |                 |                |                |
| subjects affected / exposed            | 3 / 127 (2.36%) | 0 / 32 (0.00%) | 1 / 32 (3.13%) |
| occurrences (all)                      | 3               | 0              | 1              |
| Steatorrhoea                           |                 |                |                |
| subjects affected / exposed            | 1 / 127 (0.79%) | 1 / 32 (3.13%) | 0 / 32 (0.00%) |
| occurrences (all)                      | 1               | 1              | 0              |
| Stomatitis                             |                 |                |                |
| subjects affected / exposed            | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)                      | 1               | 0              | 0              |
| Skin and subcutaneous tissue disorders |                 |                |                |

|                                                                                                                   |                      |                     |                     |
|-------------------------------------------------------------------------------------------------------------------|----------------------|---------------------|---------------------|
| Ecchymosis<br>subjects affected / exposed<br>occurrences (all)                                                    | 1 / 127 (0.79%)<br>1 | 1 / 32 (3.13%)<br>1 | 0 / 32 (0.00%)<br>0 |
| Rash<br>subjects affected / exposed<br>occurrences (all)                                                          | 3 / 127 (2.36%)<br>3 | 2 / 32 (6.25%)<br>2 | 0 / 32 (0.00%)<br>0 |
| Rash erythematous<br>subjects affected / exposed<br>occurrences (all)                                             | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 1 / 32 (3.13%)<br>1 |
| Rash papular<br>subjects affected / exposed<br>occurrences (all)                                                  | 1 / 127 (0.79%)<br>1 | 1 / 32 (3.13%)<br>1 | 0 / 32 (0.00%)<br>0 |
| Renal and urinary disorders<br>Dysuria<br>subjects affected / exposed<br>occurrences (all)                        | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)                                                    | 2 / 127 (1.57%)<br>2 | 0 / 32 (0.00%)<br>0 | 1 / 32 (3.13%)<br>1 |
| Haemoglobinuria<br>subjects affected / exposed<br>occurrences (all)                                               | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Leukocyturia<br>subjects affected / exposed<br>occurrences (all)                                                  | 1 / 127 (0.79%)<br>1 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Endocrine disorders<br>Cushing's syndrome<br>subjects affected / exposed<br>occurrences (all)                     | 1 / 127 (0.79%)<br>1 | 1 / 32 (3.13%)<br>1 | 0 / 32 (0.00%)<br>0 |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 1 / 127 (0.79%)<br>2 | 0 / 32 (0.00%)<br>0 | 0 / 32 (0.00%)<br>0 |
| Back pain<br>subjects affected / exposed<br>occurrences (all)                                                     | 6 / 127 (4.72%)<br>7 | 1 / 32 (3.13%)<br>1 | 1 / 32 (3.13%)<br>1 |

|                             |                 |                |                |
|-----------------------------|-----------------|----------------|----------------|
| Bone pain                   |                 |                |                |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)           | 1               | 0              | 0              |
| Bursitis                    |                 |                |                |
| subjects affected / exposed | 1 / 127 (0.79%) | 1 / 32 (3.13%) | 0 / 32 (0.00%) |
| occurrences (all)           | 1               | 1              | 0              |
| Joint swelling              |                 |                |                |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)           | 3               | 0              | 0              |
| Muscle spasms               |                 |                |                |
| subjects affected / exposed | 2 / 127 (1.57%) | 1 / 32 (3.13%) | 1 / 32 (3.13%) |
| occurrences (all)           | 2               | 1              | 1              |
| Musculoskeletal pain        |                 |                |                |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)           | 1               | 0              | 0              |
| Osteopenia                  |                 |                |                |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)           | 1               | 0              | 0              |
| Rheumatoid arthritis        |                 |                |                |
| subjects affected / exposed | 8 / 127 (6.30%) | 2 / 32 (6.25%) | 0 / 32 (0.00%) |
| occurrences (all)           | 10              | 3              | 0              |
| Infections and infestations |                 |                |                |
| Abscess                     |                 |                |                |
| subjects affected / exposed | 1 / 127 (0.79%) | 1 / 32 (3.13%) | 0 / 32 (0.00%) |
| occurrences (all)           | 1               | 1              | 0              |
| Acute tonsillitis           |                 |                |                |
| subjects affected / exposed | 2 / 127 (1.57%) | 0 / 32 (0.00%) | 1 / 32 (3.13%) |
| occurrences (all)           | 2               | 0              | 1              |
| Bronchitis                  |                 |                |                |
| subjects affected / exposed | 4 / 127 (3.15%) | 0 / 32 (0.00%) | 2 / 32 (6.25%) |
| occurrences (all)           | 4               | 0              | 2              |
| Cystitis                    |                 |                |                |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)           | 1               | 0              | 0              |
| Cytomegalovirus infection   |                 |                |                |



|                             |                  |                |                |
|-----------------------------|------------------|----------------|----------------|
| subjects affected / exposed | 1 / 127 (0.79%)  | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)           | 1                | 0              | 0              |
| Dysentery                   |                  |                |                |
| subjects affected / exposed | 1 / 127 (0.79%)  | 0 / 32 (0.00%) | 1 / 32 (3.13%) |
| occurrences (all)           | 1                | 0              | 1              |
| Herpes simplex              |                  |                |                |
| subjects affected / exposed | 3 / 127 (2.36%)  | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)           | 4                | 0              | 0              |
| Herpes zoster               |                  |                |                |
| subjects affected / exposed | 1 / 127 (0.79%)  | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)           | 1                | 0              | 0              |
| Laryngitis                  |                  |                |                |
| subjects affected / exposed | 1 / 127 (0.79%)  | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)           | 1                | 0              | 0              |
| Nasopharyngitis             |                  |                |                |
| subjects affected / exposed | 12 / 127 (9.45%) | 2 / 32 (6.25%) | 2 / 32 (6.25%) |
| occurrences (all)           | 12               | 2              | 2              |
| Oral herpes                 |                  |                |                |
| subjects affected / exposed | 1 / 127 (0.79%)  | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)           | 1                | 0              | 0              |
| Pneumonia                   |                  |                |                |
| subjects affected / exposed | 1 / 127 (0.79%)  | 1 / 32 (3.13%) | 0 / 32 (0.00%) |
| occurrences (all)           | 1                | 1              | 0              |
| Respiratory tract infection |                  |                |                |
| subjects affected / exposed | 1 / 127 (0.79%)  | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)           | 1                | 0              | 0              |
| Rhinitis                    |                  |                |                |
| subjects affected / exposed | 2 / 127 (1.57%)  | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)           | 2                | 0              | 0              |
| Sepsis                      |                  |                |                |
| subjects affected / exposed | 1 / 127 (0.79%)  | 0 / 32 (0.00%) | 1 / 32 (3.13%) |
| occurrences (all)           | 1                | 0              | 1              |
| Tonsillitis                 |                  |                |                |
| subjects affected / exposed | 1 / 127 (0.79%)  | 1 / 32 (3.13%) | 0 / 32 (0.00%) |
| occurrences (all)           | 1                | 1              | 0              |
| Tooth infection             |                  |                |                |

|                                         |                 |                |                |
|-----------------------------------------|-----------------|----------------|----------------|
| subjects affected / exposed             | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)                       | 1               | 0              | 0              |
| Tracheitis                              |                 |                |                |
| subjects affected / exposed             | 1 / 127 (0.79%) | 1 / 32 (3.13%) | 0 / 32 (0.00%) |
| occurrences (all)                       | 1               | 1              | 0              |
| Urinary tract infection                 |                 |                |                |
| subjects affected / exposed             | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)                       | 1               | 0              | 0              |
| Viral infection                         |                 |                |                |
| subjects affected / exposed             | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)                       | 1               | 0              | 0              |
| Viral upper respiratory tract infection |                 |                |                |
| subjects affected / exposed             | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)                       | 1               | 0              | 0              |
| Metabolism and nutrition disorders      |                 |                |                |
| Diabetes mellitus                       |                 |                |                |
| subjects affected / exposed             | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)                       | 1               | 0              | 0              |
| Hypercholesterolaemia                   |                 |                |                |
| subjects affected / exposed             | 1 / 127 (0.79%) | 0 / 32 (0.00%) | 0 / 32 (0.00%) |
| occurrences (all)                       | 1               | 0              | 0              |

| <b>Non-serious adverse events</b>                     | BT061 50 mg      | BT061 75 mg      |  |
|-------------------------------------------------------|------------------|------------------|--|
| Total subjects affected by non-serious adverse events |                  |                  |  |
| subjects affected / exposed                           | 25 / 32 (78.13%) | 21 / 31 (67.74%) |  |
| Vascular disorders                                    |                  |                  |  |
| Haematoma                                             |                  |                  |  |
| subjects affected / exposed                           | 0 / 32 (0.00%)   | 0 / 31 (0.00%)   |  |
| occurrences (all)                                     | 0                | 0                |  |
| Hypertension                                          |                  |                  |  |
| subjects affected / exposed                           | 0 / 32 (0.00%)   | 0 / 31 (0.00%)   |  |
| occurrences (all)                                     | 0                | 0                |  |
| Pelvic venous thrombosis                              |                  |                  |  |
| subjects affected / exposed                           | 0 / 32 (0.00%)   | 0 / 31 (0.00%)   |  |
| occurrences (all)                                     | 0                | 0                |  |
| Thrombophlebitis superficial                          |                  |                  |  |

|                                                                            |                     |                     |  |
|----------------------------------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                           | 0 / 32 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 |  |
| General disorders and administration<br>site conditions                    |                     |                     |  |
| Influenza like illness<br>subjects affected / exposed<br>occurrences (all) | 0 / 32 (0.00%)<br>0 | 1 / 31 (3.23%)<br>1 |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)      | 1 / 32 (3.13%)<br>1 | 0 / 31 (0.00%)<br>0 |  |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)                | 1 / 32 (3.13%)<br>4 | 0 / 31 (0.00%)<br>0 |  |
| Reproductive system and breast<br>disorders                                |                     |                     |  |
| Spermatocele<br>subjects affected / exposed<br>occurrences (all)           | 0 / 32 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 |  |
| Varicocele<br>subjects affected / exposed<br>occurrences (all)             | 0 / 32 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 |  |
| Respiratory, thoracic and mediastinal<br>disorders                         |                     |                     |  |
| Cough<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 32 (0.00%)<br>0 | 1 / 31 (3.23%)<br>1 |  |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)               | 0 / 32 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 |  |
| Dyspnoea exertional<br>subjects affected / exposed<br>occurrences (all)    | 1 / 32 (3.13%)<br>1 | 0 / 31 (0.00%)<br>0 |  |
| Psychiatric disorders                                                      |                     |                     |  |
| Depressed mood<br>subjects affected / exposed<br>occurrences (all)         | 0 / 32 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 |  |
| Investigations                                                             |                     |                     |  |

|                                                                                                         |                     |                     |  |
|---------------------------------------------------------------------------------------------------------|---------------------|---------------------|--|
| Alanine aminotransferase increased<br>subjects affected / exposed<br>occurrences (all)                  | 1 / 32 (3.13%)<br>1 | 0 / 31 (0.00%)<br>0 |  |
| Blood albumin decreased<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 32 (3.13%)<br>1 | 0 / 31 (0.00%)<br>0 |  |
| Blood pressure increased<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 32 (0.00%)<br>0 | 1 / 31 (3.23%)<br>2 |  |
| Cytomegalovirus test positive<br>subjects affected / exposed<br>occurrences (all)                       | 1 / 32 (3.13%)<br>1 | 1 / 31 (3.23%)<br>1 |  |
| Epstein-Barr virus antibody positive<br>subjects affected / exposed<br>occurrences (all)                | 0 / 32 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 |  |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)                            | 0 / 32 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 |  |
| Mycobacterium tuberculosis complex<br>test positive<br>subjects affected / exposed<br>occurrences (all) | 1 / 32 (3.13%)<br>1 | 0 / 31 (0.00%)<br>0 |  |
| Protein total decreased<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 32 (3.13%)<br>1 | 0 / 31 (0.00%)<br>0 |  |
| Transaminases increased<br>subjects affected / exposed<br>occurrences (all)                             | 0 / 32 (0.00%)<br>0 | 1 / 31 (3.23%)<br>1 |  |
| Epstein-Barr virus test positive<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 32 (0.00%)<br>0 | 1 / 31 (3.23%)<br>1 |  |
| Injury, poisoning and procedural<br>complications                                                       |                     |                     |  |
| Fall<br>subjects affected / exposed<br>occurrences (all)                                                | 0 / 32 (0.00%)<br>0 | 1 / 31 (3.23%)<br>1 |  |
| Rib fracture                                                                                            |                     |                     |  |

|                                                                                                              |                     |                     |  |
|--------------------------------------------------------------------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                             | 0 / 32 (0.00%)<br>0 | 1 / 31 (3.23%)<br>1 |  |
| Traumatic haematoma<br>subjects affected / exposed<br>occurrences (all)                                      | 0 / 32 (0.00%)<br>0 | 1 / 31 (3.23%)<br>1 |  |
| Cardiac disorders<br>Atrioventricular block first degree<br>subjects affected / exposed<br>occurrences (all) | 0 / 32 (0.00%)<br>0 | 1 / 31 (3.23%)<br>1 |  |
| Nervous system disorders<br>Cervicobrachial syndrome<br>subjects affected / exposed<br>occurrences (all)     | 0 / 32 (0.00%)<br>0 | 1 / 31 (3.23%)<br>1 |  |
| Headache<br>subjects affected / exposed<br>occurrences (all)                                                 | 1 / 32 (3.13%)<br>1 | 1 / 31 (3.23%)<br>1 |  |
| Blood and lymphatic system disorders<br>Anaemia<br>subjects affected / exposed<br>occurrences (all)          | 0 / 32 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 |  |
| Leukopenia<br>subjects affected / exposed<br>occurrences (all)                                               | 1 / 32 (3.13%)<br>1 | 0 / 31 (0.00%)<br>0 |  |
| Lymphadenopathy<br>subjects affected / exposed<br>occurrences (all)                                          | 0 / 32 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 |  |
| Ear and labyrinth disorders<br>Vertigo<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 32 (3.13%)<br>1 | 0 / 31 (0.00%)<br>0 |  |
| Eye disorders<br>Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)                          | 0 / 32 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 |  |
| Sicca syndrome<br>subjects affected / exposed<br>occurrences (all)                                           | 1 / 32 (3.13%)<br>1 | 0 / 31 (0.00%)<br>0 |  |

|                                        |                |                |  |
|----------------------------------------|----------------|----------------|--|
| Gastrointestinal disorders             |                |                |  |
| Abdominal pain                         |                |                |  |
| subjects affected / exposed            | 0 / 32 (0.00%) | 0 / 31 (0.00%) |  |
| occurrences (all)                      | 0              | 0              |  |
| Aphthous stomatitis                    |                |                |  |
| subjects affected / exposed            | 0 / 32 (0.00%) | 0 / 31 (0.00%) |  |
| occurrences (all)                      | 0              | 0              |  |
| Diarrhoea                              |                |                |  |
| subjects affected / exposed            | 1 / 32 (3.13%) | 1 / 31 (3.23%) |  |
| occurrences (all)                      | 1              | 1              |  |
| Dyspepsia                              |                |                |  |
| subjects affected / exposed            | 0 / 32 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Glossodynia                            |                |                |  |
| subjects affected / exposed            | 0 / 32 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Nausea                                 |                |                |  |
| subjects affected / exposed            | 2 / 32 (6.25%) | 0 / 31 (0.00%) |  |
| occurrences (all)                      | 2              | 0              |  |
| Steatorrhoea                           |                |                |  |
| subjects affected / exposed            | 0 / 32 (0.00%) | 0 / 31 (0.00%) |  |
| occurrences (all)                      | 0              | 0              |  |
| Stomatitis                             |                |                |  |
| subjects affected / exposed            | 0 / 32 (0.00%) | 1 / 31 (3.23%) |  |
| occurrences (all)                      | 0              | 1              |  |
| Skin and subcutaneous tissue disorders |                |                |  |
| Ecchymosis                             |                |                |  |
| subjects affected / exposed            | 0 / 32 (0.00%) | 0 / 31 (0.00%) |  |
| occurrences (all)                      | 0              | 0              |  |
| Rash                                   |                |                |  |
| subjects affected / exposed            | 1 / 32 (3.13%) | 0 / 31 (0.00%) |  |
| occurrences (all)                      | 1              | 0              |  |
| Rash erythematous                      |                |                |  |
| subjects affected / exposed            | 0 / 32 (0.00%) | 0 / 31 (0.00%) |  |
| occurrences (all)                      | 0              | 0              |  |
| Rash papular                           |                |                |  |

|                                                  |                     |                     |  |
|--------------------------------------------------|---------------------|---------------------|--|
| subjects affected / exposed<br>occurrences (all) | 0 / 32 (0.00%)<br>0 | 0 / 31 (0.00%)<br>0 |  |
| Renal and urinary disorders                      |                     |                     |  |
| Dysuria                                          |                     |                     |  |
| subjects affected / exposed                      | 1 / 32 (3.13%)      | 0 / 31 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Haematuria                                       |                     |                     |  |
| subjects affected / exposed                      | 1 / 32 (3.13%)      | 0 / 31 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Haemoglobinuria                                  |                     |                     |  |
| subjects affected / exposed                      | 1 / 32 (3.13%)      | 0 / 31 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Leukocyturia                                     |                     |                     |  |
| subjects affected / exposed                      | 1 / 32 (3.13%)      | 0 / 31 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Endocrine disorders                              |                     |                     |  |
| Cushing's syndrome                               |                     |                     |  |
| subjects affected / exposed                      | 0 / 32 (0.00%)      | 0 / 31 (0.00%)      |  |
| occurrences (all)                                | 0                   | 0                   |  |
| Musculoskeletal and connective tissue disorders  |                     |                     |  |
| Arthralgia                                       |                     |                     |  |
| subjects affected / exposed                      | 0 / 32 (0.00%)      | 1 / 31 (3.23%)      |  |
| occurrences (all)                                | 0                   | 2                   |  |
| Back pain                                        |                     |                     |  |
| subjects affected / exposed                      | 3 / 32 (9.38%)      | 1 / 31 (3.23%)      |  |
| occurrences (all)                                | 4                   | 1                   |  |
| Bone pain                                        |                     |                     |  |
| subjects affected / exposed                      | 1 / 32 (3.13%)      | 0 / 31 (0.00%)      |  |
| occurrences (all)                                | 1                   | 0                   |  |
| Bursitis                                         |                     |                     |  |
| subjects affected / exposed                      | 0 / 32 (0.00%)      | 0 / 31 (0.00%)      |  |
| occurrences (all)                                | 0                   | 0                   |  |
| Joint swelling                                   |                     |                     |  |
| subjects affected / exposed                      | 0 / 32 (0.00%)      | 1 / 31 (3.23%)      |  |
| occurrences (all)                                | 0                   | 3                   |  |
| Muscle spasms                                    |                     |                     |  |

|                             |                |                 |  |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 31 (0.00%)  |  |
| occurrences (all)           | 0              | 0               |  |
| Musculoskeletal pain        |                |                 |  |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 31 (3.23%)  |  |
| occurrences (all)           | 0              | 1               |  |
| Osteopenia                  |                |                 |  |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 31 (3.23%)  |  |
| occurrences (all)           | 0              | 1               |  |
| Rheumatoid arthritis        |                |                 |  |
| subjects affected / exposed | 2 / 32 (6.25%) | 4 / 31 (12.90%) |  |
| occurrences (all)           | 2              | 5               |  |
| Infections and infestations |                |                 |  |
| Abscess                     |                |                 |  |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 31 (0.00%)  |  |
| occurrences (all)           | 0              | 0               |  |
| Acute tonsillitis           |                |                 |  |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 31 (3.23%)  |  |
| occurrences (all)           | 0              | 1               |  |
| Bronchitis                  |                |                 |  |
| subjects affected / exposed | 1 / 32 (3.13%) | 1 / 31 (3.23%)  |  |
| occurrences (all)           | 1              | 1               |  |
| Cystitis                    |                |                 |  |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 31 (0.00%)  |  |
| occurrences (all)           | 1              | 0               |  |
| Cytomegalovirus infection   |                |                 |  |
| subjects affected / exposed | 0 / 32 (0.00%) | 1 / 31 (3.23%)  |  |
| occurrences (all)           | 0              | 1               |  |
| Dysentery                   |                |                 |  |
| subjects affected / exposed | 0 / 32 (0.00%) | 0 / 31 (0.00%)  |  |
| occurrences (all)           | 0              | 0               |  |
| Herpes simplex              |                |                 |  |
| subjects affected / exposed | 1 / 32 (3.13%) | 2 / 31 (6.45%)  |  |
| occurrences (all)           | 1              | 3               |  |
| Herpes zoster               |                |                 |  |
| subjects affected / exposed | 1 / 32 (3.13%) | 0 / 31 (0.00%)  |  |
| occurrences (all)           | 1              | 0               |  |



|                             |                 |                 |
|-----------------------------|-----------------|-----------------|
| Laryngitis                  |                 |                 |
| subjects affected / exposed | 1 / 32 (3.13%)  | 0 / 31 (0.00%)  |
| occurrences (all)           | 1               | 0               |
| Nasopharyngitis             |                 |                 |
| subjects affected / exposed | 4 / 32 (12.50%) | 4 / 31 (12.90%) |
| occurrences (all)           | 4               | 4               |
| Oral herpes                 |                 |                 |
| subjects affected / exposed | 1 / 32 (3.13%)  | 0 / 31 (0.00%)  |
| occurrences (all)           | 1               | 0               |
| Pneumonia                   |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 0 / 31 (0.00%)  |
| occurrences (all)           | 0               | 0               |
| Respiratory tract infection |                 |                 |
| subjects affected / exposed | 1 / 32 (3.13%)  | 0 / 31 (0.00%)  |
| occurrences (all)           | 1               | 0               |
| Rhinitis                    |                 |                 |
| subjects affected / exposed | 1 / 32 (3.13%)  | 1 / 31 (3.23%)  |
| occurrences (all)           | 1               | 1               |
| Sepsis                      |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 0 / 31 (0.00%)  |
| occurrences (all)           | 0               | 0               |
| Tonsillitis                 |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 0 / 31 (0.00%)  |
| occurrences (all)           | 0               | 0               |
| Tooth infection             |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 1 / 31 (3.23%)  |
| occurrences (all)           | 0               | 1               |
| Tracheitis                  |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 0 / 31 (0.00%)  |
| occurrences (all)           | 0               | 0               |
| Urinary tract infection     |                 |                 |
| subjects affected / exposed | 1 / 32 (3.13%)  | 0 / 31 (0.00%)  |
| occurrences (all)           | 1               | 0               |
| Viral infection             |                 |                 |
| subjects affected / exposed | 0 / 32 (0.00%)  | 1 / 31 (3.23%)  |
| occurrences (all)           | 0               | 1               |

|                                                                                             |                     |                     |  |
|---------------------------------------------------------------------------------------------|---------------------|---------------------|--|
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 1 / 32 (3.13%)<br>1 | 0 / 31 (0.00%)<br>0 |  |
| Metabolism and nutrition disorders                                                          |                     |                     |  |
| Diabetes mellitus<br>subjects affected / exposed<br>occurrences (all)                       | 0 / 32 (0.00%)<br>0 | 1 / 31 (3.23%)<br>1 |  |
| Hypercholesterolaemia<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 32 (3.13%)<br>1 | 0 / 31 (0.00%)<br>0 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                            |
|------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 06 December 2011 | Modification of some Incl./ Excl. criteria, incorporation of non-substantial amendments, refined diagnostic for cronic infectious disease hepatitis B,                                                                                                                                                               |
| 15 December 2011 | inclusion of two additional substudies for measurement of plasma concentration, numbers of CD3+/ CD4+ lymphocytes, level of CD4 expression, occupancy of CD4 receptors, measuring the activation of Treg cells and functional capacity of CD4 T cells.                                                               |
| 19 January 2012  | Batch extension / Placebo                                                                                                                                                                                                                                                                                            |
| 31 August 2012   | Optional increase in size of patient population by an additional 0-40 patients in order to obtain sufficient data on PK/PD assessments and T-reg activation prior to interim analysis; PK/ PD assessments are part of the main study, explanation when data on the optional additional contingent will be evaluated. |
| 16 October 2013  | Cancellation of part II of the study in favour of a larger follow-on trial with a longer treatment duration                                                                                                                                                                                                          |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported