## Sponsor

Novartis

## Generic Drug Name

Canakinumab

## Therapeutic Area of Trial

Gouty arthritis

## Approved Indication

Indicated for the treatment of Cryopyrin-Associated Periodic Syndromes (CAPS), in adults and children aged 4 years and older including:

- Familial Cold Autoinflammatory Syndrome (FCAS)/ Familial Cold Urticaria (FCU),
- Muckle-Wells Syndrome (MWS),
- Neonatal-Onset Multisystem Inflammatory Disease (NOMID)/ Chronic Infantile Neurological, Cutaneous, Articular Syndrome (CINCA).

Approved in 54 Countries: US, Switzerland, Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain, Sweden, UK, Norway, Iceland, Chile, Guatemala, Canada, Brazil, Suriname, Argentina, Australia, Curacao, Hong Kong, Singapore, El Salvador, Israel, Taiwan, Philippines, India, UAE, Malaysia, Dominican Republic, Bahrain, Turkey, New Zealand, Kuwait, Peru.

Indicated for the treatment of gouty arthritis attacks.
Approved in the Philippines.

## Study Number

CACZ885H2251E1

## Title

A 24-week open-label, multicenter, follow-up and extension study to CACZ885H2251, to assess safety, tolerability and efficacy of canakinumab (ACZ885) in patients with gout who were given canakinumab at the time of gout flare

## Phase of Development

Phase II

## Study Start/End Dates

CACZ885H2251E1 05-Jun-2009 to 04-Aug-2010

## Study Design/Methodology

A multicenter, open-label, non-randomized study without a comparator. Patients had the option of entering this safety extension study if they had completed the core study CACZ885H2251. Patients willing to enter this extension safety study were offered the option to treat any acute flare of gout, on demand, with canakinumab 150 mg and asked to collect further efficacy data. Safety and tolerability data were collected for all patients, irrespective of whether or not they had an acute flare of gout. Patients who experienced an acute flare of gout were asked to seek immediate treatment with canakinumab by visiting the study center as soon as possible.

## Centres

A total of 75 centers in 18 countries: Argentina (1), Belgium (2), Columbia (4), Czech Republic (4), Germany (4), Guatemala (5), Hungary (4), Poland (2), Portugal (2), Russia (7), Singapore (1), Slovakia (6), South Africa (1), Spain (2), Taiwan (4), Turkey (7), UK (2), and U.S. (17).

## Publication

NA

## Objectives

Primary objective(s)

To evaluate, in the extension study, the safety and tolerability in the following groups:

- Group A – patients who were randomized to canakinumab in the core study and who were treated with canakinumab (for at least one flare) in the extension study.
- Group B – patients who were randomized to canakinumab in the core study and who did not receive treatment with canakinumab in the extension study.
- Group C – patients who were randomized to colchicine in the core study and who were treated with canakinumab (for at least one flare) in the extension study.
- Group D – patients who were randomized to colchicine in the core study and who did not receive treatment with canakinumab in the extension study.

Secondary objective(s)

1. To evaluate the long-term follow-up safety and tolerability of prophylactic treatment of canakinumab (received in the core study) as observed in the core + extension study (combined) in Groups B and D as defined above, and
2. To assess the efficacy of on-demand canakinumab in the treatment of newly occurring acute flares of gout in the extension study in patients who were treated with canakinumab (for at least one flare) during the extension study.

## Test Product (s), Dose(s), and Mode(s) of Administration

Canakinumab (ACZ885) was supplied in individual 6 mL glass vials containing 150 mg canakinumab. Patients with an occurrence of acute flare of gout were to be administered, on demand, at the study site, a single s.c. dose of 150 mg canakinumab. If a patient had more than one acute flare of gout during this extension study, the individual doses of 150 mg canakinumab had to be administered at least 2 weeks apart.

## Reference Product(s), Dose(s), and Mode(s) of Administration

NA

## Criteria for Evaluation

**Efficacy:**

Efficacy assessments included patient's assessment of gout pain (0-100 mm VAS), patient's global assessment of response to treatment (5-point Likert scale), use of rescue medication after study drug intake, physician's global assessment of response to treatment (5-point Likert scale), physician's assessment of tenderness, swelling and erythema in most affected joint. Data on patient's assessment of pain intensity (0-100 mm VAS), patient's assessment of the response to treatment (5-point Likert scale) and use of analgesic gout medication were collected using patient diaries. Patients were to be provided with a diary at visit 9 (roll over) be completed when flares occur (pre-treatment diary). At flare visits, the (pre-treatment) diary was to be kept at the study site and a new (post-treatment) diary was to be given to the patient.

**Safety**:

Safety analyses were performed on 2 Safety Sets. Safety Set 1 consisted of all patients from the core study who entered the extension study. Safety Set 2 consisted of all patients who received study drug and had at least one post-baseline safety assessment during the core study. All reported safety analyses in this CTRD record were performed on Safety Set 1.

Safety assessments included collection of all adverse events (AEs), serious adverse events (SAEs) with their severity and relationship to study drug, and pregnancies.

## Statistical Methods

Safety Set 1 consisted of all patients from the core study who entered the extension study. Patients were analyzed according to treatment received in the core and extension studies.

The Efficacy Set consisted of all patients who received at least one dose of canakinumab in the extension study (i.e. limited to Groups A and C).

All efficacy assessments were summarized by flare. Summary statistics for VAS were provided by time point for actual measurements and change from baseline. Frequency tables for the patient's and physician's assessments of response to treatment, physician's assessment of tenderness, swelling and erythema in most affected joint were produced.

Summary statistics were provided for the amount of rescue medication taken by rescue medication type and treatment. For patients enrolled in the extension study, summaries of safety data were provided by group (Groups A, B, C and D) for AEs/SAEs using Safety Set 1 with data collected during the extension study.

## Study Population: Inclusion/Exclusion Criteria and Demographics

Ages Eligible for Study: 18 years to 80 years
Genders Eligible for Study: Both

**Inclusion criteria:**

1. Patients who completed the CACZ885H2251 core study.
2. Patients who signed a written informed consent before any study procedure was performed.

**Exclusion criteria:**

1. Patients for whom continuation in the extension study was not considered appropriate by the treating physician.
2. Pregnant or nursing (lactating) women, where pregnancy was defined as the state of a female after conception and until the termination of gestation, confirmed by a positive pregnancy test (serum or urine).
3. Female patients who were physiologically capable of becoming pregnant, unless they were:
    - Female patients whose career, lifestyle, or sexual orientation precluded intercourse with a male partner.
    - Female patients whose partners had been sterilized by vasectomy or other means.
    - Using an acceptable method of contraception with a failure rate (Pearl Index (PI)) < 1.
    - Reliable contraception had to be maintained throughout the study and for 2 months after study drug discontinuation.

## Number of Subjects

| Patient disposition by group | Group A N=75 n (%) | Group B N=181 n (%) | Group C N=25 n (%) | Group D N=60 n (%) | Total N=341 n (%) |
|---|---|---|---|---|---|
| **Entered extension study** | 75 (100.0) | 181 (100.0) | 25 (100.0) | 60 (100.0) | 341 (100.0) |
| **Completed extension study** | 75 (100.0) | 173 (95.6) | 24 (96.0) | 58 (96.7) | 330 (96.8) |
| **Discontinued extension study** | 0 | 8 (4.4) | 1 (4.0) | 2 (3.3) | 11 (3.2) |
| **Reason for discontinuation** | | | | | |
| Abnormal laboratory value(s) | 0 | 1 (0.6) | 0 | 0 | 1 (0.3) |
| Subject withdrew consent | 0 | 3 (1.7) | 0 | 1 (1.7) | 4 (1.2) |
| Lost to follow-up | 0 | 2 (1.1) | 1 (4.0) | 1 (1.7) | 4 (1.2) |
| Death | 0 | 2 (1.1) | 0 | 0 | 2 (0.6) |

## Demographic and Background Characteristics

| | Group A N=75 | Group B N=181 | Group C N=25 | Group D N=60 | Total N=341 |
|---|---|---|---|---|---|
| **Sex** - n (%) | | | | | |
| Male | 73 (97.3) | 168 (92.8) | 25 (100.0) | 53 (88.3) | 319 (93.5) |
| Female | 2 (2.7) | 13 (7.2) | 0 | 7 (11.7) | 22 (6.5) |
| **Age (years)** | | | | | |
| n | 75 | 181 | 25 | 60 | 341 |
| Mean | 50.7 | 53.8 | 52.0 | 51.5 | 52.6 |
| S.D. | 10.20 | 11.39 | 11.00 | 9.45 | 10.83 |
| Min | 27 | 23 | 28 | 31 | 23 |
| Median | 49.0 | 54.0 | 53.0 | 52.5 | 52.0 |
| Max | 78 | 79 | 73 | 77 | 79 |
| **Race** - n (%) | | | | | |
| Caucasian | 46 (61.3) | 143 (79.0) | 19 (76.0) | 49 (81.7) | 257 (75.4) |
| Black | 2 (2.7) | 6 (3.3) | 1 (4.0) | 1 (1.7) | 10 (2.9) |
| Asian | 11 (14.7) | 10 (5.5) | 2 (8.0) | 2 (3.3) | 25 (7.3) |
| Native American | 1 (1.3) | 3 (1.7) | 0 | 1 (1.7) | 5 (1.5) |
| Pacific islander | 0 | 0 | 0 | 2 (3.3) | 2 (0.6) |
| Other | 15 (20.0) | 19 (10.5) | 3 (12.0) | 5 (8.3) | 42 (12.3) |
| **BMI (kg/m²)** | | | | | |
| n | 75 | 181 | 25 | 60 | 341 |
| Mean | 30.65 | 29.77 | 29.73 | 30.43 | 30.08 |
| S.D. | 4.341 | 4.301 | 4.179 | 4.703 | 4.373 |
| Min | 17.0 | 18.4 | 22.1 | 22.9 | 17.0 |
| Median | 30.42 | 29.41 | 29.10 | 29.66 | 29.69 |
| Max | 39.4 | 39.9 | 39.7 | 39.8 | 39.9 |

## Disease history and baseline characteristics

| | Group A N=75 | Group B N=181 | Group C N=25 | Group D N=60 | Total N=341 |
|---|---|---|---|---|---|
| **Number of flares in the last year** | | | | | |
| n | 75 | 181 | 25 | 60 | 341 |
| Mean | 4.5 | 3.7 | 5.1 | 3.3 | 3.9 |
| S.D. | 3.18 | 2.36 | 3.40 | 1.92 | 2.62 |
| Min | 1 | 2 | 2 | 1 | 1 |
| Median | 4.0 | 3.0 | 4.0 | 3.0 | 3.0 |
| Max | 20 | 15 | 15 | 12 | 20 |
| **Duration of gout** - n (%) | | | | | |
| < 1 year | 1 (1.3) | 11 (6.1) | 0 | 6 (10.0) | 18 (5.3) |
| 1-5 years | 17 (22.7) | 69 (38.1) | 7 (28.0) | 25 (41.7) | 118 (34.6) |
| 6-10 years | 18 (24.0) | 45 (24.9) | 6 (24.0) | 15 (25.0) | 84 (24.6) |
| > 10 years | 39 (52.0) | 56 (30.9) | 12 (48.0) | 14 (23.3) | 121 (35.5) |
| **Allopurinol dose at baseline (mg daily)** | | | | | |
| n | 75 | 181 | 25 | 60 | 341 |
| Mean | 268.0 | 253.0 | 260.0 | 261.7 | 258.4 |
| S.D. | 61.86 | 69.56 | 70.71 | 64.02 | 67.05 |
| Min | 100 | 100 | 100 | 100 | 100 |
| Median | 300.0 | 300.0 | 300.0 | 300.0 | 300.0 |
| Max | 300 | 300 | 300 | 300 | 300 |
| **Urate (mg/dL)** | | | | | |
| n | 75 | 181 | 25 | 60 | 341 |
| Mean | 9.6 | 8.4 | 9.3 | 8.4 | 8.7 |
| S.D. | 2.03 | 2.00 | 2.46 | 1.90 | 2.08 |
| Min | 5 | 0 | 3 | 4 | 0 |
| Median | 9.6 | 8.5 | 9.3 | 8.8 | 8.9 |
| Max | 14 | 15 | 16 | 13 | 16 |
| **Urate** - n (%) | | | | | |
| <9 mg/dL | 27 (36.0) | 109 (60.2) | 11 (44.0) | 35 (58.3) | 182 (53.4) |
| ≥9 mg/dL | 48 (64.0) | 72 (39.8) | 14 (56.0) | 25 (41.7) | 159 (46.6) |

## Primary Objective Result(s)

As the primary objective of this extension study was to evaluate the safety and tolerability of canakinumab 150 mg s.c. in Group A, B, C and D, there is no primary efficacy variable. All efficacy variables are associated with the secondary objectives of the study.

## Secondary Objective Result(s)

**Patient's assessment of gout pain (0-100 mm VAS) during the first flare in patients treated with canakinumab by timepoint and group (Efficacy set)**

| | Group A N=75 | | Group C N=25 | | Total N=100 | |
|---|---|---|---|---|---|---|
| **Timepoint / Statistics** | **Pain (VAS)** | **Difference (1)** | **Pain (VAS)** | **Difference (1)** | **Pain (VAS)** | **Difference (1)** |
| Pre-dose | | | | | | |
| n | 65 | | 19 | | 84 | |
| Mean | 61.3 | | 71.8 | | 63.7 | |
| S.D. | 27.13 | | 20.86 | | 26.11 | |
| Min | 9 | | 13 | | 9 | |
| Median | 69.0 | | 78.0 | | 70.5 | |
| Max | 100 | | 97 | | 100 | |
| 24 hours | | | | | | |
| n | 65 | 65 | 18 | 18 | 83 | 83 |
| Mean | 23.8 | -37.4 | 29.0 | -42.4 | 25.0 | -38.5 |
| S.D. | 23.32 | 26.34 | 22.85 | 19.78 | 23.18 | 25.04 |
| Min | 0 | -96 | 0 | -74 | 0 | -96 |
| Median | 16.0 | -33.0 | 32.0 | -41.0 | 19.0 | -38.0 |
| Max | 91 | 7 | 65 | -6 | 91 | 7 |
| 3 days | | | | | | |
| n | 54 | 54 | 15 | 15 | 69 | 69 |
| Mean | 12.4 | -47.5 | 6.8 | -62.9 | 11.2 | -50.8 |
| S.D. | 16.82 | 25.59 | 9.03 | 22.30 | 15.58 | 25.56 |
| Min | 0 | -100 | 0 | -97 | 0 | -100 |
| Median | 5.5 | -49.0 | 1.0 | -66.0 | 4.0 | -51.0 |
| Max | 58 | 2 | 26 | -13 | 58 | 2 |
| 4 days | | | | | | |
| n | 54 | 54 | 15 | 15 | 69 | 69 |
| Mean | 8.8 | -51.0 | 2.7 | -66.9 | 7.5 | -54.5 |
| S.D. | 14.32 | 26.22 | 5.06 | 20.70 | 13.09 | 25.84 |
| Min | 0 | -100 | 0 | -97 | 0 | -100 |
| Median | 1.5 | -51.0 | 0.0 | -65.0 | 1.0 | -56.0 |
| Max | 50 | 0 | 15 | -13 | 50 | 0 |
| 5–7 days (Average) | | | | | | |
| n | 52 | 52 | 13 | 13 | 65 | 65 |
| Mean | 8.1 | -51.7 | 2.1 | -67.4 | 6.9 | -54.9 |
| S.D. | 15.86 | 27.30 | 4.70 | 21.69 | 14.50 | 26.87 |
| Min | 0 | -100 | 0 | -97 | 0 | -100 |
| Median | 0.5 | -52.0 | 0.0 | -67.3 | 0.3 | -56.3 |
| Max | 76 | 2 | 14 | -13 | 76 | 2 |

0–100mm VAS: 0=no pain, 100=unbearable pain.
Includes pain assessments from patient diary booklet 2.
(1) Difference from time of study drug administration (pre-dose).
Only those patients with a value at both timepoints, at pre-dose and at the respective later timepoint (if applicable) were included. Difference from time of study drug administration = (later-measurement – measurement just before study drug administration).

**Patient's global assessment of response to treatment (5-point Likert scale) in patients treated with canakinumab by flare order and group (Efficacy set)**

| Flare order | Assessment | Group A N=75 n (%) | Group C N=25 n (%) | Total N=100 n (%) |
|---|---|---|---|---|
| 1. gout flare | -Total | 63 | 21 | 84 |
| | Excellent | 40 (63.5) | 7 (33.3) | 47 (56.0) |
| | Good | 17 (27.0) | 14 (66.7) | 31 (36.9) |
| | Acceptable | 5 (7.9) | 0 | 5 (6.0) |
| | Slight | 1 (1.6) | 0 | 1 (1.2) |
| | Poor | 0 | 0 | 0 |
| 2. gout flare | -Total | 11 | 5 | 16 |
| | Excellent | 4 (36.4) | 4 (80.0) | 8 (50.0) |
| | Good | 6 (54.5) | 1 (20.0) | 7 (43.8) |
| | Acceptable | 1 (9.1) | 0 | 1 (6.3) |
| | Slight | 0 | 0 | 0 |
| | Poor | 0 | 0 | 0 |
| 3. gout flare | -Total | 3 | 1 | 4 |
| | Excellent | 2 (66.7) | 0 | 2 (50.0) |
| | Good | 1 (33.3) | 1 (100.0) | 2 (50.0) |
| | Acceptable | 0 | 0 | 0 |
| | Slight | 0 | 0 | 0 |
| | Poor | 0 | 0 | 0 |

Total is the number of patients with assessments at the respective flare and used as the denominator for the % of patients in each assessment category.

**Physician's global assessment of response to treatment (5-point Likert scale) in patients treated with canakinumab by flare order and group (Efficacy set)**

| Flare order | Assessment | Group A N=75 n (%) | Group C N=25 n (%) | Total N=100 n (%) |
|---|---|---|---|---|
| 1. gout flare | -Total | 69 | 23 | 92 |
| | Very good | 37 (53.6) | 13 (56.5) | 50 (54.3) |
| | Good | 28 (40.6) | 10 (43.5) | 38 (41.3) |
| | Fair | 2 (2.9) | 0 | 2 (2.2) |
| | Poor | 2 (2.9) | 0 | 2 (2.2) |
| | Very poor | 0 | 0 | 0 |
| 2. gout flare | -Total | 12 | 5 | 17 |
| | Very good | 5 (41.7) | 3 (60.0) | 8 (47.1) |
| | Good | 7 (58.3) | 2 (40.0) | 9 (52.9) |
| | Fair | 0 | 0 | 0 |
| | Poor | 0 | 0 | 0 |
| | Very poor | 0 | 0 | 0 |
| 3. gout flare | -Total | 3 | 1 | 4 |
| | Very good | 1 (33.3) | 0 | 1 (25.0) |
| | Good | 2 (66.7) | 1 (100.0) | 3 (75.0) |
| | Fair | 0 | 0 | 0 |
| | Poor | 0 | 0 | 0 |
| | Very poor | 0 | 0 | 0 |

Total is the number of patients with assessments at the respective flare and used as the denominator for the % of patients in each assessment category.

**Physician's assessment of tenderness, swelling and erythema in most affected joint during the first flare in patients treated with canakinumab by parameter, visit and group (Efficacy set)**

| Parameter | Visit | Assessment | Group A N=75 n (%) | Group C N=25 n (%) | Total N=100 n (%) |
|---|---|---|---|---|---|
| Tenderness | Flare visit | -Total | 69 | 24 | 93 |
| | | No pain | 2 (2.9) | 0 | 2 (2.2) |
| | | Pain | 27 (39.1) | 2 (8.3) | 29 (31.2) |
| | | Pain and winces | 23 (33.3) | 10 (41.7) | 33 (35.5) |
| | | Pain, winces and withdraws | 17 (24.6) | 12 (50.0) | 29 (31.2) |
| | Control Visit | -Total | 69 | 24 | 93 |
| | | No pain | 60 (87.0) | 21 (87.5) | 81 (87.1) |
| | | Pain | 8 (11.6) | 3 (12.5) | 11 (11.8) |
| | | Pain and winces | 1 (1.4) | 0 | 1 (1.1) |
| | | Pain, winces and withdraws | 0 | 0 | 0 |
| Joint swelling | Flare visit | -Total | 69 | 24 | 93 |
| | | No swelling | 5 (7.2) | 0 | 5 (5.4) |
| | | Palpable | 20 (29.0) | 2 (8.3) | 22 (23.7) |
| | | Visible | 31 (44.9) | 17 (70.8) | 48 (51.6) |
| | | Bulging beyond the joint margins | 13 (18.8) | 5 (20.8) | 18 (19.4) |
| | Control Visit | -Total | 69 | 24 | 93 |
| | | No swelling | 61 (88.4) | 22 (91.7) | 83 (89.2) |
| | | Palpable | 6 (8.7) | 2 (8.3) | 8 (8.6) |
| | | Visible | 2 (2.9) | 0 | 2 (2.2) |
| | | Bulging beyond the joint margins | 0 | 0 | 0 |
| Erythema | Flare visit | -Total | 69 | 24 | 93 |
| | | Absent | 21 (30.4) | 4 (16.7) | 25 (26.9) |
| | | Present | 44 (63.8) | 20 (83.3) | 64 (68.8) |
| | | Not assessed | 0 | 0 | 0 |
| | Control Visit | -Total | 69 | 24 | 93 |
| | | Absent | 66 (95.7) | 24 (100.0) | 90 (96.8) |
| | | Present | 3 (4.3) | 0 | 3 (3.2) |
| | | Not assessed | 0 | 0 | 0 |

Total is the number of patients with assessments at the respective visit and used as the denominator for the % of patients in each assessment category.

**Amount of rescue medication after study drug intake in patients treated with canakinumab by flare order, medication and group (Efficacy set)**

| Flare order | Medication | Statistics | Group A N=75 | Group C N=25 | Total N=100 |
|---|---|---|---|---|---|
| 1. gout flare | Naproxen (mg) | n | 68 | 24 | 92 |
| | | Mean | 1086.8 | 954.6 | 1052.3 |
| | | S.D. | 1592.72 | 1130.19 | 1481.21 |
| | | Min | 0 | 0 | 0 |
| | | Median | 0.0 | 580.0 | 0.0 |
| | | Max | 6000 | 3500 | 6000 |
| | Prednisolone (mg) | n | 68 | 24 | 92 |
| | | Mean | 4.6 | 4.2 | 4.5 |

| | | | | | |
|---|---|---|---|---|---|
| | | S.D. | 20.84 | 20.41 | 20.62 |
| | | Min | 0 | 0 | 0 |
| | | Median | 0.0 | 0.0 | 0.0 |
| | | Max | 160 | 100 | 160 |
| 2. gout flare | Naproxen (mg) | n | 12 | 5 | 17 |
| | | Mean | 650.0 | 200.0 | 517.6 |
| | | S.D. | 642.79 | 447.21 | 615.41 |
| | | Min | 0 | 0 | 0 |
| | | Median | 500.0 | 0.0 | 500.0 |
| | | Max | 1750 | 1000 | 1750 |
| | Prednisolone (mg) | n | 12 | 5 | 17 |
| | | Mean | 1.3 | 0.0 | 0.9 |
| | | S.D. | 3.11 | 0.00 | 2.64 |
| | | Min | 0 | 0 | 0 |
| | | Median | 0.0 | 0.0 | 0.0 |
| | | Max | 10 | 0 | 10 |
| 3. gout flare | Naproxen (mg) | n | 4 | 1 | 5 |
| | | Mean | 250.0 | 0.0 | 200.0 |
| | | S.D. | 500.00 | | 447.21 |
| | | Min | 0 | 0 | 0 |
| | | Median | 0.0 | 0.0 | 0.0 |
| | | Max | 1000 | 0 | 1000 |
| | Prednisolone (mg) | n | 4 | 1 | 5 |
| | | Mean | 0.0 | 0.0 | 0.0 |
| | | S.D. | 0.00 | | 0.00 |
| | | Min | 0 | 0 | 0 |
| | | Median | 0.0 | 0.0 | 0.0 |
| | | Max | 0 | 0 | 0 |

## Safety Results

## Adverse Events by System Organ Class

| Primary system organ class | Group A N=75 n (%) | Group B N=181 n (%) | Group C N=25 n (%) | Group D N=60 n (%) | Total N=341 n (%) |
|---|---|---|---|---|---|
| **Total no. of patients with any AE** | 31 (41.3) | 52 (28.7) | 9 (36.0) | 15 (25.0) | 107 (31.4) |
| Infections and infestations | 12 (16.0) | 14 (7.7) | 3 (12.0) | 4 (6.7) | 33 (9.7) |
| Musculoskeletal and connective tissue disorders | 15 (20.0) | 15 (8.3) | 0 | 1 (1.7) | 31 (9.1) |
| Nervous system disorders | 6 (8.0) | 6 (3.3) | 1 (4.0) | 1 (1.7) | 14 (4.1) |
| Vascular disorders | 7 (9.3) | 5 (2.8) | 2 (8.0) | 0 | 14 (4.1) |
| Gastrointestinal disorders | 4 (5.3) | 7 (3.9) | 1 (4.0) | 0 | 12 (3.5) |
| Investigations | 1 (1.3) | 4 (2.2) | 0 | 4 (6.7) | 9 (2.6) |
| Blood and lymphatic system disorders | 4 (5.3) | 2 (1.1) | 0 | 1 (1.7) | 7 (2.1) |
| General disorders and administration site conditions | 2 (2.7) | 3 (1.7) | 1 (4.0) | 1 (1.7) | 7 (2.1) |
| Injury, poisoning and procedural complications | 2 (2.7) | 4 (2.2) | 0 | 1 (1.7) | 7 (2.1) |
| Respiratory, thoracic and mediastinal disorders | 5 (6.7) | 2 (1.1) | 0 | 0 | 7 (2.1) |
| Cardiac disorders | 0 | 6 (3.3) | 0 | 0 | 6 (1.8) |
| Reproductive system and breast disorders | 3 (4.0) | 2 (1.1) | 0 | 1 (1.7) | 6 (1.8) |
| Metabolism and nutrition disorders | 1 (1.3) | 1 (0.6) | 2 (8.0) | 1 (1.7) | 5 (1.5) |
| Skin and subcutaneous tissue disorders | 2 (2.7) | 2 (1.1) | 0 | 1 (1.7) | 5 (1.5) |
| Psychiatric disorders | 2 (2.7) | 0 | 0 | 1 (1.7) | 3 (0.9) |
| Renal and urinary disorders | 1 (1.3) | 1 (0.6) | 1 (4.0) | 0 | 3 (0.9) |
| Eye disorders | 1 (1.3) | 1 (0.6) | 0 | 0 | 2 (0.6) |
| Hepatobiliary disorders | 0 | 2 (1.1) | 0 | 0 | 2 (0.6) |

Primary system organ classes are sorted by descending frequency of the total column.
A patient with multiple occurrences of an AE under one group is counted only once in the AE category for that group.

## Most Frequently Reported AEs Overall by Preferred Term n (%)

**Frequent AEs (at least 5% in any group)**

| Preferred term | Group A N=75 n (%) | Group B N=181 n (%) | Group C N=25 n (%) | Group D N=60 n (%) | Total N=341 n (%) |
|---|---|---|---|---|---|
| **Total no. of patients with any AE** | 31 (41.3) | 52 (28.7) | 9 (36.0) | 15 (25.0) | 107 (31.4) |
| Arthralgia | 4 (5.3) | 6 (3.3) | 0 | 1 (1.7) | 11 (3.2) |
| Hypertension | 6 (8.0) | 3 (1.7) | 2 (8.0) | 0 | 11 (3.2) |
| Upper respiratory tract infection | 5 (6.7) | 4 (2.2) | 1 (4.0) | 0 | 10 (2.9) |
| Cough | 4 (5.3) | 0 | 0 | 0 | 4 (1.2) |
| Hypertriglyceridemia | 0 | 1 (0.6) | 2 (8.0) | 0 | 3 (0.9) |

## Serious Adverse Events and Deaths

**Deaths, other serious adverse events or related discontinuations by group**

| | Group A N=75 n (%) | Group B N=181 n (%) | Group C N=25 n (%) | Group D N=60 n (%) | Total N=341 n (%) |
|---|---|---|---|---|---|
| Patients with any AE | 31 (41.3) | 52 (28.7) | 9 (36.0) | 15 (25.0) | 107 (31.4) |
| Death | 0 | 2 (1.1) | 0 | 0 | 2 (0.6) |
| SAEs | 4 (5.3) | 6 (3.3) | 0 | 1 (1.7) | 11 (3.2) |
| Discontinued due to AEs | 0 | N/A | 0 | N/A | 0 |

**SAEs:**

Group A: 1 deep vein thrombosis, 1 diverticulitis followed by prostatitis, 1 gout tophus, 1 inguinal hernia

Group B: 1 abdominal hernia, 1 incisional hernia, 1 transient ischemic attack, 1 heat exhaustion, 1 myocardial fibrosis that led to death, 1 fatal gunshot wound to the head

Group D: 1 meniscus lesion

## Other Relevant Findings

NA

**Date of Clinical Trial Report**

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