**Sponsor**

Novartis

**Generic Drug Name**

BCT197

**Therapeutic Area of Trial**

Chronic Obstructive Pulmonary Disease (COPD)

**Approved Indication**

Indicated for the treatment of COPD exacerbations.

**Protocol Number**

CBCT197A2201

**Title**

An exploratory, randomized, double-blind, placebo controlled, multi-center study to assess the efficacy, safety and tolerability of a single and a repeated dose of oral BCT197 in patients with an acute COPD exacerbation.

**Study Phase**

Phase II

**Study Start/End Dates**

First patient enrolled: 16-Mar-2011

Last patient completed: 15-May-2013

**Study Design/Methodology**

This was an exploratory, double-blind, randomized, placebo-controlled, multi-center, adaptive parallel-group design study in four parts in patients with acute COPD exacerbation. In Part I, patients were randomized to receive either a single dose of 75mg BCT197, placebo or 40 mg oral prednisone in the ratio of 1:1:1. In Part II patients were randomized to receive either a single dose of 20 mg BCT197 or placebo in the ratio of 5:1. Patients in Parts I and II received their single dose on Day 1 of the study, and in Parts III & IV on day1 and Day 6. In Parts III and IV patients were randomized to receive either BCT197 or placebo in a ratio of 5:1 at a dose of 20 mg and 75mg, respectively.

**Centers**

The study was run in three countries: Bulgaria – 3 sites, Romania – 1 site and Russia – 4 sites.

**Publication**

Not applicable

## Objectives

**Primary objective:**
to assess the efficacy of a single and a repeated dose of BCT197 in COPD patients presenting with an exacerbation by means of an improvement in $FEV_1$ relative to placebo.
**Secondary objectives:**
The assessment of safety and tolerability of BCT197
Measurement of the time to recovery using the EXACT-PRO tool
Assessment of the time to the next exacerbation, of the number of responders at Day 30
Assessment of dyspnea as measured by the Borg CR10 scale© at Day 5
Assessment of quality of life and of the length of hospitalization following initial admission.
The determination of the PK of BCT197 and its metabolites in plasma

## Test Product, Doses, and Mode of Administration

BCT197 and matching placebo was administered orally as 5 mg and 10mg capsules.
A single dose was administered on Day 1 in Parts I and II, and as two single doses on Days 1 and 6 in Parts III and IV.
The dose for Part I was 75mg, Part II 20mg, Part III 20mg and Part IV was 75mg.

## Statistical Methods

FEV1 change from baseline from all study parts were analyzed in the same model. Placebo patients were pooled across study parts. FEV1 values measured on Days 3, 5, 8, 10,14 and 30 were analyzed in a model that included effects for baseline (Day 1, pre-dose FEV1 value), treatment (placebo, prednisone, BCT197 75mg, BCT197 20mg, BCT197 20mg repeat dose and BCT197 75mg repeat dose), time (class variable: Day 3, 5, 8, 10, 14 and 30), treatment by time interaction and baseline by time interaction. An unstructured covariance matrix was used to model the correlations of FEV1 values measured on the same patient.
Interim analyses were performed as planned during the study which resulted in repeating Part I then continuing with the other planned parts of the study.

## Study Population: Inclusion/Exclusion Criteria and Demographics

Ages Eligible for Study: 40 Years to 80 Years
Genders Eligible for Study: Both

Inclusion Criteria:

- Patients with COPD (Stage II to IV) with a COPD exacerbation.
- Smoking history of 10 pack years.
- Females must not be of child bearing potential

Exclusion Criteria:

- Use of steroids in the last 30 days or calcium channel blockers in the last 48 hours.
- Other protocol-defined inclusion/exclusion criteria may apply

## Participant Flow

| | Treatment Group | | | | | | Total |
|---|---|---|---|---|---|---|---|
| | A | B/E/G/I | C | D | F | H | |
| | N=31 | N=45 | N=30 | N=25 | N=27 | N=25 | N=183 |
| Patients | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Completed | 30 (97) | 44 (98) | 26 (87) | 23 (92) | 24 (89) | 22 (88) | 169 (92) |
| Discontinued | 1 (3) | 1 (2) | 4 (13) | 2 (8) | 3 (11) | 3 (12) | 14 (8) |
| **Main cause of discontinuation** | | | | | | | |
| Death | 1 (3) | 0 | 2 (7) | 1 (4) | 1 (4) | 1 (4) | 6 (3) |
| Withdrew consent | 0 | 1 (2) | 1 (3) | 0 | 1 (4) | 1 (4) | 4 (2) |
| Loss to follow-up | 0 | 0 | 1 (3) | 1 (4) | 1 (4) | 1 (4) | 4 (2) |

Group A (75 mg BCT197); Group B/E/G/I (placebo); Group C (40 mg prednisone); Group D (20 mg BCT197); Group F (20 mg BCT197 Repeat); Group H (75 mg BCT197 Repeat).

## Baseline Characteristics

| | | Treatment group | | | | | | Total |
|---|---|---|---|---|---|---|---|---|
| | | A | B/E/G/I | C | D | F | H | |
| | | N=31 | N=45 | N=30 | N=25 | N=27 | N=25 | N=183 |
| Age (years) | Mean (SD) | 60 (8.6) | 61 (6.6) | 63 (8.0) | 62 (8.7) | 61 (9.1) | 64 (6.7) | 62 (7.9) |
| | Range | 44, 75 | 46, 75 | 45, 77 | 43, 77 | 41, 76 | 40, 76 | 41, 77 |
| Gender – n (%) | Male | 23 (74) | 32 (71) | 26 (87) | 21 (84) | 23 (85) | 21 (84) | 146 (80) |
| | Female | 8 (26) | 13 (29) | 4 (13) | 4 (16) | 4 (15) | 4 (16) | 37 (20) |
| Race – n (%) | Caucasian | 31 (100) | 45 (100) | 30 (100) | 25 (100) | 25 (100) | 25 (100) | 183 (100) |
| Height (cm) | Mean (SD) | 166 (9.0) | 168 (8.2) | 167 (7.9) | 168 (7.1) | 168 (7.6) | 168 (7.5) | 168 (7.9) |
| | Range | 147, 187 | 153, 185 | 151, 186 | 155, 181 | 150, 182 | 150, 186 | 147, 187 |
| Weight (kg) | Mean (SD) | 77.2 (19.60) | 78.6 (20.10) | 70.6 (13.32) | 71.3 (15.24) | 73.7 ((14.65) | 71.0 (16.84) | 74.3 (17.29) |
| | Range | 50.0, 122.0 | 45.0, 130.0 | 48.0, 98.0 | 44.0, 109.0 | 47.0, 106.0 | 43.0, 110.0 | 43.0, 130.0 |
| BMI ($kg/m^2$) | Mean (SD) | 28.1 (6.66) | 27.8 (6.75) | 25.4 (4.62) | 25.1 (4.81) | 26.1 (5.20) | 25.2 (5.55) | 26.5 (5.86) |
| | Range | 17.7, 46.7 | 16.2, 46.9 | 17.4, 33.5 | 16.6, 35.6 | 17.5, 36.5 | 15.9, 35.5 | 15.9, 46.9 |

Group A (75 mg BCT197); Group B/E/G/I (placebo); Group C (40 mg prednisone); Group D (20 mg BCT197); Group F (20 mg BCT197 Repeat); Group H (75 mg BCT197 Repeat). BMI = Body mass index

## Outcome Measures

## Primary Outcome Results

Summary of the statistical analysis of change from baseline in $FEV_1$(mL) by time for all parts of the study are shown in the table below.

| | | Change from baseline | Comparison with placebo | |
|---|---|---|---|---|
| Day | Group | LS Mean (95% CI) | Mean (95% CI) | P value |
| 3 | Placebo (n=45) | 51 (-15, 116) | | |
| | BCT197 75 mg (n=30) | 138 (58, 218) | 87 (-16, 190) | 0.097 |
| | Prednisone (n=30) | 37 (-43, 117) | -13 (-117, 90) | 0.80 |
| | BCT197 20 mg (n=25) | 144 (56, 232) | 93 (-16, 202) | 0.094 |
| | BCT197 20 mg Rpt (n=27) | 95 (9, 180) | 44 (-64, 152) | 0.42 |
| | BCT197 75 mg Rpt (n=25) | 143 (55, 231) | 92 (-18, 202) | 0.099 |
| 5 | Placebo (n=45) | 101 (40, 162) | | |
| | BCT197 75 mg (n=30) | 155 (81, 229) | 54 (-42, 150) | 0.27 |
| | Prednisone (n=30) | 49 (-26, 123) | -52 (-149, 45) | 0.29 |
| | BCT197 20 mg (n=25) | 106 (25, 188) | 5 (-96, 107) | 0.92 |
| | BCT197 20 mg Rpt (n=26) | 134 (55, 214) | 34 (-67, 134) | 0.51 |
| | BCT197 75 mg Rpt (n=25) | 201 (119, 282) | 100 (-2, 202) | 0.056 |
| 8 | Placebo (n=24) | 79 (-5, 162) | | |
| | BCT197 75 mg (n=14) | 191 (87, 296) | 113 (-21, 246) | 0.098 |
| | Prednisone (n=15) | 96 (-7, 199) | 17 (-116, 150) | 0.80 |
| | BCT197 20 mg (n=8) | 28 (-99, 154) | -51 (-202, 100) | 0.51 |
| | BCT197 20 mg Rpt (n=26) | 138 (40, 236) | 59 (-69, 188) | 0.36 |
| | BCT197 75 mg Rpt (n=25) | 231 (130, 331) | 152 (21, 283) | 0.022 |
| 10 | Placebo (n=24) | 127 (37, 217) | | |
| | BCT197 75 mg (n=14) | 165 (51, 278) | 38 (-107, 183) | 0.61 |
| | Prednisone (n=15) | 55 (-57, 167) | -72 (-216, 72) | 0.32 |
| | BCT197 20 mg (n=7) | 55 (-89, 198) | -72 (-241, 97) | 0.40 |
| | BCT197 20 mg Rpt (n=26) | 109 (6, 212) | -18 (-155, 119) | 0.80 |
| | BCT197 75 mg Rpt (n=25) | 250 (145, 356) | 124 (-16, 263) | 0.082 |
| 14 | Placebo (n=45) | 132 (49, 214) | | |
| | BCT197 75 mg (n=30) | 119 (18, 220) | -12 (-143, 118) | 0.85 |
| | Prednisone (n=30) | 81 (-20, 183) | -50 (-182, 81) | 0.45 |
| | BCT197 20 mg (n=25) | 41 (-70, 152) | -90 (-228, 48) | 0.20 |
| | BCT197 20 mg Rpt (n=26) | 95 (-13, 204) | -37 (-173, 100) | 0.60 |
| | BCT197 75 mg Rpt (n=25) | 229 (118, 340) | 97 (-42, 236) | 0.17 |

| | | | | |
|---|---|---|---|---|
| 30 | Placebo (n=44) | 96 (9, 182) | | |
| | BCT197 75 mg (n=30) | 156 (51, 261) | 60 (-75, 196) | 0.38 |
| | Prednisone (n=28) | 103 (-4, 209) | 7 (-131, 145) | 0.92 |
| | BCT197 20 mg (n=25) | 118 (2, 233) | 22 (-122, 165) | 0.76 |
| | BCT197 20 mg Rpt (n=24) | 82 (-33, 196) | -14 (-158, 129) | 0.84 |
| | BCT197 75 mg Rpt (n=24) | 164 (48, 280) | 68 (-77, 214) | 0.36 |

Rpt = Repeat; n = the number of subjects with data available on each day;

## Secondary Outcome Results

Summary of the statistical analysis of EXACT-PRO 14 point patient reported outcome AUC from day 1 to day 14 for all parts of the study. There was no evidence of any difference between the BCT197 treatment groups and placebo.

| | -----Group------ | | ---------- Difference (95%CI) p-value ---------- | | | | |
|---|---|---|---|---|---|---|---|
| | LS Mean<br>n | 95% CI | Group<br>B/E/G/I<br>N=45 | Group C<br>N=30 | Group D<br>N=25 | Group A<br>N=31 | Group F<br>N=27 | Group H<br>N=25 |
| B/E/G/I:<br>Placebo | 42.44<br>n=45 | (40.41,<br>44.46) | | 3.33<br>(0.14,6.52)<br>0.0410 | -0.30<br>(-3.92,3.32)<br>0.8696 | -1.37<br>(-4.57,1.83)<br>0.3980 | -0.54<br>(-3.82,2.74)<br>0.7461 | -1.48<br>(-4.96,2.00)<br>0.4010 |
| C: Prednisone | 45.77<br>n=30 | (43.30,<br>48.24) | | | -3.63<br>(-7.51,0.25)<br>0.0665 | -4.70<br>(-8.20,-1.20)<br>0.0088 | -3.87<br>(-7.44,-0.30)<br>0.0338 | -4.81<br>(-8.57,-1.06)<br>0.0123 |
| D: 20 mg<br>BCT197 | 42.13<br>n=25 | (39.14,<br>45.13) | | | | -1.07<br>(-4.95,2.80)<br>0.5856 | -0.24<br>(-4.18,3.71)<br>0.9056 | -1.18<br>(-5.30,2.94)<br>0.5714 |
| A: 75 mg<br>BCT197 | 41.06<br>n=31 | (38.59,<br>43.53) | | | | | 0.83<br>(-2.73,4.40)<br>0.6440 | -0.11<br>(-3.87,3.65)<br>0.9538 |
| F: 20 mg<br>BCT197<br>Repeat | 41.90<br>n=27 | (39.33,<br>44.47) | | | | | | -0.94<br>(-4.77,2.88)<br>0.6260 |
| H: 75 mg<br>BCT197<br>Repeat | 40.95<br>n=25 | (38.12,<br>43.78) | | | | | | |

Notes:
Group A (75 mg BCT197); Group B/E/G/I (placebo); Group C (40 mg prednisone); Group D (20 mg BCT197);
Group F (20 mg BCT197 Repeat); Group H (75 mg BCT197 Repeat);
Improvement from baseline = EXACT-PRO rolling average score at Day 1 - EXACT-PRO rolling average score;
Least Square Means (LSMeans) for each treatment group are obtained from the model;
EXACT-PRO rolling average AUC from Day 1 to Day 14 = Intercept + S1*treatment + S2*baseline + Error,
where baseline is the 3 day rolling average from Day 1.
Using the MIXED procedure, a two-sided 95% confidence interval for difference in EXACT-PRO rolling average AUC is obtained.

## Safety Results

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

| | | Treatment Group | | | | | |
|---|---|---|---|---|---|---|---|
| | | A | B/E/G/I | C | D | F | H |
| | | N=31 | N=45 | N=30 | N=25 | N=27 | N=25 |
| | | n (%) | n (%) | n (%) | n (%) | n (%) | n (%) |
| Patients with at least one AE | | 12 (39) | 26 (58) | 16 (53) | 13 (52) | 15 (56) | 16 (64) |
| **Primary SOC** | **Preferred term** | | | | | | |
| Respiratory, thoracic & mediastinal disorders | Chronic obstructive pulmonary disease | 1 (3) | 12 (27) | 5 (17) | 4 (16) | 5 (19) | 6 (24) |
| | Rhinorrhea | 0 | 2 (4) | 0 | 0 | 0 | 0 |
| Investigations | Alanine aminotransferase increased | 0 | 0 | 0 | 1 (4) | 0 | 1 (4) |
| | Aspartate aminotransferase increased | 0 | 0 | 0 | 1 (4) | 0 | 1 (4) |
| | Blood glucose increased | 0 | 0 | 0 | 0 | 1 (4) | 1 (4) |
| | Occult blood | 3 (10) | 3 (7) | 3 (10) | 5 (20) | 4 (15) | 0 |
| Infections & infestations | Nasopharyngitis | 2 (7) | 2 (4) | 3 (10) | 4 (16) | 4 (15) | 1 (4) |
| | Pneumonia | 0 | 1 (2) | 1 (3) | 0 | 1 (4) | 2 (8) |
| | Urinary tract infection bacterial | 0 | 0 | 0 | 1 (4) | 1 (4) | 0 |
| | Viral upper respiratory tract infection | 0 | 1 (2) | 1 (3) | 0 | 0 | 0 |
| Nervous system disorders | Dizziness | 2 (7) | 0 | 0 | 0 | 0 | 3 (12) |
| | Headache | 1 (3) | 3 (7) | 3 (10) | 1 (4) | 1 (4) | 0 |
| Gastrointestinal disorders | Abdominal pain upper | 1 (3) | 0 | 1 (3) | 0 | 1 (4) | 0 |
| | Diarrhea | 1 (3) | 2 (4) | 0 | 0 | 1 (4) | 2 (8) |
| | Dyspepsia | 0 | 0 | 0 | 1 (4) | 1 (4) | 0 |
| | Nausea | 0 | 3 (7) | 2 (7) | 0 | 0 | 2 (8) |
| Vascular disorders | Hypertension | 1 (3) | 1 (2) | 2 (7) | 1 (4) | 1 (4) | 0 |
| | Hypertensive crisis | 0 | 0 | 1 (3) | 1 (4) | 0 | 1 (4) |
| | Peripheral arterial occlusive disease | 0 | 1 (2) | 0 | 1 (4) | 0 | 0 |
| Cardiac disorders | Cardiac failure acute | 1 (3) | 0 | 1 (3) | 0 | 0 | 0 |
| | Cor pulmonale | 0 | 0 | 0 | 0 | 1 (4) | 1 (4) |
| Musculoskeletal & connective tissue disorders | Back pain | 0 | 1 (2) | 0 | 1 (4) | 0 | 0 |
| | Neck pain | 0 | 0 | 0 | 1 (4) | 1 (4) | 0 |
| Ear & labyrinth disorders | Vertigo | 1 (3) | 1 (2) | 1 (3) | 0 | 0 | 0 |
| Psychiatric disorders | Insomnia | 0 | 0 | 1 (3) | 1 (4) | 1 (4) | 0 |
| Blood & lymphatic system disorders | Eosinophilia | 0 | 0 | 0 | 0 | 0 | 2 (8) |
| Skin & subcutaneous tissue disorders | Rash | 0 | 0 | 0 | 0 | 0 | 2 (8) |

SOC are presented in descending order of frequency in total group, preferred terms presented in alphabetical order within SOC

Group A (75 mg BCT197); Group B/E/G/I (placebo); Group C (40 mg prednisone); Group D (20 mg BCT197); Group F (20 mg BCT197 Repeat); Group H (75 mg BCT197 Repeat).

## Serious Adverse Events and Deaths

| | Treatment group | | | | | |
|---|---|---|---|---|---|---|
| | A | B/E/G/I | C | D | F | H |
| | N=31 | N=45 | N=30 | N=25 | N=27 | N=25 |
| **Patients with SAEs** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** | **n (%)** |
| Death | 1 (3) | 0 | 2 (7) | 1 (4) | 1 (4) | 1 (4) |
| SAEs | 1 (3) | 4 (9) | 3 (10) | 1 (4) | 2 (7) | 2 (8) |
| Discontinued due to AEs | 0 | 0 | 0 | 0 | 0 | 0 |

Group A (75 mg BCT197); Group B/E/G/I (placebo); Group C (40 mg prednisone); Group D (20 mg BCT197); Group F (20 mg BCT197 Repeat); Group H (75 mg BCT197 Repeat).

Source:

## Incidence of SAEs

| Primary system organ class | | | Respiratory[2] | Neoplasms[3] | Infections and infestations | |
|---|---|---|---|---|---|---|
| Preferred term | | | COPD[4] | Bladder cancer | Pneumonia | Sinusitis |
| Group | N | Patients with any SAE[1] -- n(%) | n (%) | n (%) | n (%) | n (%) |
| Group A | 31 | 1 (3) | 0 | 0 | 0 | 1 (3) |
| Group B/E/G/I | 45 | 4 (9) | 3 (7) | 0 | 1 (2) | 0 |
| Group C | 30 | 3 (10) | 3 (10) | 0 | 1 (3) | 0 |
| Group D | 25 | 1 (4) | 0 | 1 (4) | 0 | 0 |
| Group F | 27 | 2 (7) | 2 (7) | 0 | 1 (4) | 0 |
| Group H | 25 | 2 (8) | 2 (8) | 0 | 0 | 0 |

[1] excluding deaths, [2] Respiratory, thoracic and mediastinal disorders, [3] Neoplasms benign, malignant & unspecified, [4] preferred term for COPD exacerbation.

Group A (75 mg BCT197); Group B/E/G/I (placebo); Group C (40 mg prednisone); Group D (20 mg BCT197); Group F (20 mg BCT197 Repeat); Group H (75 mg BCT197 Repeat).

## Other Relevant Findings

None

## Date of Clinical Trial Report

18- Feb-2014

## Date Inclusion on Novartis Clinical Trial Results Database

25 April, 2014

## Date of Latest Update