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2 SYNOPSIS

Name of Sponsor/Company: **Asubio Pharmaceuticals, Inc.**	**Individual Study Table Referring to Part of the Dossier**	**(*For National Authority Use only*)**
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Title of Study:

A Phase 2b, Multicenter, Randomized, Double-Blind, Parallel, Placebo-Controlled Study to Evaluate the Efficacy and Safety of SUN11031 for Injection Administered Subcutaneously Twice Daily for 12 Weeks to Subjects Having Cachexia Associated with Chronic Obstructive Pulmonary Disease

Investigator(s): Principal Investigators from 45 sites

Study Center(s): Multicenter study (45 sites)

Publication (reference): There have been no publications based on this study.

Studied Period (years):	**Phase of Development:** 2b
15 May 2008 (date of first subject enrollment) 08 October 2009 (date last subject completed)	

Objectives:

The primary objective of this study was to evaluate the effect of SUN11031 for injection (a synthetic human ghrelin [hereafter referred to as SUN11031]) versus placebo administered subcutaneously to subjects with cachexia associated with chronic obstructive pulmonary disease (COPD) on the change in distance walked during the six-minute walk test (6MWT) between baseline and the end of 12 weeks of dosing.

The secondary objectives of the study were:

- To evaluate the effect of SUN11031 versus placebo administered subcutaneously to subjects with cachexia associated with COPD on the change in distance walked during the 6MWT between baseline and Days 29 and 57 after 4 and 8 weeks of dosing, respectively
- To evaluate the safety of SUN11031 administered subcutaneously twice daily (bid) for 12 consecutive weeks in subjects with cachexia associated with COPD
- To explore the effect of SUN11031 administered subcutaneously to subjects with cachexia associated with COPD on changes in body weight, body composition, appetite, dyspnea, functional physical performance (handgrip strength, the Short Physical Performance Battery [SPPB] and its components, and maximal inspiratory pressure [PI_{max}]), and in laboratory indicators of nutritional status
- To evaluate the pharmacokinetics (PK) of SUN11031 and the associated expression of the biomarkers growth hormone (GH), cortisol, insulin-like growth factor-1 (IGF-1), C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) following subcutaneous administration of SUN11031 to subjects with cachexia associated with COPD

Methodology:

This was a phase 2b, multicenter, randomized, double-blind, parallel, placebo-controlled study conducted on an outpatient basis. The study included a Screening Visit (within 14±7 days of treatment initiation [ie, Days -21 to -7]), a Baseline Visit (Days -6 to -3), a 12-week Treatment Period with study visits at Days 1, 8, 15, 22, 29, 43, 57, and 85, and 1 to 2 Follow-up Visits (Days 99 and 113). A window of ±3 days was allowed for study visits during the Treatment Period (except Day 1); a window of ±7 days was allowed for the Follow-up Visits. The total number of study visits was 11 to 12 visits. The total duration of subject participation was anticipated to be approximately 16 to 19 weeks. Visits were scheduled to occur weekly for the first month on treatment (Days 8, 15, 22, and 29), biweekly the second month on treatment (Days 43 and 57), and at the end of the 3-month Treatment Period (Day 85). A Follow-up Visit (Follow-up 1) was conducted at Day 99 (±7 days); a second Follow-up Visit (Follow-up 2) was conducted at Day 113 (±7 days) for subjects who had serious adverse events (SAEs),

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treatment-emergent adverse events (TEAEs), or notable safety findings at the first Follow-up Visit. All clinically significant TEAEs were followed until resolution, until they became stable, or until they were considered no longer clinically significant. Subjects were advised to take their breakfast (in the morning) and dinner (in the evening) meals approximately 30 minutes after dosing with study drug. Subjects, or a suitable alternative household member or health care provider, were trained to administer study drug, and study drug was dispensed to the subjects at each study visit and weekly between visits as needed.

Number of Subjects (planned and analyzed):

Planned: up to 225 male or female adults.

Randomized: 227 subjects (76 to placebo, 75 to 20 µg/kg bid, and 76 to 40 µg/kg bid).

Safety Population (all randomly assigned subjects who received at least 1 dose of study treatment): 224 subjects (73 subjects treated with placebo, 75 subjects treated with 20 µg/kg bid, and 76 subjects treated with 40 µg/kg bid).

Intent-to-Treat (ITT) Population (all subjects in the Safety Population who had a baseline and at least 1 valid on-treatment assessment of distance walked during the 6MWT): 214 subjects (72 subjects treated with placebo, 73 subjects treated with 20 µg/kg bid, and 69 subjects treated with 40 µg/kg bid).

Efficacy Evaluable (EE) Population (all subjects in the ITT Population who completed at least 8 weeks of treatment and had a distance walked during the 6MWT at Day 57 and achieved treatment compliance of greater than or equal to 80%): 188 subjects (65 subjects treated with placebo, 59 subjects treated with 20 µg/kg bid, and 64 subjects treated with 40 µg/kg bid).

PK Population (all subject who underwent plasma PK sampling during the study): 223 subjects (73 subjects treated with placebo, 74 subjects treated with 20 µg/kg bid, and 76 subjects treated with 40 µg/kg bid).

Diagnosis and Main Criteria for Inclusion:

Male or non-pregnant female subjects 50 year or older with a clinical diagnosis of COPD for 12 or more months based on chest x-ray and spirometry, with documented involuntary nonedematous weight loss of more than 5% of the subject's usual body weight over the past 12 months or body mass index (BMI) less than or equal to 21 kg/m^2 for males or BMI less than or equal to 20 kg/m^2 for females, and having walked a distance of at least 100 but no more than 450 meters during the 6MWT. Female subjects were required to be clinically sterile or practicing a medically acceptable method of birth control.

Test Product; Dose and Mode of Administration; Batch Number:

SUN11031 7 mg multi-use vials; 20 µg/kg bid subcutaneous injection; Lot numbers 6Y25 and [redacted].
SUN11031 14 mg multi-use vials; 40 µg/kg bid subcutaneous injection; Lot numbers 6Y27 and [redacted]
Diluent for SUN11031 (5 mL fill in a 5 mL vial); Lot numbers [redacted], [redacted], [redacted], [redacted], and [redacted].

Duration of Treatment:

85 days (on the last day of the 12-week Treatment Period, only the morning dose was administered)

Reference Therapy, Dose and Mode of Administration, Batch Number:

Matching SUN11031 placebo multi-use vials; volume of placebo matched the volume of active drug and was administered subcutaneously bid; Lot numbers [redacted] and [redacted].
Diluent for SUN11031 placebo; Lot numbers [redacted] and [redacted].

Criteria for Evaluation:

Efficacy

- Six-minute walk test (screening, baseline, and Days 29, 57, and 85)
- Body weight and BMI (screening, baseline, and Days 1 through 99 [and 113 if applicable])
- Appetite assessment via a visual analog scale (VAS [screening, Day 1, and Days 15 through 85])

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- Handgrip strength (baseline and Days 29, 57, and 85)
- Short Physical Performance Battery and its components (balance test, gait speed test, and chair stand test [baseline and Days 29, 57, and 85])
- Maximal inspiratory pressure (PI_{max} [baseline and Days 29, 57, and 85])
- Body composition (lean body mass [LBM] and fat mass) on dual-energy x-ray absorptiometry (DXA [baseline and Days 29, 85, and 99])
- Fat-Free mass index (FFMI [baseline and Days 29, 85, and 99])
- Modified Medical Research Council (MMRC) dyspnea scale (baseline and Days 8, 29, 57, and 85)
- Laboratory indicators of nutritional status (prealbumin, total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], and triglycerides [assessed at screening and Days 1, 8, 29, 57, 85, and 99])

Pharmacokinetics and Pharmacodynamics

Blood samples for PK analyses of SUN11031 and its metabolite desacyl-ghrelin were collected from all treatment groups at 6 time points at Days 1, 29, 57, and 85 using a sparse sampling schedule designed to support population PK and pharmacometric modeling. Ghrelin exposures were modeled and corresponded to specific pharmacodynamic (PD) endpoints for PKPD correlations. Plasma samples were assayed for SUN11031 and desacyl-ghrelin using an enzyme-linked immunosorbent assay (ELISA) method.

Biomarkers

Two biomarkers (GH and cortisol) were measured according to a sparse PK sampling schedule, GH at Days 1, 29, 57, and 85 and cortisol at Days 1 and 85. Four other biomarkers (IGF-1, CRP, TNF-α, and IL-6) were measured at Days 1, 29, 57, and 85 before the morning dose. These biomarkers were quantified using a one-step immunoenzymatic assay (GH, IGF-1, TNF-α, and IL-6), competitive binding immunoenzymatic assay (cortisol), and immuno-nephelometry assay (CRP).

Safety

Safety and tolerability were assessed throughout the study by monitoring treatment-emergent adverse events (TEAEs) and SAEs; use of concomitant medications; lung function as measured by forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC captured with standardized spirometry; laboratory studies (hematology, serum chemistry, and urinalysis), including an oral glucose tolerance test (OGTT) and venous blood glucose measurements collected after an overnight fast and 2 hours after the start of breakfast, glycosylated hemoglobin (HbA_{1c}), and antibody to human ghrelin; orthostatic vital signs (blood pressure, radial or brachial pulse rate), and other vital signs, including respiration rate, oral temperature, and pulse oximetry; physical examinations, including an assessment of exacerbation of COPD (Winnipeg criteria); and 12-lead electrocardiograms (ECGs).

Statistical and Analytical Methods:

Descriptive statistics (including sample size [n], mean, median, minimum, and maximum values) are presented in summary tables for all continuous parameters. Discrete variables are summarized using counts and percentages. Percentages were based on the number of subjects with nonmissing observations. All data are provided in listings for all subjects. All predefined analyses were performed using S-PLUS scripts (S-PLUS 8.1 for Windows, Professional Developer) and validated by an independent biostatistics group using SAS (version 9.1). All post-hoc analyses were performed using SAS (version 9.1). Statistical testing was only performed for efficacy parameters and included comparison of each of the two active treatment groups to placebo. All statistical tests were conducted at the two-sided 0.05 significance level, unless otherwise specified. The last available value from any Screening Visit was used as the definition of screening for efficacy and safety data. The last available value from scheduled

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or unscheduled visits prior to dosing was used as the definition of baseline for efficacy and safety data.

Efficacy

Predefined

The primary efficacy analysis was a comparison of the mean change from baseline to Day 85 in the distance walked in 6MWT for each of the 2 active treatment groups compared to placebo for subjects in the ITT Population. The between-treatment comparisons were performed using analysis of covariance (ANCOVA) with the corresponding baseline assessment as the covariate and treatment as the only factor. Missing efficacy data were imputed using a last postbaseline observation carried forward (LOCF) approach. Supportive analyses of the primary efficacy endpoint were performed for the ITT Population on observed cases only (with no LOCF imputation) and for the EE Population (using LOCF).

Secondary efficacy variables were analyzed for the ITT and EE populations using the same approach as used for the primary efficacy variable, including analyses of mean change and mean percent change from baseline using LOCF and ANCOVA with factor treatment and the corresponding baseline assessment as the covariate. Because all secondary efficacy analyses were exploratory, no adjustments were made for multiple comparisons or multiple endpoints, including no step-down procedure.

Subgroup Analyses

If there was an adequate number of subjects in a given subgroup, select efficacy endpoints were analyzed using the ITT and EE populations for the following proposed subgroups :

- Sex (male versus female)
- Age (younger than 65 years versus 65 years or older)
- Region (South America, Central America, North America, Eastern Europe)
- Site (for sites with 15 or more subjects)
- Body mass index (less than median value versus greater than or equal to median value)
- Forced expiratory volume in 1 second (less than median value versus greater than or equal to median value)
- Combination of FEV_1 and BMI (FEV_1 less than median value combined with BMI less than median value; FEV_1 greater than or equal to median value combined with BMI less than median value; FEV_1 less than median value combined with BMI greater than or equal to median value; FEV_1 greater than or equal to median value combined with BMI greater than or equal to median value)

The median used to define the subgroups above was the median at baseline pooled across treatments.

Responder Analyses

If there was an adequate number of subjects in a given responder analysis category, select efficacy endpoints were analyzed using the ITT and EE populations.

Several responder analyses were performed for the ITT and EE populations and by subgroups. Comparisons for each of the 2 active treatment groups compared to placebo were performed using Cochran-Mantel-Haenszel (CMH) test controlling for country.

Post-hoc Analyses

Data from subjects in the ITT Population with a baseline BMI less than the median of 18.9 kg/m^2 indicated that these subjects responded more favorably to drug therapy than the ITT Population as a whole. Post-hoc analysis was conducted using a definition of advanced cachexia as described by Schols' criteria which included BMI less than 21 kg/m^2 and FFMI less than 16 kg/m^2 for men and less than 15 kg/m^2 for women at baseline.

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Pharmacokinetics and Pharmacodynamics

Non-Modeling Analysis

For plasma concentrations of ghrelin, desacyl-ghrelin, and biomarkers (GH, cortisol, IGF-1, CRP, TNF-α, and IL-6) descriptive statistics (n, mean, SD, coefficient of variation, median, minimum, maximum, and geometric mean) are provided across time points by treatment.

Modeling Analysis

Ghrelin results were thought to be more important than those of its metabolite desacyl-ghrelin and were used in the PKPD analysis. A prior population PK model (N=50) developed from healthy volunteers (ASBI 301) and the maximum a posteriori Bayesian estimates from the observed ghrelin data of the current study were used. The ASBI 304 data demonstrated that PK in subjects with cachexia associated with COPD and healthy states were comparable based on PK data from prior studies in healthy volunteers (ASBI 301) and in subjects with cachexia associated with COPD (ASBI 304). The model used was a two-compartment linear model with the first-order absorption using the first-order conditional estimation method with interaction. Exposure-response datasets were developed from source SAS XPORT data sets. Objectives of these analyses included the exploratory evaluation of:

- The exposure-response relationship between steady-state plasma exposure parameters (area under the concentration-time curve at steady state [AUC_{ss}]) of ghrelin at Day 85 and improvement in several efficacy and PD analyses between baseline and Days 8 and 85

Safety

All safety summaries were based on the Safety Population and are presented by treatment received.

Adverse Events

All collected data are presented in the listings but only TEAEs are summarized. Adverse events were classified by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA), version 11.1, and the incidence was summarized by treatment.

The occurrence of TEAEs including frequency, severity, and relatedness is summarized by treatment according to preferred term and SOC.

Lung Function via Spirometry

Summary statistics are presented for FEV_1, FVC, and FEV_1/FVC captured via spirometry, and mean change from baseline to Day 85, and for all intervening visits except at Day 1, analyzed and presented for each of the 3 parameters. Abnormalities in spirometry measurements are presented in shift tables.

Clinical Laboratory Parameters, Glucose Metabolism, and Antibody to Human Ghrelin

Summary statistics of laboratory measurements (hematology, serum chemistry, and urinalysis) and change from baseline by laboratory type are presented by treatment group and time point. Summary statistics of glucose metabolism parameters (OGTT, fasting and postprandial venous blood glucose measurements, and HbA_{1c}) and change from baseline by parameter are presented by treatment group and time point. Abnormalities in laboratory measurements and glucose metabolism are presented in shift tables. Summary statistics of antibody to human ghrelin are presented by treatment group and time point.

Vital Signs and Pulse Oximetry

Vital signs and pulse oximetry and change from baseline are summarized by treatment group and time point. Measures included blood pressure (standing and recumbent [mm Hg]), radial or brachial heart rate (standing and recumbent [beats per minute]), respiratory rate (breaths per minute), and oral or tympanic temperature (°C). Abnormalities in vital signs are presented in shift tables.

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Physical Examinations

Listings of the results of physical examinations for subjects in the safety population are provided.

Winnipeg Criteria for COPD Exacerbation

Summary statistics of the actual values and change from baseline for Winnipeg criteria for COPD exacerbations at each time point are summarized and abnormalities are presented in shift tables.

Electrocardiogram

Twelve-lead ECG data (RR, PR, QRS, and QT intervals) are summarized by treatment group and time point. Twelve-lead ECG data (from screening to follow-up) and change from baseline are summarized by category, treatment group, and time point.

Results:

Study Subjects and Conduct:

This study was performed at 45 sites (11 sites in the US and 34 sites outside the US). A total of 278 subjects were screened, 51 of these subjects were not randomized or treated, and 3 randomized subjects did not receive a dose of study drug. Of the 224 treated subjects, 192 subjects (85.7%) completed and were fairly well distributed across the 3 treatment groups (67 [91.8%] placebo subjects, 60 [80.0%] 20 µg/kg bid subjects, and 65 [85.5%] 40 µg/kg bid subjects).

The majority of subjects in the ITT Population were male (140 [65.4%] subjects). In the ITT Population, the mean (SD) age was 65.6 (8.70) years, median age was 65.0 years, and the range (minimum to maximum) of ages was 47 to 89 years. The majority of subjects in the ITT Population were white (193 [90.2%] subjects). Demographic data for the Safety and EE populations were similar to what was observed in the ITT Population.

Efficacy Results:

Any p-value ≤0.05 was considered to be statistically significant.

Predefined Primary Efficacy Endpoint in ITT Population

SUN11031 administration for 85 days did not result in improvement in the distance walked during the 6MWT versus placebo. Mean increases from baseline in distance walked during the 6MWT at Day 85 were statistically significantly larger for placebo compared to SUN11031 20 µg/kg and were numerically larger for placebo compared to SUN11031 40 µg/kg. At Day 85, mean (SD) change from baseline in distance walked during the 6MWT was 28.50 (54.722) meters in the placebo group, 5.85 (53.388) meters in the 20 µg/kg bid group (P=0.025; favoring placebo), and 10.04 (62.160) meters in the 40 µg/kg bid group (P=0.073). Supportive analysis of the primary efficacy endpoint in the ITT Population on observed cases only (no LOCF imputation) were similar to those using LOCF.

Predefined Secondary Efficacy Endpoints in ITT Population

Secondary Strength and Functional Endpoints

No consistent statistically significant differences between active and placebo were observed in the 6MWT, handgrip strength of either the dominant or nondominant hand, PI_{max}, or overall SPPB and its components.

Body weight and BMI

Statistically significant increases from baseline with active treatment versus placebo in mean body weight were observed from Day 8 (first on-treatment measurement) and continued to Day 85. At Day 85, mean change from baseline in body weight was 0.90 (1.705) kg in the placebo group, 1.75 (2.271) kg in the 20 µg/kg bid group (P=0.020), and 2.44 (2.178) kg in the 40 µg/kg bid group (P<0.001). Body mass index is proportional to body weight and the results for BMI, as expected, were similar to those for body weight.

Body Composition (LBM and Fat Mass)

Statistically significant increases from baseline with active treatment versus placebo in mean LBM were observed

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from Day 29 (first on-treatment measurement) and continued to Day 85. At Day 85, mean change from baseline in LBM was 0.29 (1.055) kg in the placebo group, 1.36 (1.239) kg in the 20 µg/kg bid group (P<0.001), and 1.44 (1.502) kg in the 40 µg/kg bid group (P<0.001). However, no differences between active and placebo treatment were observed in the analysis of mean change from baseline in fat mass.

Appetite Assessment Via a VAS

For the primary appetite assessment question, "How hungry do you feel?" assessed postdose, 10 minutes before breakfast and again 30 minutes after breakfast, no statistically significant differences between active and placebo were observed at Day 85.

Laboratory Indicators of Nutritional Status

At Day 85, mean change from baseline in prealbumin was -0.92 (4.697) mg/dL in the placebo group, 1.06 (5.475) mg/dL in the 20 µg/kg bid group (P=0.008), and 0.34 (5.561) mg/dL in the 40 µg/kg bid group (P=0.039). At Day 85, mean change from baseline in triglycerides was -1.9 (31.76) mg/dL in the placebo group, 7.5 (30.49) mg/dL in the 20 µg/kg bid group (P=0.158), and 13.1 (35.01) mg/dL in the 40 µg/kg bid group (P=0.014).

Subgroup Analyses of Predefined Secondary Efficacy Endpoints

For each select efficacy endpoint predetermined to be analyzed by subgroup (distance walked during the 6MWT, BMI, handgrip strength, SPPB and components by quartiles, PI_{max}, MMRC dyspnea scale, and laboratory indicators of nutritional status) all subgroup analyses (sex, age, region, site, BMI, FEV_1, and combination of BMI and FEV_1) showed similar results across the subgroups as well as the primary ITT analysis for a given endpoint. An exception was for subjects with a baseline BMI less than 18.9 kg/m^2, where mean changes and mean percent changes from baseline relative to placebo in overall SPPB quartile scores were numerically similar for all three treatment groups.

Responder Analyses of Predefined Secondary Efficacy Endpoints

Responder analyses using various predefined responder categories of select endpoints (6MWT, body weight, SPPB and components epidemiological and quartile scores, LBM, COPD exacerbations, and *Strong for Life*) in the ITT Population overall showed similar results to the primary analyses of these endpoints in the ITT Population as a whole. Responder analyses by subgroups showed similar results to those seen in the ITT Population as a whole. Select responder analyses are described in further detail below.

Body weight

Significantly more ITT subjects treated with 40 µg/kg bid experienced an increase in body weight (>0%) at Day 85 compared to placebo (65.3% for placebo, 78.1% for 20 µg/kg bid [P=0.095], and 85.5% for 40 µg/kg bid [P=0.007]). Significantly more ITT subjects treated with either dose of SUN11031 experienced an increase in body weight of greater than or equal to 3% at Day 85 compared to placebo (33.3% for placebo, 54.8% for 20 µg/kg bid [P=0.005], and 65.2% for 40 µg/kg bid [P=0.001]). Significantly more ITT subjects treated with either dose of SUN11031 experienced an increase in body weight of greater than or equal to 2 kg at Day 85 compared to placebo (25.0% for placebo, 49.3% for 20 µg/kg bid [P=0.001], and 62.3% for 40 µg/kg bid [P<0.001]).

LBM

Significantly more ITT subjects treated with either dose of SUN11031 experienced an increase in LBM of greater than or equal to 3% at Day 85 compared to placebo (17.6% for placebo, 61.4% for 20 µg/kg bid [P<0.001], and 58.8% for 40 µg/kg bid [P<0.001]). Significantly more ITT subjects treated with either dose of SUN11031 experienced an increase in LBM of greater than or equal to 4% at Day 85 compared to placebo (11.8% for placebo, 45.7% for 20 µg/kg bid [P<0.001], and 44.1% for 40 µg/kg bid [P<0.001]).

Predefined Efficacy Analyses in the EE Population

Analyses of predefined efficacy endpoints in the EE Population, including subgroup and responder analyses, were

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comparable to those in the ITT Population as described above.

Post-hoc Analyses

Exploratory post-hoc analyses were conducted in subjects with advanced cachexia at baseline based on Schols' criteria (BMI less than 21 kg/m^2 and FFMI less than 16 kg/m^2 for men and less than 15 kg/m^2 for women at baseline) and showed that subjects from this post-hoc population who also gained LBM or body weight showed statistically significant improvements in functional performance (SPPB and nondominant handgrip strength) on SUN11031 at the 40 µg/kg bid dose.

Lean body mass in Subjects With Advanced Cachexia at Baseline Based on Schols' Criteria

Responder analysis of improvement in LBM at Day 85 showed that statistically significantly more SUN11031-treated subjects in both treatment groups were responders (22 [56.4%] for placebo subjects, 36 [81.8%] for 20 µg/kg bid subjects [*P*=0.017], and 30 [88.2%] of 40 µg/kg bid subjects [*P*=0.001]).

Functional Assessments in Subjects With Advanced Cachexia at Baseline Based on Schols' Criteria and an Increase in LBM at Day 85

The percentage of subjects treated with 40 µg/kg bid with an improvement at Day 85 in 6MWT (19 [55.9%] subjects [*P*=0.030]) and overall SPPB quartile score (20 [58.8%] subjects [*P*=0.005]) was statistically significantly larger than those treated with placebo (14 [35.9%] subjects and 10 [25.6%] subjects, respectively). Responder analysis of improvement in handgrip strength (dominant and nondominant hand) and PI_{max} at Day 85 did not demonstrate a statistically significant difference between 40 µg/kg bid and placebo treatment groups. The percentage of subjects treated with 20 µg/kg bid with an improvement at Day 85 in nondominant hand handgrip strength (21 [48.8%] subjects [*P*=0.032]) and PI_{max} (27 [62.8%] subjects [*P*=0.004]) was statistically significantly larger than those treated with placebo (10 [25.6%] subjects and 12 [30.8%] subjects, respectively). Subjects treated with 20 µg/kg bid did not show a significant difference from placebo in improvement at Day 85 in responder analysis of 6MWT, overall SPPB quartile score, or handgrip strength of the dominant hand.

Overall SPPB Quartile Scores in Various Post-hoc Subsets of ITT Subjects

Post-hoc analysis showed that ITT subjects with advanced cachexia at baseline based on Schols' criteria treated with SUN11031 did not experience an improvement in the overall SPPB quartile scores versus placebo. The ITT subjects with advanced cachexia at baseline based on Schols' criteria that also had an improvement in LBM at Day 85 compared to baseline treated with 40 µg/kg bid experienced a statistically significant improvement versus placebo in mean percent change from baseline in overall SPPB quartile scores by Day 57 (3.8 [16.96]% for placebo subjects and 15.0 [21.22]% for 40 µg/kg bid subjects [*P*=0.044]). This significant difference continued at Day 85 (6.2 [16.27]% for placebo subjects and 20.0 [22.68]% for 40 µg/kg bid subjects [*P*=0.012]). Similar results were observed in subjects with advanced cachexia at baseline based on Schols' criteria and body weight gain from baseline at Days 8 or 29. Significant differences observed at the 40 µg/kg bid dose were not observed in the 20 µg/kg bid group.

Body Weight as a Predictor of Improvement in LBM in ITT Population

Post-hoc responder analysis of ITT subjects with body weight gain at Days 8, 15, and 29 compared to baseline who also achieved a gain in LBM at Day 85 compared to baseline showed that the majority of actively treated subjects (86%) who gained weight by Day 8 also experienced an improvement in LBM at Day 85. Across all time points (Days 8, 15, and 29), the simple diagnostic criterion of weight gain from baseline was likely to select subjects with a LBM gain at Day 85 in the ITT Population (85% to 88%).

Other Strength and Functional Endpoints in Subjects With Advanced Cachexia at Baseline Based on Schols' Criteria and an Improvement in LBM at Day 85

At each time point, mean increases from baseline in distance walked during the 6MWT, PI_{max}, and handgrip strength in the dominant hand were similar for the 3 treatment groups. Mean change from baseline in handgrip strength of the nondominant hand at Day 85 was -1.45 (7.405) kg in the placebo group, 3.19 (8.271) kg in the

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20 µg/kg bid group (*P*=0.021), and 1.93 (5.042) kg in the 40 µg/kg bid group (*P*=0.100).

Lean Body Mass in Subjects With Advanced Cachexia at Baseline Based on Schols' Criteria

Statistically significant increases in LBM were observed in mean change from baseline in LBM at Days 29 and 85 for the 40 µg/kg bid group and at Day 85 for the 20 µg/kg bid group compared to placebo. At Day 85, mean change from baseline in LBM was 0.35 (1.122) kg for placebo subjects, 1.24 (1.267) kg for 20 µg/kg bid subjects (*P*=0.002), and 1.36 (1.145) kg for 40 µg/kg bid subjects (*P*=0.002).

Pharmacokinetic and Pharmacodynamic Results:

SUN11031 and Desacyl-Ghrelin

Within the study, the bioanalysis of SUN11031 and desacyl-ghrelin fulfilled the validation criteria, including the incurred sample reanalysis for acceptance. However, it was found that the concentration values of ghrelin overall in this study were about 50% of those for corresponding doses evaluated in previous studies of SUN11031, specifically, a phase 1 study conducted in healthy volunteers (ASBI 301) and a phase 2 study conducted in subjects with cachexia associated with COPD (ASBI 304). The differences were thought to be accounted for by assay variability and different study conditions.

Predefined Analyses of PK and Biomarkers for the Study Population

Absolute mean (SD) GH levels significantly increased from baseline in the active treatment groups compared to placebo at Day 85 at 0.5 hours after dosing (1.14 [3.565] ng/mL for placebo; 13.66 [15.830] ng/mL for 20 µg/kg bid [*P*<0.001], and 17.29 [16.995] ng/mL for 40 µg/kg bid [*P*<0.001]). The pattern of cortisol responses to SUN11031 administration over time was similar to that of GH.

Long-term administration of SUN11031 increased absolute mean IGF-1 levels in both actively treated groups compared to placebo at Day 29; however, the increase was statistically significantly different from placebo only in the 40 µg/kg bid group. Thereafter, on Day 57, the increase in IGF-1 was maintained only in the 40 µg/kg bid group. At Day 85, the IGF-1 values for the 40 µg/kg bid group remained statistically significantly increased compared to the placebo group : 84.7 (29.10) ng/mL for placebo, 87.1 (39.74) ng/mL for 20 µg/kg bid (*P*=0.199), and 94.6 (34.56) ng/mL for 40 µg/kg bid (*P*=0.013). No clinically meaningful changes in CRP, TNF-α, or IL-6 with SUN11031 treatment were observed.

Post-hoc Non-Modeling Analysis of IGF-1 in subjects with advanced cachexia at baseline based on Schols' criteria

The 40 µg/kg bid group induced a nonsignificant but consistent increase in IGF-1 at Days 29, 57, and 85 whereas the 20 µg/kg bid group was associated with nonsignificant and inconsistent increases in IGF-1 values. At Day 85, mean changes from baseline were 7.7 (27.24) ng/mL for placebo, 9.9 (25.33) ng/mL for 20 µg/kg bid (*P*=0.826), and 17.9 (28.81) ng/mL for 40 µg/kg bid (*P*=0.418).

Predefined Modeling Analysis of Ghrelin

In contrast to a small number of samples per subject in typical sparse sampling schemes, the sparse sampling scheme used in this study collected 6 samples per subject and therefore the resultant Bayesian estimates were heavily influenced by the observed concentrations. Pharmacokinetics of SUN11031 was linear over time, implying a rapid achievement of steady-state conditions, and dose proportionality that was maintained over the Treatment Period.

No obvious relationship was observed between 2-hour postload value from OGTT (mmol/L; Day 8) and predicted AUC_{ss} (pg·h/mL; Day 85). Similarly, there was no obvious relationship between the change in 2-hour postprandial glucose between baseline and Day 85 versus increasing drug exposure, using the original PKPD plan.

Graphic trends in changes in some PD parameters (eg, body weight, IGF-1, and chair stand time) as compared to the AUC of ghrelin levels were observed. Two PD parameters, body weight and chair stand time, had apparent trends of improvement with increasing ghrelin AUC in the general population and were further evaluated in post-hoc analysis.

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Post-hoc Modeling Analysis in subjects with advanced cachexia at baseline based on Schols' criteria
Subset analyses demonstrated a consistent increase in body weight gain and improvement in chair stand time with ghrelin exposure.

Safety Results:

The percentages of subjects who had at least one TEAE were similar among the 3 treatment groups (58 of the 73 subjects [79.5%] treated with placebo, 59 of the 75 subjects [78.7%] treated with 20 µg/kg bid, and 56 of the 76 subjects [73.7%] treated with 40 µg/kg bid). The majority of TEAEs were mild or moderate in severity.

The percentages of subjects who had at least one TEAE resulting in premature discontinuation of study drug were similar among the 3 treatment groups (5 [6.8%] subjects treated with placebo, 7 [9.3%] subjects treated with 20 µg/kg bid, and 5 [6.6%] subjects treated with 40 µg/kg bid).

When combining both active treatment groups (75 subjects treated with 20 µg/kg bid and 76 subjects treated with 40 µg/kg bid), the most frequently reported TEAEs (greater than or equal to 5% of 151 subjects treated with SUN11031) were (by decreasing frequency): COPD (36 [23.8%]), injection site hematoma and weight decreased (10 [6.6%] each), headache (9 [6.0%]), bronchitis and nasopharyngitis (8 [5.3%] each). The most frequently observed (in at least 5% of subjects in any treatment group) TEAEs are presented by preferred term below.

Most Frequently Reported Treatment-Emergent Adverse Events (in ≥5% of Subjects in Any Treatment Group) — Safety

Preferred Term, n (%)	Placebo N=73	SUN11031 20 µg/kg bid N=75	SUN11031 40 µg/kg bid N=76
COPD	23 (31.5)	20 (26.7)	16 (21.1)
Injection site hematoma	7 (9.6)	3 (4.0)	7 (9.2)
Headache	5 (6.8)	4 (5.3)	5 (6.6)
Weight decreased	3 (4.1)	6 (8.0)	4 (5.3)
Bronchitis	4 (5.5)	5 (6.7)	3 (3.9)
Diarrhea	7 (9.6)	2 (2.7)	1 (1.3)
Nasopharyngitis	1 (1.4)	6 (8.0)	2 (2.6)
Nausea	3 (4.1)	1 (1.3)	5 (6.6)
Back pain	1 (1.4)	4 (5.3)	3 (3.9)
Injection site pain	2 (2.7)	4 (5.3)	2 (2.6)
Abdominal pain upper	0 (0.0)	4 (5.3)	3 (3.9)
Hypertension	4 (5.5)	1 (1.3)	1 (1.3)
Insomnia	1 (1.4)	0 (0.0)	4 (5.3)
Hyperhidrosis	0 (0.0)	2 (2.7)	4 (5.3)

Data Source: Table 14.3.1.6
Note: Percentages were based on the number of subjects in the Safety Population within each treatment group. The number of subjects with TEAEs cannot be added because a subject may have had more than one TEAE.

Abbreviations: bid = twice daily; COPD = chronic obstructive pulmonary disease; N = number of subjects; n = number of subjects with at least one TEAE in a given category; TEAE = treatment-emergent adverse event

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Six placebo subjects had an SAE including COPD, ECG QT prolonged, intestinal perforation, pneumonia, and acute renal failure in 1 subject each; COPD and hypotension in 1 subject. The intestinal perforation resulted in death and no SAE was reported to be life threatening. Two of these SAEs resulted in discontinuation from the study (pneumonia and acute renal failure). None of these SAEs were assessed as being related to study drug by the investigator. Five placebo subjects had a TEAE resulting in withdrawal from the study (SAEs of acute renal failure and pneumonia in 1 subject each; COPD; gastroenteritis, and glucose intolerance impaired in 1 subject each).

Six SUN11031 20 µg/kg bid subjects had an SAE including acute myocardial infarction, pneumothorax, and small intestinal perforation in 1 subject each; COPD in 2 subjects; and COPD and atrial fibrillation in 1 subject. None of these SAEs resulted in death or was reported to be life threatening. Three of these SAEs resulted in discontinuation from the study (acute myocardial infarction, COPD [1 subject], and small intestinal perforation). Acute myocardial infarction was assessed as being related to study drug by the investigator. Seven SUN11031 20 µg/kg bid subjects had a TEAE resulting in withdrawal from the study (SAEs of acute myocardial infarction, COPD, and small intestinal perforation; COPD [2 subjects], hyperglycemia and infection parasitic in 1 subject each).

Eight SUN11031 40 µg/kg bid subjects had an SAE including chest pain, cholecystitis, gastritis, hypertensive crisis, pneumonia (resulting in death), senile dementia, and suicidal ideation in 1 subject each; and COPD and death due to completed suicide in 1 subject. No SAEs were reported to be life threatening. Two of these SAEs resulted in discontinuation from the study (pneumonia and suicidal ideations). None of these SAEs were assessed as being related to study drug by the investigator. Five SUN11031 40 µg/kg bid subjects had a TEAE resulting in withdrawal from the study (SAEs of pneumonia and suicidal ideations; blood pressure increased, depression, and nausea in 1 subject each).

There were no clinically meaningful changes from baseline at any visit in the active treatment groups compared to placebo for any of the hematology, chemistry, urinalysis, or glucose metabolism parameters. No clinically meaningful differences were observed among treatment groups in the incidences of elevated fasting blood glucose from safety and OGTT. No clinically meaningful differences in shift tables were observed for any of the hematology, chemistry, laboratory indicators of nutritional status, urinalysis, or glucose metabolism parameters in the active treatment groups compared to placebo. No subject in the Safety Population tested positive for antibody to human ghrelin at screening or Day 85.

There were no clinically meaningful mean changes from baseline at any visit in the active treatment groups compared to placebo for any of the vital signs or spirometry measurements. No clinically meaningful differences in shift tables were observed for any of the vital signs measurements or spirometry measurements in the active treatment groups compared to placebo.

There were no clinically meaningful changes from baseline at any visit in the active treatment groups compared to placebo in Winnipeg criteria for COPD exacerbation. No clinically meaningful differences in shift tables were observed in Winnipeg criteria for COPD exacerbation in the active treatment groups compared to placebo.

Changes in mean values over time for ECG parameters were low and no clinically meaningful changes in ECGs in either active treatment group compared to placebo were observed.

There were no clinically meaningful changes in physical examination findings in either active treatment group compared to placebo.

Post-hoc in subjects with advanced cachexia at baseline based on Schols' criteria and an increase in LBM at Day 85 compared to baseline

A statistically significant increase from baseline in fasting insulin was observed on Day 8 in the 40 µg/kg bid group, but not the 20 µg/kg bid group, compared to placebo (-0.19 [2.847] µIU/mL for placebo, 0.31 [2.983] µIU/mL for 20 µg/kg bid, [*P*=0.560], and 1.94 [1.806] µIU/mL for 40 µg/kg bid, [*P*=0.015]).

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Conclusions:

Predefined Efficacy

In the ITT Population of subjects with cachexia associated with COPD, selected according to the consensus definition of cachexia, as compared with placebo, treatment with SUN11031:

- Did not improve physical performance as measured by 6MWT and SPPB
- Did show some improvement at some time points in appetite; however, these differences were not maintained throughout the study
- Significantly increased body weight and LBM at both dose levels with no significant change in fat mass
  - Significant increases from baseline in body weight occurred as early as Day 8 in the active treatment groups compared to placebo. At Day 99, 2 weeks after the last dose of study drug, body weight in all treatment groups decreased but the mean increase from baseline in weight in the active treatment groups remained numerically higher than for placebo and the 40 µg/kg bid group remained significantly greater than for placebo
  - Corresponding significant increases from baseline in LBM were observed by Day 29, the earliest on-treatment evaluation of LBM, with active treatment compared to placebo. At Day 99, 2 weeks after the last dose of study drug, LBM decreased in all 3 treatment groups but the mean increase from baseline in LBM in the active treatment groups remained significantly greater than for placebo
- Subgroup analyses by sex, age, median BMI and median FEV_1 at baseline were similar to those in the ITT Population

Post-hoc Efficacy

- While in the ITT Population using the consensus definition of cachexia, there was no evidence of improvement relative to placebo in numbers of responders to treatment, significantly more subjects with advanced cachexia defined by Schols' criteria who were on active treatment as compared with placebo experienced LBM gain and function/strength improvement when considered together in responder analyses. In this subgroup:
  - In the 40 µg/kg bid group, in both the 6MWT and SPPB, significantly more subjects experienced LBM gain and improvement from baseline of greater than 0 versus placebo at Day 85, while significantly more subjects in the 20 µg/kg bid group experienced LBM gain and improvement greater than 0 in nondominant handgrip strength and PI_{max}
  - In subjects with LBM gain at Day 85 or body weight gain at Day 29, statistically significant improvements were seen at the 40 µg/kg bid dose in magnitude of functional performance as measured with the SPPB. In subjects with LBM gain at Day 85, statistically significant improvements were seen at the 20 µg/kg bid dose in nondominant handgrip strength
- Cachexia severity and LBM increase appeared to be associated with improvement in outcome with the 40 µg/kg bid group, but improvement was not observed with the 20 µg/kg bid group, despite similar levels of weight and LBM improvement. This may be associated with the observed changes in IGF-1 which were consistent and sustained although nonsignificant in the 40 µg/kg bid group but smaller and transient and also nonsignificant in the 20 µg/kg bid group

Predefined and Post-hoc Analyses of PKPD and Biomarkers

- Bioanalyses of ghrelin and desacyl-ghrelin fulfilled the validation criteria and the differences with previous results were thought to be within acceptance limits
- At Day 85, 30 minutes after dosing, mean change from baseline in GH was significantly higher in both active

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treatment groups compared to placebo. A similar increase pattern was observed for cortisol concentrations

- A sustained and significant increase in IGF-1 was seen in the 40 µg/kg bid group compared to placebo at Days 29, 57, and 85 but a corresponding increase in the 20 µg/kg bid group was seen only at Day 29
- No clinically meaningful changes were seen in levels of the remaining biomarkers of inflammation (CRP, TNF-α, or IL-6)
- Pharmacokinetics of SUN11031 was approximately linear over time, implying a rapid achievement of steady-state conditions, and dose proportionality that was maintained over the Treatment Period
- No PKPD relationships were observed for the 2-hour OGTT on Day 8 or fasting or postprandial venous blood glucose levels on Day 85
- The subset of the study population with advanced cachexia defined by Schols' criteria demonstrated a consistently positive relationship to improvements in body weight gain and chair stand time with ghrelin exposure

Safety

- SUN11031 was safe and well tolerated in both 20 µg/kg bid and 40 µg/kg bid groups
- No medically important treatment-related changes in any of the hematology, chemistry, urinalysis, or glucose metabolism parameters; ghrelin antibody levels; or vital signs were observed
- Local tolerance of the injections was good
- Adherence to the 3-month bid injection regimen appeared to be high

Date of the Report: 03 September 2010