FINAL CLINICAL STUDY REPORT

Study Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled, Multicenter, Dose-ranging Study of Cicletanine in Subjects with Pulmonary Arterial Hypertension
Name of Test Drug:	Cicletanine hydrochloride
Dose and Formulation:	Cicletanine HCl oral capsules Doses: 150 and 300 mg once daily (qd), 150 mg twice daily (bid)
Indication:	Pulmonary arterial hypertension (PAH)
Sponsor:	Gilead Sciences, Inc. 333 Lakeside Drive Foster City, CA 94404 USA
Study No.:	GS-US-235-0101
Phase of Development:	Phase 2
IND No.:	32,283
EudraCT No.:	2008-007455-26
Study Start Date:	16 March 2009 (First subject screened)
Study End Date	22 February 2012 (Last subject observation)
Principal or Coordinating Investigator:	Name: Aaron B. Waxman, MD, PhD Affiliation: PPD Telephone: PPD Fax: PPD
Gilead Responsible Medical Monitor:	Name: Hunter Gillies Telephone: PPD Fax: PPD
Report Date:	22 August 2012

CONFIDENTIAL AND PROPRIETARY INFORMATION

This study was conducted in accordance with the guidelines of Good Clinical Practice, including archiving of essential documents.

STUDY SYNOPSIS

Study GS-US-235-0101:
Gilead Sciences, Inc.
333 Lakeside Drive
Foster City, CA 94404
USA

Title of Study: Study GS-US-235-0101
Investigators: Multicenter
Study Centers: 42 sites in 9 countries (Australia, Austria, Canada, Germany, Israel, Mexico, Spain, United Kingdom [UK], and United States [US])
Publications: Waxman A, Oudiz R, Shapiro S, Gomberg-Maitland M, Keogh A, Badesch D, Frantz R, Gregory Elliott C, Gillies H, Walker G. Cicletanine in pulmonary arterial hypertension (PAH): Results from a phase 2 randomized placebo-controlled trial. Abstract accepted for presentation at: European Respiratory Society Vienna Annual Congress 2012; 01–05 September 2012.
Study Period: 16 March 2009 (First subject screened) 22 February 2012 (Last subject observation)
Phase of Development: Phase 2
Objectives: The primary objective of this study was as follows: • To compare the change in exercise capacity following treatment with cicletanine HCl or placebo in subjects with pulmonary arterial hypertension (PAH) The secondary objectives of this study were as follows: • To compare the change in other clinical measures of PAH following treatment with cicletanine HCl or placebo in subjects with PAH • To compare the safety and tolerability of cicletanine HCl to placebo in subjects with PAH Additionally, the long-term safety, tolerability, and efficacy of cicletanine HCl treatment was evaluated.

Methodology: This Phase 2, randomized, double-blind, placebo-controlled, multicenter, dose-ranging study compared the efficacy, safety, and tolerability of cicletanine HCl (CIC) to placebo in subjects with PAH. Study drug was administered alone, or on the background of stable PAH therapy. The study consists of 3 periods: a screening period, a 12-week placebo-controlled treatment period, and a long-term, blinded extension period. This clinical study report (CSR) includes data from 2 datasets: the initial 12-week dataset and the full study active treatment dataset (all data while subjects were on active treatment during the entire study duration including the long-term extension period).

Eligible subjects were stratified based on the underlying etiology of PAH (2 strata: those with idiopathic PAH or familial PAH [IPAH/FPAH] and all others) and background parenteral prostanoid use (yes/no) and were randomized 1:1:1:1 to receive either CIC 150 mg qd, 150 mg bid, or 300 mg qd or matching placebo for the initial 12 weeks. Subjects randomized to CIC active treatment groups received a lower dosage initially for the first 2 weeks as follows: CIC 75 mg qd, 75 mg bid, and 150 mg qd for the 150-mg qd, 150-mg bid, and 300-mg qd groups, respectively.

Blinded dose reductions of study drug were permitted if the subject did not tolerate the assigned drug dosage (300 mg qd to 150 mg qd, 150 mg qd to 75 mg qd, 150 mg bid to 75 mg bid, 75 mg bid to 75 mg qd, or placebo to placebo). If the subject tolerated the reduced drug dosage, a blinded rechallenge (up-titration) was permitted.

No changes to background PAH therapy dosage levels were permitted in the first 12 weeks of the study, except if drug-related adverse events (AEs) could not be resolved with a reduction in the study drug dosage level.

Because subjects could have received placebo, the investigator could have chosen to implement an early escape procedure for subjects who met at least 2 of the 5 defined criteria after study treatment for 4 weeks:

- A decrease from baseline of at least 20% in the distance walked during the 6-minute walk test (6MWT)
- An increase of 1 or more World Health Organization (WHO) Functional Class
- Worsening right ventricular failure (eg, as indicated by increased jugular venous pressure, new/worsening hepatomegaly, ascites, or peripheral edema)
- Rapidly progressing cardiogenic, hepatic, or renal failure
- Refractory systolic hypotension (systolic blood pressure [SBP] less than 85 mmHg)

Requests for early escape were to be reviewed by the Gilead medical monitor and adjudicated by an independent committee.

Methodology, continued:

Subjects who completed all Week 12 procedures (or who were discontinued using the early escape procedure and were found to have taken placebo) were eligible for blinded (to dose), long-term treatment with CIC. Completer subjects who had received CIC during the first 12 weeks of the study continued blinded treatment at their current dose. Subjects who had received placebo during the first 12 weeks were randomized in a blinded manner to 1 of the 3 active treatment groups (150 mg qd, 150 mg bid, or 300 mg qd). These subjects up-titrated to these doses after 2 initial weeks at one-half the dose, as in the initial 12-week period.

Number of Subjects (Planned and Analyzed):
Planned: 160 subjects (40 subjects per arm)
12-week dataset:
Randomized subjects: N=162
Full analysis set (FAS): N=162
Safety FAS (SFAS): N=162
Per protocol analysis set (PPAS): N=153
Pharmacokinetic FAS (PKFAS): N=144
and PK Steady-state FAS (PKSSFAS): N=20
Cardiopulmonary hemodynamic substudy: N=42
Fractional exhaled nitric oxide (FE_{NO}) substudy: N=6
Full study active treatment dataset:
Long-term FAS (LT-FAS): N=160
Long-term safety FAS (LT-SFAS): N=160

Diagnosis and Main Criteria for Inclusion: Eligible subjects were men or women between 16 and 70 years of age, inclusive, with IPAH, FPAH; or PAH associated with connective tissue disease (PAH-CTD), congenital heart defects (repaired), drug and toxin use, or human immunodeficiency virus (HIV) infection.

Subjects had to have a documented mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg, pulmonary vascular resistance (PVR) > 240 dyne·s/cm^5, and pulmonary capillary wedge pressure (PCWP) or left ventricle end diastolic pressure (LVEDP) of ≤ 15 mmHg based on a right heart catheterization (RHC) completed prior to or during screening.

Subjects had to walk a distance of at least 100 m but no more than 450 m during the screening 6MWT to be eligible for randomization.

At screening, eligible subjects could have been taking one of the following PAH treatment regimens, as long as they had been receiving it for at least 12 weeks with a stable dose for at least 4 consecutive weeks just prior to screening:

- Monotherapy with an endothelin receptor antagonist (ERA; eg, ambrisentan, bosentan, sitaxsentan), a phosphodiesterase type-5 inhibitor (PDE5i; eg, sildenafil, tadalafil), or a parenteral prostanoid (intravenous [IV] epoprostenol, IV or subcutaneous [SC] treprostinil) approved for the treatment of PAH
- Combination therapy with 2 eligible PAH treatments (any combination of ERA, PDE5i, or parenteral prostanoid)

Diagnosis and Main Criteria for Inclusion, continued:

Alternatively, subjects taking no background PAH therapy (if the subject did not have access to or could not tolerate currently approved PAH medical therapies) were also eligible.

Duration of Treatment: 12-week placebo-controlled treatment period followed by a long-term, blinded CIC treatment period

Test Product, Dose, Mode of Administration, and Batch No.: Cicletanine HCl capsules (oral)

Dosages: 75 mg qd, 75 mg bid, 150 mg qd, 150 mg bid, or 300 mg qd

Lot Numbers:

Cicletanine 75 mg: BM0802A1, BM0901A1,

Cicletanine 150 mg: BM0803A1, BM1002A1

Placebo: BM0801A1, BM0801A2, BM1001A1

Reference Therapy, Dose, Mode of Administration, and Batch No.: Placebo capsules (oral) (identical in appearance to cicletanine HCl capsules)

Criteria for Evaluation:

Efficacy: Efficacy measures of 6-minute walk distance (6MWD), dyspnea index score, WHO functional class, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were evaluated at baseline and Weeks 2, 4, 8, and 12. Quality of life (QOL) questionnaires (SF-36® Health Survey; Cambridge Pulmonary Hypertension Outcome Review [CAMPHOR] QOL) and nitric oxide (NO)-related biomarkers (serum L-arginine [ARG], L-citrulline [CIT], and asymmetric dimethylarginine [ADMA]) were evaluated at baseline and Week 12. Time to clinical worsening (TTCW) and survival status were evaluated at Week 12.

Cardiopulmonary hemodynamics and FE_{NO} were measured in subsets of subjects at select investigational sites. For the hemodynamic substudy, subjects underwent one RHC between screening and baseline and a second RHC within the 2-week period prior to the Week 12 visit. FE_{NO} was measured at baseline and Weeks 4, 12, and 24.

In the extension period, 6MWD, dyspnea index score, WHO functional class, and NT-proBNP were evaluated at Weeks 14, 16, 20, 24, 36, 48, and 60 and then every 24 weeks. Assessments of QOL and clinical worsening were performed at Weeks 24, 36, 48, 60, and then every 24 weeks. At Week 24, FE_{NO} and ARG, CIT, and ADMA were evaluated. Vital status was evaluated every 6 months in the long-term extension period.

Pharmacokinetics: Predose (trough) plasma concentrations of study drug and/or a concomitantly administered ERA or PDE5i (if applicable) were determined in all subjects at baseline, Week 2, and Week 4.

Pharmacokinetics, continued:

In addition, steady-state plasma pharmacokinetics (PK) of the study drug was assessed in a subset of subjects. Subjects who agreed to participate in this substudy were required to give additional blood samples over a 24-hour period at 2 visits, the first between Weeks 1 and 2 and the second between Weeks 3 and 12 of the study.

Safety: Safety was monitored at all study visits (initial 12-week and extension periods) with assessments of AEs, clinical laboratory tests, vital signs, and concomitant medication usage. Physical examination (PE) findings were documented at screening and Weeks 12, 24, 36, 48, and 60 and then every 24 weeks. Electrocardiogram (ECG) results were reported at screening and at Weeks 4, 12, 16, 24, 36, 48, and 60 and then every 24 weeks.

Statistical Methods:

Efficacy: The primary analysis of efficacy was the change in 6MWD from baseline to Week 12 in the combined 300-mg group (150 mg bid + 300 mg qd). A 2-sided stratified Wilcoxon rank-sum test was used to test the null hypothesis of no additional treatment effect as a result of taking CIC rather than placebo for the FAS, using last-observation-carried-forward (LOCF) methodology.

In addition, Hodges-Lehmann estimates of treatment effect and associated 95% confidence intervals (CIs) were reported. Using methods analogous to the primary analysis, the primary endpoint values were compared for individual treatment groups vs. placebo and for all CIC groups vs. placebo.

Several sensitivity analyses were performed for the primary endpoint: Wilcoxon rank-sum and mixed-models repeated measures (MMRM) analyses using observed data (no imputation of missing data) in the FAS, and a Wilcoxon rank-sum analysis using LOCF in the PPAS.

Correlations between the primary efficacy variable and Week 12 change in mean right atrial pressure (mRAP) (cardiopulmonary hemodynamic substudy) and Week 12 change in body weight were examined.

Summary statistics for absolute and change-from-baseline values for the primary efficacy variable and for the secondary numeric efficacy variables (dyspnea index, WHO functional class, NT-proBNP, SF-36 Health Survey scales, and cardiopulmonary hemodynamic parameters) were calculated by visit using both LOCF and observed case approaches. Time to clinical worsening was displayed as Kaplan-Meier (KM) curves, and the frequency of each event was tabulated.

Additional efficacy endpoints included change from baseline in 6MWD, dyspnea index, WHO functional class, SF-36 Health Survey, NT-proBNP, and TTCW at Weeks 2, 4, and 8; change from baseline in FE_{NO}; CAMPHOR QOL; serum ARG, CIT, and ADMA; and survival status.

Efficacy, continued

The efficacy measures 6MWD, dyspnea index, WHO functional class, TTCW, NT-proBNP, and SF-36 Health Survey physical functioning scale were analyzed by subgroup (demographics, PAH etiology, WHO functional class at baseline, concomitant PAH medication, treatment duration, interim study completers, and baseline 6MWD, NT-proBNP, diuretic usage, and mRAP).

Efficacy data collected in the extension period were listed by subject but were not summarized.

Pharmacokinetics: Effect of steady-state CIC on the steady-state trough plasma concentrations of concomitantly administered oral PAH medications was assessed by comparing trough plasma concentrations of the PAH medications prior to initiation of CIC therapy on Day 1 with Week 2 and Week 4 data. In the steady-state PK substudy, plasma CIC profiles were determined for 24-hour periods after Weeks 1 and 3, and PK parameters were estimated. Dose proportionality of CIC PK was investigated using a mixed model fit to the log-transformed dose-normalized parameters.

Safety: Safety data collected during the study (from randomization through the last visit) were listed by subject. AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 14.1. Safety data were summarized by treatment group through Week 12 using the 12-week dataset and through the end of the study using the full study active treatment dataset. Shift tables were constructed for clinical laboratory (12-week dataset) and ECG results (both datasets). Time to the first occurrence of key AEs through Week 12 was presented using KM curves.

AE data from the initial 12 weeks were analyzed by the subgroups listed above (see Efficacy Statistical Methods).

SUMMARY – RESULTS:

Subject Disposition and Demographics: In this study, 162 subjects were enrolled and initially randomized, 41 to placebo treatment, 39 to the CIC 150-mg qd group, 40 to the CIC 150-mg bid group, and 42 to the CIC 300-mg qd group. Of these subjects, 157 (96.9%) completed Week 12; AEs were the reason for discontinuation by Week 12 in 1 subject each in the placebo, CIC 150-mg qd, and CIC 300-mg qd groups. After 12 weeks of treatment, 39 subjects in the placebo group were re-randomized to active treatment, and 121 additional subjects in the active treatment groups continued in the same treatment groups in the long-term extension period. Over 70% of subjects in the study were discontinued from the study because of study termination. Other reasons for discontinuation included AEs (10%), withdrawal of consent (6%), and clinical status did not improve (2.5%).

In the 12-week dataset, the mean age was 47.0 ± 12.6 years. The majority of enrolled subjects (87.0%) were female. Subjects enrolled were primarily Caucasian (69.1%); 19.1% were “Other”, 8.6% were Black, 2.5% were multiracial, and 0.6% was Native Hawaiian or Pacific Islander. Demographics were generally similar in the 4 treatment groups. Demographics in the 12-week and full study datasets were very similar.

Efficacy Results: The primary endpoint analysis for this study was the comparison of change from baseline in 6MWD at Week 12 for the CIC All 300 group versus placebo. Median changes from baseline in 6MWD were 9.0, 14.0, 17.5, and 12.0 m in the placebo and CIC 150-mg qd, 150-mg bid, and 300-mg qd groups, respectively. The primary efficacy analysis (stratified Wilcoxon rank-sum test) indicated that treatment with a daily dose of CIC 300 mg did not result in a statistically significant improvement (p=0.50) in exercise tolerance compared with placebo. Although the LS means treatment effect estimate suggested a statistically significant separation between the CIC All 300 group and placebo, examination of the distributions of each treatment group revealed that the placebo group distribution did not meet the assumptions of normality. The data were skewed to the left due to 4 subjects, including 1 subject who died prior to Week 12 and had an imputed value of 0. In agreement with this, the Hodges-Lehmann treatment effect estimate and CI of [7 (–8, 24)] also showed no statistically significant difference, since this nonparametric estimate is less influenced by outliers.

Similar results using median changes and the Wilcoxon rank-sum test were observed for the comparison of the individual CIC treatment groups versus placebo, as were results of additional sensitivity analyses and analyses at other time points (Weeks 2, 4, and 8). Generally, no statistically significant 6MWD differences (active vs. placebo) were seen in the examined subgroups.

Results for the other efficacy measures (dyspnea index, WHO functional class, SF-36 Health Survey, CAMPHOR QOL, TTCW, NO biomarkers) were similar to those for 6MWD (no statistically significant differences in change from baseline between placebo and active treatment groups). Mean changes in NT-proBNP concentrations were significantly different for both the CIC 150-mg bid group and the CIC All 300 group compared with placebo. However, the magnitude of these changes in the active treatment groups was not considered clinically meaningful. In the cardiopulmonary hemodynamic substudy, the changes from baseline in PVR, mPAP, mRAP, cardiac index, and PCWP or LVEDP in the CIC All 300 group also were not significantly different than placebo. Because of the fixed-sequence approach used to control the Type 1 error rate for the primary and secondary efficacy endpoints and the fact that the primary efficacy endpoint was not met, all secondary efficacy endpoint data are considered descriptive.

Pharmacokinetic Results: Concurrent CIC did not appear to affect trough concentrations of the concurrently administered PAH drugs ambrisentan, bosentan, or tadalafil, as evidenced by trough concentration contrast ratios of ~1 for Week 0 vs Week 2 and Week 4. For 4-hydroxymethyl ambrisentan, sildenafil, and N-desmethyl sildenafil, no effect was seen at Week 2 but the trough concentration contrast ratios were somewhat higher at Week 4. Since all trough concentration data were pooled for all subjects irrespective of ambrisentan, sildenafil, or CIC dose levels, it is unclear if the observed changes in sildenafil and metabolite trough concentrations were related to CIC doses.

Pharmacokinetic Results, continued: Steady-state CIC plasma concentrations increased with increasing dose for both qd and bid dosing, suggesting a dose-related increase in CIC exposure. In all CIC dose groups, median T_{max} values ranged from 1 to 2 hours and median $T_{½}$ values ranged from 4.1 to 7.0 hours. Exposure values were variable in the qd and bid dose groups (percent coefficient of variation [%CV] for C_{max} 13.7% to 55.9% and %CV for AUC_{tau} 6.9% to 43.7%). Dose proportionality analyses showed that the increase in CIC exposure with increasing dose was dose proportional following bid doses (CIC 75 and 150 mg bid [N=10 and 7, respectively]) but appeared to be slightly less than dose proportional following qd doses (CIC 75, 150, and 300 mg qd [N=6, 9, and 3, respectively]).

Safety Results: The safety and tolerability of CIC in this population was similar to that seen in previous uncontrolled PAH studies, and demonstrated an expected safety profile, given the thiazide-like diuretic nature of CIC. Safety findings for the full study including long-term extension period showed a consistent profile to those in the initial 12 weeks, but were at times more extensive, likely due to the 3 times longer duration of treatment and/or duration of time in this study population with compromised health status.

Over the initial 12-week period, 85% to 93% of subjects in each of the treatment groups reported AEs, and 39% to 45% of subjects had AEs considered related to study drug. Most AEs were mild or moderate. Adverse events of severe intensity were reported by 12% to 25% of subjects. In the full study including long-term extension period, 91.9% of subjects reported AEs, 45.0% of subjects reported AEs considered related to study treatment, and 33.8% of subjects reported severe AEs.

Two deaths occurred during the initial 12 weeks: sudden death (unrelated) in a subject on placebo and intracranial hemorrhage (unrelated) in a subject who had taken CIC 150 mg qd. Serious AEs (SAEs) were reported in 13% to 22% of subjects in each treatment group. Almost all SAE preferred terms were each seen in a single subject. A total of 8 subjects prematurely discontinued study drug because of treatment-emergent AEs, 2 with placebo, 1 with CIC 150 mg qd, 2 with CIC 150 mg bid, and 3 with CIC 300 mg qd.

In the full study including long-term extension period, 6 subjects had AE(s) that led to death. Serious AEs were reported in 34.4% of subjects overall. Adverse events that led to premature discontinuation of study drug were reported in 10.0% of subjects, and withdrawal from the study due to an AE was reported in 10.6% of subjects. No clear dose relationship was seen in any of these AE measures in the LT-SFAS.

The most frequently reported AEs in the initial 12 weeks were headache (19%), dizziness (19%), nausea (14%), hypokalemia (14%), fatigue (12%), and upper respiratory tract infection (URTI) (12%). Dizziness, hypokalemia, and fatigue are consistent with CIC's diuretic properties. Headache and nausea have been reported with the use of the coadministered PAH medications. The most frequently reported AEs in the full study including long-term extension period were similar to those seen in the first 12 weeks.

Safety Results, continued:

In the initial 12 weeks, marked laboratory abnormalities were seen in 20% to 24% of subjects with each treatment, including placebo. The most frequent marked laboratory abnormality was INR (12% of subjects with placebo and 22%, 13%, and 15% with CIC 150 mg qd, 150 mg bid, and 300 mg qd, respectively). Marked changes in platelets were seen in 4 subjects. In the full study including long-term extension period, marked laboratory abnormalities were reported in 31.3% of subjects, with 21.3% experiencing a marked INR abnormality and 3.1% experiencing a marked abnormality in activated partial thromboplastin time (aPTT) or platelets.

Minimal fluctuations in mean sodium and magnesium concentrations were seen in the initial 12 weeks and also in the full study including long-term extension, with most subjects' values remaining in the normal range. Mean potassium and chloride levels tended to be decreased postbaseline for all active treatment groups in the initial 12 weeks and the full study including long-term extension period.

Over the initial 12-week treatment period and the full study including long-term extension period, mean values for ALT and AST tended to increase from baseline values; changes to mean AP, total bilirubin, and GGT were minor. Laboratory abnormalities of any grade in a liver function test (LFT) analyte were seen in less than one-third of subjects in both analysis periods. Marked ALT and GGT abnormalities were each seen in single subjects in both periods, and a marked AST abnormality was seen in a single placebo subject in the initial 12 weeks.

Increases in postbaseline mean INR up to 1.3 were seen in both the initial 12-week period and the full study including long-term extension period, with generally greater increases in the active treatment groups in the initial 12 weeks and no apparent dose effect in the full study analysis. Postbaseline increases in prothrombin time (PT) were also seen in both periods, as were increases in aPTT.

No clinically significant changes from baseline in mean blood pressure (BP) were seen in either the initial 12-week period or the full study including long-term extension period.

No clinically significant effects were seen in heart rate, body weight, or physical examination findings during the study. No worsening trends in postbaseline ECGs were seen in the initial 12-week period or in the full study including long-term extension period.

No clear difference was seen in the usage of the most common concomitant medications between the placebo and active treatment groups in the initial 12 weeks. Percentages of subjects receiving diuretics remained approximately the same over the initial 12 weeks; changes/additions of diuretics occurred in 15% to 30% of subjects in each treatment group, primarily because of AEs.

CONCLUSIONS: This Phase 2, placebo-controlled study of CIC in PAH failed to meet its primary endpoint of change from baseline in 6MWD after 12 weeks of treatment. Descriptive results of the secondary efficacy endpoints were generally consistent with the primary endpoint results. Based on these results, it was decided that Gilead would not pursue further development of CIC for PAH.

Concurrent CIC did not appear to affect trough concentrations of the concurrently administered PAH drugs ambrisentan, bosentan, or tadalafil. For sildenafil, no effect was seen at Week 2 but trough concentrations were somewhat higher at Week 4.

Steady-state CIC plasma concentrations increased with increasing dose for both qd and bid dosing, suggesting a dose-related increase in CIC exposure. Median T_{max} values ranged from 1 to 2 hours and median $T_{½}$ values ranged from 4.1 to 7.0 hours. Exposure values were variable in the dose groups. Dose proportionality analyses showed that the increase in CIC exposure with increasing dose was dose proportional following bid doses (CIC 75 and 150 mg bid) but slightly less than dose proportional following qd doses (CIC 75, 150, and 300 mg qd).

In general, CIC was well tolerated in this study. The safety and tolerability of CIC in this population was similar to that seen in previous uncontrolled PAH studies, and demonstrated an expected safety profile, given the thiazide-like diuretic nature of CIC. The most common AEs reported were expected effects related to CIC's thiazide-like diuretic properties or known adverse reactions associated with concomitant PAH therapies. Postbaseline changes in laboratory parameters seen in this study were consistent with CIC's diuretic effect, with the exception of the transaminase increases. Safety findings for the full study including long-term extension period showed a consistent profile to those in the initial 12 weeks, but were at times more extensive, likely due to the 3 times longer duration of treatment and/or duration of time this study population spent with compromised health status.