2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:** **Volume:** **Page:**	**(For National Authority Use Only)**
Name of Study Drug: Adalimumab		
Name of Active Ingredient: Adalimumab		

Title of Study:

A Phase 2, Randomized, Double-Blind, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Two Adalimumab Dosing Regimens in Chinese Subjects with Moderately to Severely Active Crohn's Disease and Elevated High-Sensitivity C-reactive Protein

Coordinating Investigator:

Professor Kaichun Wu, [redacted]

Study Sites: 6 sites in China

Publications: 1

Studied Period (Years): First Subject First Visit: 23 December 2013 Last Subject Last Visit: 11 February 2015	**Phase of Development:** 2

Objectives:

The primary objective of the study was to characterize the pharmacokinetics (PK) of adalimumab following subcutaneous (SC) administration of 2 dosing regimens in Chinese subjects with moderately to severely active Crohn's disease (CD) and elevated high sensitivity C-reactive protein (hs-CRP).

Methodology:

At Baseline (Week 0), subjects who met all inclusion criteria and none of the exclusion criteria were randomized in a 1:1 ratio to receive 1 of 2 adalimumab dosing regimens (standard induction or low induction), with randomization stratified by CD activity (Crohn's Disease Activity Index [CDAI] ≤ 300, > 300). Subjects randomized to the standard induction dose regimen were to receive blinded adalimumab 160 mg at Week 0, 80 mg at Week 2, and 40 mg at Week 4 and Week 6. Subjects randomized to the low induction dose regimen were to receive blinded adalimumab 80 mg at Week 0, and 40 mg at Week 2, Week 4, and Week 6. At Week 8, all subjects had the opportunity to enroll in an 18-week open-label extension (OLE) period to receive open-label adalimumab 40 mg every other week (eow). Adalimumab 40 mg eow was to be administered until Week 26; no study drug was to be administered at the final visit (Week 26). If the subject qualified for dose escalation (disease flare or nonresponse at or after Week 12, as defined below), the subject may have escalated to adalimumab 80 mg eow.

Methodology (Continued):

All subjects were screened for tuberculosis (TB) consisting of QuantiFERON-TB Gold In-Tube test and chest x-ray (CXR) or chest computerized tomography (CT) scan; all subjects who initiated TB prophylaxis based on either the TB screening results or investigator discretion were to receive TB prophylaxis for at least 21 days prior to Baseline. Hematocrit and hs-CRP values obtained at Day –7 were then to be used to calculate the Baseline CDAI to confirm eligibility for study enrollment. Enrolled subjects also needed to meet the hs-CRP criteria prior to starting TB prophylaxis. Subjects who initiated TB prophylaxis were to continue the prophylaxis regimen for the duration of the subject's participation in the study. All subjects were to have repeat CXR/chest CT scans performed to evaluate for TB during the study at Weeks 8, 16, and 26/Premature Discontinuation. TB prophylaxis was only to be initiated during the Screening period and was not permitted to be initiated during the study; if TB prophylaxis was warranted after the subject was randomized, the subject was to be withdrawn from the study.

At Week 4, all subjects who were on oral steroids were to have a mandatory steroid dose taper; if the investigator felt that the steroid taper was not advisable for a particular subject at Week 4, the subject was to be withdrawn from the study.

Subjects who experienced nonresponse (defined as lack of attainment of a CDAI decrease of ≥ 70 points compared to Baseline [Week 0] on 2 consecutive visits, at least 1 week apart) from Week 4 up to Week 12 (before adalimumab dose escalation was allowed) were to be withdrawn from the study.

At or after Week 12, any subject who experienced a disease flare (defined as a recurrence of active disease, specifically an increase in CDAI when compared to Week 4 of ≥ 70 points and a CDAI above 220) or nonresponse may have increased his/her dose to open-label adalimumab 80 mg eow. If the subject received open-label adalimumab 80 mg eow and continued to demonstrate disease flare or sustained nonresponse, he/she was to be withdrawn from the study.

Study duration was up to 39 weeks, which included a Screening period of up to 35 days, an 8-week double-blind (DB) treatment period, an optional 18-week OLE period, and a 70-day follow-up period. The 70-day follow-up visit was to occur 70 days from the last dose of study drug to obtain information on any new or ongoing adverse events (AEs).

Number of Subjects (Planned and Analyzed):

Planned: 30 subjects; Analyzed: 30 subjects

Diagnosis and Main Criteria for Inclusion:

Subjects were eligible for study participation if they met all of the following inclusion criteria:

- Male or female of Chinese descent with full Chinese parentage 18 to 70 years (inclusive) of age at Baseline (Week 0).
- Confirmed diagnosis of CD for at least 3 months prior to Baseline (Week 0) (i.e., diagnosis confirmed by endoscopy, radiologic evaluation, and/or histology).
- Subject had hs-CRP ≥ 3 mg/L during the entire Screening period.
- CDAI ≥ 220 and ≤ 450 at Baseline (Week 0) despite concurrent or prior treatment with an adequate course, in the opinion of the investigator, of at least 1 of the following (oral corticosteroids or immunosuppressants or both as defined below):
    - Subject taking oral corticosteroids, excluding budesonide:
        - Oral corticosteroid dose had to be ≤ 20 mg/day (prednisone or equivalent);
        - Dose had been stable for at least 10 days prior to Baseline (Week 0) and the duration of the current steroid course had been at least 14 days prior to Baseline (Week 0).

Diagnosis and Main Criteria for Inclusion (Continued):

- Subject taking oral budesonide:
  - Dose must not have exceeded 9 mg/day;
  - Dose had been stable for at least 10 days prior to Baseline (Week 0) and the duration of the current steroid course had been at least 14 days prior to Baseline (Week 0).

and/or,

- At least a consecutive 42-day course of azathioprine (AZA), 6-mercaptopurine (6-MP), or methotrexate (MTX) prior to Baseline (Week 0), with a minimum dose of AZA ≥ 0.75 mg/kg/day or 6-MP ≥ 0.5 mg/kg/day (rounded to the nearest available tablet formulation) or MTX ≥ 15 mg (SC/intramuscular [IM]) per week or a dose that was the highest tolerated by the subject [e.g., due to leukopenia, elevated liver enzymes, nausea] during that time).
  - Subject had to be on a stable dose for at least 28 days prior to Baseline (Week 0).
    - For subject taking AZA, the dose must not have exceeded 3 mg/kg/day.
    - For subject taking 6-MP, the dose was not to have exceeded 1 mg/kg/day.
    - For subject taking IM/SC MTX, dose was not to have exceeded 25 mg per week.
    - Note: Oral MTX use was allowed during the study (at a stable dose for 28 days prior to Baseline); however, use of oral MTX was not sufficient for inclusion into the study.

  If subject was on both an oral corticosteroid and an immunosuppressant, both of the drugs needed to meet the above criteria.

and/or,

- Concurrent therapy with corticosteroids or immunosuppressants (AZA, 6-MP, or intramuscular/SC MTX) was not required for subjects who were not currently taking these medications but had been treated during the past 1 year and had confirmed documentation of failure to respond, or had been treated during the past 5 years and had confirmed documentation indicating lack of tolerability.
- Subject had a negative TB Screening assessment. If the subject had evidence of a latent TB infection during the Screening assessment, the subject had to initiate and complete a minimum of 3 weeks (or per local guidelines, whichever was longer) of an ongoing TB prophylaxis, prior to Baseline.

Subjects must not have met any of the following exclusion criteria:

- Subject with a current diagnosis of ulcerative colitis or indeterminate colitis.
- Subject who had discontinued AZA, 6-MP, MTX, or another immunomodulator (e.g., thalidomide) or an oral aminosalicylate within 14 days of Baseline (Week 0), or for subjects taking oral MTX or another immunodulator (e.g., thalidomide or an oral aminosalicylate, had not been on a stable dose for at least 28 days prior to Baseline.
- Subject who was taking both oral budesonide and prednisone (or equivalent) simultaneously, with the exception of nonsystemic steroids (e.g., inhalers or dermatological preparations), during the Screening period and during the study.

Diagnosis and Main Criteria for Inclusion (Continued):

- Subjects who were taking intravenous (IV) corticosteroids within 14 days prior to Screening, during the Screening period and during the study or who had discontinued oral corticosteroids within 14 days before Baseline (Week 0).
- Subject who had had a surgical bowel resection within the past 6 months or was planning any resection at any time point in the future or a subject with symptomatic known obstructive strictures, an internal or external fistula (with the exception of an anal fistula without abscess), an ostomy or ileoanal pouch, or short bowel syndrome.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Adalimumab 40 mg/0.8 mL, prefilled SC syringes; Bulk Product Lot Number: 13-000648

Duration of Treatment: Up to 26 weeks: 8-week DB treatment period; optional 18-week OLE period

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Placebo for adalimumab, prefilled syringe; Bulk Product Lot Number: 12-007038

Criteria for Evaluation

Efficacy:

The efficacy endpoints of the study were: proportion of subjects with clinical remission (CDAI < 150) over time, proportion of subjects with clinical response (decrease in CDAI ≥ 70 points from Baseline [Week 0]) over time, and change from Baseline in CDAI, in hs-CRP level, in fecal calprotectin level, and in laboratory and nutritional parameters (e.g., hemoglobin, hematocrit, albumin, total protein concentration, and weight) over time. After the last protocol amendment but prior to statistical analysis plan (SAP) version 2.0 finalization, efficacy endpoints and corresponding analyses for subjects who dose-escalated (i.e., proportion of subjects who dose escalated at or after Week 12 and clinical remission/response status of dose-escalators at Week 26) were added.

Safety:

AEs, physical examinations, vital signs, and laboratory data were assessed throughout the study. In addition, TB evaluation and CXRs/CT scans were performed throughout the study.

Statistical Methods

Three SAPs were written for this study, and all were completed prior to the final database lock. The initial SAP (version 1.0, dated 08 July 2014), completed prior to the 8-week DB treatment period of the study database lock (13 August 2014) and reflecting a database cutoff of 30 July 2014 (the last subject's last Week 8 DB visit), included an analysis of PK and efficacy variables as well as safety data collected through the 8-week DB treatment period. SAP version 2.0 (dated 11 February 2015) added the definition of visit windows for the OLE period data and the efficacy analyses for dose-escalators; the most current (final) SAP version 3.0 (dated 25 February 2015) added the definition of visit windows for the analyses of laboratory and vital sign data.

Efficacy:

No statistical hypothesis was tested. All efficacy endpoints were summarized descriptively. For categorical efficacy variables, data were summarized by descriptive statistics (number and percent of subjects with 95% confidence interval [CI]). For continuous efficacy variables, data were summarized by number of observations, mean, standard deviation (SD), 95% CI, 1st quartile, median, 3rd quartile, minimum, and maximum. Efficacy results were presented by individual treatment group and overall.

Statistical Methods (Continued)

Safety:

Treatment-emergent AEs (TEAEs) for the DB period were defined as events that began or worsened either on or after the first dose of the study drug and up to the first dose of study drug in the OLE period for subjects who entered the OLE period or events that began or worsened either on or after the first dose of study drug and within 70 days after the last dose of study drug in the DB treatment period for subjects who didn't enter the OLE period. For the OLE period and the entire study, TEAEs were defined as events that began or worsened on or after the first dose of open-label study drug and up to 70 days after the last dose of study drug. An overview of TEAEs, including AEs of special interest such as AEs leading to death and AEs leading to premature discontinuation, AEs by Medical Dictionary for Drug Regulatory Activities (MedDRA version 17.1) system organ class (SOC) and preferred term (PT), AEs by maximum relationship to study drug, and AEs by maximum severity were summarized by number and percentage. A subject who reported more than 1 TEAE of the same PT was counted only once for that PT using the most extreme occurrence (i.e., most severe for the severity and most related for the relationship). A subject who reported 2 or more occurrences of the same AE within a SOC or 2 or more different PTs within the same SOC was counted only once for that SOC total. An AE with severity or relationship unknown remained categorized with characteristic unknown, unless another report of the same AE occurred with the most extreme severity (i.e., severe) or relationship (i.e., reasonable possibility); in those cases, the AE was counted as having the extreme characteristic. The number and percent of subjects with TEAEs and AEs of special interest was provided by treatment group; a by-subject listing was also provided for the AE categories of special interest. AEs per 100 patient years of exposure were calculated for the AE overviews of the OLE period and the entire study.

Changes in laboratory data and vital signs were summarized using descriptive statistics. For laboratory parameters, shift tables from Baseline to the final value of the DB period and of the entire study according to the normal range for each laboratory parameter were provided; listings were provided for abnormal values, whereby the normal range of the analyzing laboratory was used. For selected laboratory parameters, a listing of all subjects with any laboratory determinations meeting Common Toxicity Criteria (CTC) Version 3.0 (or later) of Grade ≥ 3 was provided, along with the entire course of the parameter.

Summary/Conclusions

This is the final report for Study M14-232, which presents the efficacy and safety data for adalimumab treatment of Chinese subjects with moderately to severely active CD and elevated hs-CRP during both the 8-week DB treatment and the OLE study periods. An interim analysis was performed at the end of the 8-week DB treatment period (data cutoff of 30 July 2014; database lock 13 August 2014) to characterize the PK and to evaluate the efficacy and safety of adalimumab following SC administration of the 2 adalimumab dosing regimens studied. The efficacy and safety results of that analysis were presented in an interim Clinical Study Report (CSR; R&D/14/0807) and are also included in this final report. The results for the analyses of PK variables, along with a comparison of PK in Chinese subjects in Study M14-232 with Japanese and Western subjects from other studies, are provided separately in a PK report (R&D/14/1022).

Summary/Conclusions (Continued)

Efficacy Results:

Thirty subjects from 6 sites in China were randomized. The majority of subjects were male; the mean age was 34.5 years; and most were nonusers of nicotine and alcohol. Demographic characteristics were similar between the adalimumab 180/60 mg and 80/40 mg treatment groups, including weight and body mass index (BMI). Overall, Baseline characteristics reflected a population with moderate to severely active CD. Mean CDAI was 315.42; approximately equal proportions of subjects had CD disease severity ≤ 300 and > 300; and fecal calprotectin levels were elevated. Observed differences (adalimumab 80/40 mg versus 160/80 mg) included a higher elevated mean hs-CRP in the adalimumab 160/80 mg group (31.90 versus 53.65 mg/L), a lower mean albumin concentration in the adalimumab 160/80 mg group (37.0 versus 34.0 mg/mL), and a shorter disease duration in the adalimumab 80/40 mg group (1.65 versus 3.61 years). At Baseline, 2 subjects in the 160/80 mg group had an anal/internal fissure, and 1 subject in each dosing group had a draining perianal/anal fistula; no subject had more than 1 fistula/fissure. Overall, the majority (60.0%) of subjects had ileal-colonic CD, and the majority (70.0%) reported use of immunosuppressants (AZA, MTX, and thalidomide) at Baseline; a smaller percentage of subjects reported use of aminosalicylates (30.0%) and corticosteroids (26.7%). In addition, the majority of subjects had negative/normal results for each of the following tests: QuantiFERON-TB Gold In-Tube, CXR or CT scan, and ECG.

The results from the DB treatment period of this study demonstrated that both studied doses of adalimumab induced clinical remission (defined as achievement of CDAI < 150) and clinical response (defined as a decrease in CDAI ≥ 70 points from Baseline) of CD in the majority of subjects at Week 4; greater rates of remission were observed with the adalimumab 160/80 mg dose compared to the 80/40 mg dose as early as Week 2 and were sustained through Week 8. The adalimumab 160/80 mg dose achieved greater reductions in hs-CRP and fecal calprotectin through Week 8 (end of the DB treatment period).

Detailed results through Week 8 for the intent-to-treat (ITT) population, which included all subjects who were randomized and received at least 1 injection of DB study drug (n = 15 for each treatment group), were as follows:

- Clinical remission was consistently achieved by a larger proportion of subjects in the adalimumab 160/80 mg than 80/40 mg treatment group at all timepoints through Week 8; at Week 8, remission rates were 66.7% versus 60%, respectively. The standard induction dose of adalimumab 160/80 mg led to more rapid achievement of remission: nearly one-half (46.7%) of the subjects in the 160/80 mg group achieved remission at Week 2 compared to 26.7% in the 80/40 mg group.
- Clinical response was achieved by a larger proportion of subjects in the adalimumab 160/80 mg than 80/40 mg treatment group early on at Week 2 (80.0% versus 66.7%); the response rate was similar in both groups at Week 4 and generally sustained through Week 8.
- CDAI scores were consistently numerically lower in the adalimumab 160/80 mg than the 80/40 mg treatment group, with increasingly larger mean decreases from Baseline (Week 0) (indicating improvement of disease) occurring from Week 2 through Week 8. The initially larger decrease from Baseline to Week 2 for subjects in the adalimumab 160/80 mg group (–143.79 versus –108.91) indicated a more rapid response.
- Larger decreases (improvement) from Baseline in hs-CRP levels occurred in the adalimumab 160/80 mg compared with the 80/40 mg treatment group as early as Week 1 (median decrease of –24.51 versus –7.70 mg/L), and these were maintained through Week 8. During this time, median hs-CRP values were consistently numerically lower for the adalimumab 160/80 mg than the 80/40 mg treatment group.

Summary/Conclusions (Continued)

Efficacy Results (Continued):

Larger median decreases from Baseline in fecal calprotectin levels occurred in the adalimumab 160/80 mg compared with the 80/40 mg treatment group at Week 4 and Week 8, indicating improvement in inflammation. Median fecal calprotectin levels were numerically lower for the adalimumab 160/80 mg than the 80/40 mg treatment group at both timepoints.

For selected laboratory and nutritional parameters over time, mean increases for the adalimumab 160/80 mg compared with the 80/40 treatment mg group were greater for hemoglobin, albumin, and total protein concentration, and were similar for weight and hematocrit.

From Week 8 through Week 26 (OLE period), with continued open-label adalimumab 40 mg eow treatment, the majority of subjects (66.7% – 73.3% in the adalimumab 160/80 mg group; 60% – 66.7% in the adalimumab 80/40 mg group) achieved clinical remission as well as clinical response (66.7% – 86.7% in each treatment group). Mean and median CDAI scores continued to decrease in both treatment groups. Decreases (improvement) from Baseline in hs-CRP were maintained, and mean laboratory and nutritional parameter increases (hemoglobin, hematocrit, albumin, total protein concentration, and weight) were generally maintained or increased (further improvement) in both treatment groups.

Three subjects dose-escalated at or after Week 12; the 1 subject in the adalimumab 160/80 mg group achieved clinical remission at Week 26.

Safety Results:

Mean duration of exposure to adalimumab through the 8-week DB treatment period was comparable, 54.9 days in the adalimumab 80/40 mg group and 53.9 days in the adalimumab 160/80 mg treatment group, for total doses of 197.3 mg and 320.0 mg of adalimumab, respectively. Through the entire study, the mean duration of exposure to adalimumab (154.1, 154.7 days) and the mean total number of injections (15.1, 15.5) were comparable between the adalimumab 80/40 mg and 160/80 mg treatment groups. Mean total dose was 482.7 mg and 621.3 mg of adalimumab, respectively.

The results from Study M14-232 demonstrated that both studied doses of adalimumab (80/40 mg and 160/80 mg), followed by 40 mg eow through Week 26, were generally safe and well tolerated in Chinese subjects with moderately to severely active CD and elevated hs-CRP. No deaths occurred. A small proportion of subjects experienced SAEs, discontinuations due to SAEs, and AEs of special interest (Safety Analysis Set, defined as all subjects who received at least 1 injection of study drug [N = 30]). The overall type and rate of TEAEs were similar in the 2 treatment groups and are consistent with the known safety profile of adalimumab.

During the DB treatment period, 2 subjects (6.7%) experienced SAEs (1 in the adalimumab 80/40 mg group [aggravated Crohn's disease] and 1 in the adalimumab 160/80 mg group [aggravated Crohn's disease, intestinal obstruction, lung infection, TB gastrointestinal]). These subjects discontinued study drug due to the SAEs of Crohn's disease and TB gastrointestinal, respectively. A third subject, in the adalimumab 80/40 mg group, interrupted study drug during the DB period due to AEs and later discontinued from the study due to those AEs (worsening leukopenia and worsening neutropenia).

During the OLE period, with continued open-label adalimumab 40 mg eow treatment 3 subjects (11.1%) experienced SAEs, including 2 subjects in the adalimumab 160/80 mg group [both with aggravated Crohn's disease, which led to discontinuation for 1 subject]). Three subjects (11.1%) discontinued study drug due to an AE (1 in each treatment group for a positive mycobacterium TB complex test and 1 in the adalimumab 160/80 mg group for aggravated Crohn's disease).

Summary/Conclusions (Continued)

Safety Results (Continued):

AEs of special interest experienced during the study, which included infections, active and latent TB, intestinal stricture, and hematological disorders, were reported by a total of 13 subjects (7 in the adalimumab 80/40 mg treatment group; 6 in the 160/80 mg group). The majority of subjects with AEs of special interest were taking at least 1 immunosuppressant (defined as AZA, 6-MP, thalidomide), aminosalicylate, and/or corticosteroid (tapering) as prior and continuing medications during the study.

During the DB treatment period, 3 infections (2 that were serious) were reported; all occurred in the same subject in the adalimumab 160/80 mg group and included the serious lung infection and TB gastrointestinal infection noted above that remained ongoing plus a case of nasopharyngitis, which resolved within 4 days. During the OLE period, 3 subjects (2 in the adalimumab 80/40 mg and 1 in the 160/80 mg group) reported 4 infections. All of those infections were nonserious; most were of short duration and considered to have a reasonable possibility of being related to study drug by the investigator. All were mild, and all resolved with or without concomitant medication treatment.

One subject in the adalimumab 160/80 mg treatment group was identified as having active TB (positive QuantiFERON–TB Gold in-Tube text of Day 29) during the DB period. The subject was hospitalized, discontinued study drug, and began anti-TB therapy. During the OLE period, 3 subjects (1 in the adalimumab 80/40 mg treatment group; 2 in the adalimumab 160/80 mg treatment group) had a positive mycobacterium TB complex test. Subsequent additional TB evaluation by CT scan and/or T-SPOT revealed no abnormal findings and/or negative results for all subjects.

An intestinal obstruction, which was serious and remained ongoing at the end of the study, was reported in 1 subject (160/80 mg group) during the DB treatment period.

Nonserious hematologic disorders (anemia, neutropenia, and leukopenia) were reported in 7 subjects during the study. Four of these subjects also had laboratory abnormalities, and 1 of these discontinued study drug for the AEs/associated laboratory abnormalities (worsening leukopenia and worsening neutropenia).

Mean changes in laboratory parameter values (hematology, clinical chemistry, and urinalysis) from Baseline to Week 8 (end of the DB period) and over time to the end of the study (Week 26), except for improvements in hemoglobin, hematocrit, albumin, and total protein concentration, were not considered to be clinically meaningful. Shifts in hematology and clinical chemistry values from normal or high at Baseline to low at the final value or normal or low at Baseline to high at the final value were generally infrequent and not considered clinically meaningful. The 15.4% of subjects (4/26) who had a shift from normal to low WBC count was not unexpected given the AE reports of leukopenia.

Mean changes from Baseline values for vital sign parameters, except for the improvement in weight, were not considered clinically meaningful during the DB and OLE periods. No safety concerns were identified. No pregnancies were reported.

Pharmacokinetic Results:

As reported in the PK report (R&D/14/1022), PK assessment of adalimumab in Chinese patients with moderately to severely active CD and elevated hs-CRP showed that between Week 1 and Week 4 (induction phase), the mean serum adalimumab concentration was approximately 2-fold higher in subjects who received 160/80 mg compared with 80/40 mg at Week 0/2. In addition, serum adalimumab concentrations in Chinese patients with CD were comparable to those in Japanese and Western patients with CD.

Conclusions:

In conclusion, the efficacy results from the DB treatment period of Study M14-232 demonstrated that, compared with the adalimumab 80/40 mg dosing regimen, the adalimumab 160/80 mg dosing regimen led to more rapid achievement of clinical remission and clinical response as well as more rapid improvement in objective measures of disease (hs-CRP and fecal calprotectin) in Chinese subjects with moderately to severely active CD and elevated hs-CRP. The adalimumab 160/80 mg dosing regimen induced responses by Week 2 and maintained the responses through Week 8 (the end of DB treatment period). The efficacy results from the OLE period (Week 8 through Week 26) demonstrated that the majority of subjects in both treatment groups sustained clinical response and remission with continued open-label adalimumab 40 mg eow treatment. Additionally, adalimumab was generally safe and well-tolerated when administered at 80/40 mg or 160/80 mg doses at Weeks 0/2 followed by 40 mg eow as evidenced by AE, laboratory, and vital sign results through Week 26.