2. SYNOPSIS

<table>
<tr><td>Name of Company:</td><td>INDIVIDUAL STUDY TABLE</td><td>(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
CF101</td><td rowspan="2">Referring to Part IV of the Dossier
Volume: Page:</td><td rowspan="2"></td></tr>
<tr><td>Name of Active Ingredient:
CF101 (methyl 1-[N6-(3-iodobenzyl)-adenin-9-yl]-β-D-ribofuronamide)</td></tr>
<tr><td colspan="3">Title of the Study: A Phase 2, Randomized, Double-Blind, Dose-Ranging, Placebo-Controlled Study of the Safety and Activity of Daily CF101 Administered Orally in Patients with Moderate-to-Severe Plaque Psoriasis</td></tr>
<tr><td colspan="3">Investigator(s)/Center(s): 8 sites in Israel and Bulgaria</td></tr>
<tr><td colspan="3">Study Number: CF101-201PS</td></tr>
<tr><td colspan="3">Publication (Reference): None</td></tr>
<tr><td>Study Dates:
02 July 2007 to 18 August 2009</td><td>Study Status:
Completed</td><td>Phase of Development:
Phase [2]</td></tr>
<tr><td colspan="3">Objectives:
<u>Primary</u>
• Evaluate the activity of oral CF101 when administered at 1 mg, 2 mg, or 4 mg twice daily for 12 weeks, compared with placebo, in patients with moderate-to-severe plaque psoriasis; and
• Evaluate the safety of oral CF101 in this patient population.
<u>Secondary</u>
• Explore the relationship between peripheral blood mononuclear cell (PBMC) adenosine 3 receptor (A3AR) expression level at Baseline and response to therapy.</td></tr>
<tr><td colspan="3">Methodology: This was a Phase 2, randomized, double-blind, dose-ranging, placebo-controlled study in adult males and females, aged 18 to 70 years of age, inclusive, with a diagnosis of moderate-to-severe chronic plaque-type psoriasis with body surface area involvement ≥10%. Patients were enrolled sequentially in Cohorts 0, 1, 2, and 3. Cohorts 1, 2, and 3 began treatment only after treatment of the preceding cohort was complete. Cohort 0 received study medication in capsule form, after which study medication was changed to tablets for subsequent cohorts. Within each cohort, patients were randomized to receive CF101 1 mg (Cohorts 0 and 1), CF101 2 mg (Cohort 2), CF101 4 mg (Cohort 3), or matching placebo tablets (all cohorts), given orally every 12 hours for 12 weeks, in a 3:1 ratio of CF101 to placebo. A Screening Period of up to 4 weeks preceded a 12-week treatment period, followed by a 2-week follow-up period.

At the Screening Visit (Visit 1, performed within 28 days prior to randomization), patients who provided written informed consent had screening procedures performed, including a complete medical history, medication history, physical examination (including height, weight, sitting blood pressure [BP], pulse rate and temperature), and clinical laboratory tests. In addition, at Baseline, analysis of A3 adenosine receptor expression level was carried out on peripheral blood mononuclear cells. Disease activity was assessed using the Psoriasis Area Severity Index (PASI) and the Physician's Global Assessment (PGA).

At Visit 2, eligible patients were randomized to their assigned medication (CF101 1 mg, 2 mg, 4 mg, or matching placebo) to be taken orally every 12 hours for 12 weeks. Patients returned for assessments and a new supply of study medication at Weeks 2, 4, 8, and 12, and at Week 14 for a final follow-up assessment.</td></tr>
</table>

Number of Patients: Approximately 90 patients were to be enrolled to achieve 80 patients who completed all evaluations, at up to 6 investigative sites.

A total of 62 patients were randomized into Cohorts 1, 2, and 3 (CF101: 1 mg = 14; 2 mg = 17; 4 mg = 15; Placebo = 15). A total of 61 patients received study treatment. Fourteen patients were randomized in Cohort 0 to receive either CF101 1 mg or matching placebo capsules, bringing the total number of randomized patients to 76.

Indication and Criteria for Inclusion: Patients were adult men and women, at least 18 years of age, with a diagnosis of moderate-to-severe chronic plaque-type psoriasis with body surface area involvement ≥10% as judged by the Investigator, duration of psoriasis of at least 6 months, PASI score ≥10, and body weight ≤100 kg. Females of child-bearing potential had to have negative urine pregnancy tests and been willing to use 2 methods of contraception to be eligible for, and continue participation in, the study.

Test Treatment, Dose, and Mode of Administration:

Cohort 0: CF101 (methyl 1-[N6-(3-iodobenzyl)-adenin-9-yl]-β-D-ribofuronamide) 1 mg oral capsule every 12 hours (Lot # 4907.003)

Cohort 1: CF101 1 mg tablet every 12 hours (Lot # L0109721)

Cohort 2: CF101 2 mg tablet every 12 hours (Lot # L0109722)

Cohort 3: CF101 4 mg tablet every 12 hours (Lot # L0109723)

Reference Treatment, Dose, and Mode of Administration:

Cohort 0: Matching oral vehicle-filled placebo capsule every 12 hours. (Lot # 4902.002/4902.002A)

Cohort 1: Matching oral placebo tablet every 12 hours (Lot # L0109718)

Cohort 2: Matching oral placebo tablet every 12 hours (Lot # L0109718)

Cohort 3: Matching oral placebo tablet every 12 hours (Lot # L0109718)

Duration of Treatment: 12 weeks

Treatment Schedule: Patients were instructed to take study medication every 12 hours on an empty stomach, at least 1 hour before or 2 hours after a meal. Patients took study medication twice daily for 12 weeks.

Criteria for Evaluation:

Safety:

- Treatment-emergent adverse event (AE) reporting
- Vital signs
- Physical examination
- Clinical laboratory tests (blood chemistry, hematology, and urinalysis)
- ECG findings

Efficacy: Prior to any analyses, it was decided that this study would be viewed as an exploratory Phase 2 study, without specification of a primary efficacy endpoint, to provide information to plan for subsequent studies. Efficacy endpoints to be analyzed for this goal were:

- Change from PASI (psoriasis area and severity index) from Baseline (PASI CFB), calculated as the post-baseline visit PASI score minus the Baseline PASI score, for each visit.
- Percent change in PASI from Baseline (PASI PCFB), calculated as the post-baseline visit PASI score minus the Baseline PASI score divided by the Baseline PASI score, for each visit.
- PASI 50, a binary (Yes/No) variable, indicating whether a patient achieved a 50% improvement from Baseline of the PASI score (PASI PCFB $\leq$ -50%), was calculated for Weeks 2, 4, 8, and 12.
- PASI 75, a binary (Yes/No) variable, indicating whether a patient achieved a 75% improvement from Baseline of the PASI score (PASI PCFB $\leq$ -75%), was calculated for Weeks 2, 4, 8, and 12.
- PASI score was assessed in 4 areas of the body on the CRF: head, upper extremities (arms), trunk to groin, and lower extremities (legs to top of buttocks).
- PGA success frequency distribution by visit.

Exploratory:

- Analysis of the peripheral blood mononuclear cell A3AR expression level collected at Baseline will be provided in a separate report.

Statistical Methods:

Patients were assigned to Cohorts 0, 1, 2, and 3. Within each cohort, patients were randomly assigned to either CF101 or placebo in a 3:1 ratio. Initially, patients were entered into Cohort 0, which received study treatment in capsule form. Cohorts 1, 2, and 3, each receiving study treatment in tablet form, were enrolled in sequence after enrollment in the preceding cort was completed. The CF101 dose for Cohorts 0 and 1 was 1 mg; for Cohort 2, 2 mg; and for Cohort 3, 4 mg. Results are presented for all cohorts.

All statistical analyses were performed using SAS Version 9.0 (SAS Institute, NC, USA) software. The data were summarized descriptively by treatment group and visit. The descriptive statistics included number of patients (n), mean, standard deviation, median, minimum, and maximum for continuous safety and efficacy variables. Categorical variables were summarized using counts and percentages. All safety and efficacy data were included in individual patient listings. Patients who received placebo capsules or tablets in Cohorts 0, 1, 2, and 3 were pooled over cohorts for final presentation. All statistical testing was performed at the 0.05 level of significance, without adjustment for multiple comparisons.

Demographic and baseline vital signs and concomitant disease characteristics were summarized using descriptive statistics.

Prior to analysis, missing data were imputed for PASI CFB and PCFB using LOCF. Descriptive statistics for PASI CFB and PCFB are provided by treatment group and visit.

Missing post-baseline data for PASI 50 and PASI 75 were imputed using the imputed values of PASI PCFB. Tables are provided showing the proportion of patients having PASI 50 and PASI 75 at Weeks 2, 4, 8, 12, and 14. Statistical comparisons between placebo and the active treatments are provided using the Fisher's exact test.

Descriptive statistics are provided for the PASI score at Baseline, Weeks 2, 4, 8, 12, and 14. Listings of all data are provided.

Safety endpoints, including treatment-emergent adverse events, clinical laboratory safety tests (liver and kidney tests, hematology and urinalysis), physical examinations, ECGs, and vital signs were summarized by treatment group using descriptive statistics.

Adverse events were coded using MedDRA (Version 9.0). Treatment emergent adverse events were summarized by treatment group, and are presented by severity and causal relationship to study agent. Patients experiencing serious adverse events have been listed. Concomitant medications were coded using the WHO Drug dictionary and summarized by treatment group.

Vital signs measurements were summarized using descriptive statistics by treatment group and visit.

Exploratory PBMC A3AR data will be summarized and presented in a separate report.

Results:

Efficacy:

Before any data analyses were performed, it was decided that the efficacy analyses would be exploratory, as this study was intended to provide inofrmation for the planning of future studies.

- Statistically significant improvements in PASI scores relative to placebo were seen in the CF101 2 mg group at Week 12 (-8.77 vs. -2.17; *P*=0.031 using a 2-sample t-test), as well as at Week 8 (-6.22 vs. -0.99; *P*=0.047) and Week 14 (-9.49 vs. -3.01; *P*=0.048). At other time points, the differences between CF101 2 mg and placebo were not statistically significant, but improvements with CF101 2 mg were greater than those with placebo. No statistically significant differences were seen between either CF101 1 mg or CF101 4 mg and placebo at any time point, but the mean reductions with CF101 4 mg were greater than those with placebo at all time points.

- Summary statistics for the change in PASI scores from baseline showed greater reductions with CF101 1 mg and 2 mg than with placebo at Week 2. All three CF101 groups showed greater mean reductions at Week 4. The CF101 2 mg and 4 mg groups showed greater mean reductions in PASI scores than placebo at Week 12, as well as at Week 8.

- Analysis of the frequency distribution and treatment differences for PGA scores in the ITT population showed no statistically significant differences between the CF101 treatment groups and placebo. However, examination of the results showed that 2 patients in the CF101 1 mg group and 1 patient in the placebo group had Baseline scores of 1 (psoriasis signs and symptoms Slight) and therefore were classified as responders at Baseline. Re-analysis of the data for patients with Baseline scores > 1 (0 and 1 being indicators of response) showed that the PGA success rate was statistically significantly higher for the CF101 2 mg group (23.5%) than in the placebo group (0.0%) (*P*=0.045) at Week 12.

- No treatment group showed a statistically significant difference in PASI 75 or PASI 50 scores, compared with placebo, at any point during the study.

- Through Week 4, no patient in any treatment group showed success for PASI 75. Sporadic successes for PASI 75 were seen with CF101 at Weeks 8 and 12.

- For PASI 50, the CF101 1 mg and 2 mg groups showed a higher percentage of response than placebo at Week 8 (12.5% and 11.8%, respectively, vs 6.7%) and Week 12 (20.8% and 35.3%, respectively, vs 15.8%). The CF101 4 mg group had response rates that were the same as with placebo at both time points.

Safety:

- No deaths occurred during this study.
- One serious adverse event (moderate arrhythmia) occurred in the Cohort 2 placebo group during this study and was not related to study medication.
- In the safety population, the incidence of treatment-emergent adverse events was lowest in the CF101 4 mg group (13.3%); the incidence was 58.3% in the CF101 1 mg group, 17.6% in the CF101 2 mg group, and 21.1% in the placebo group.
- Two adverse events were rated as severe (pruritus in Cohort 0, CF101 1 mg and rash in Cohort 1 CF101 1 mg); most adverse events were of mild or moderate intensity.
- No clear patterns of difference between the CF101 treatment groups and the placebo group were evident for individual system organ classes.
- Three patients (1 in Cohort 0, CF101 1 mg; 1 in Cohort 1 CF101 1 mg; and 1 in Cohort 0 placebo) had adverse events that resulted in discontinuation from the study. None of these events were considered related to study treatment.
- Blood chemistry, hematology, and urinalysis results raised no safety concerns.
- The mean values for systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate, respiratory rate, and temperature were within the normal range at baseline and end point in all treatment groups. There were no clinically important changes in mean vital signs from baseline to end point for any treatment group. No abnormalities in vital signs values were reported as adverse events during the study.
- No treatment-related patterns of change were evident for QT or QT_cB interval or the percentage of patients with ST segment or cardiac rhythm abnormalities at Week 12.

Conclusions:

Efficacy:

- Statistically significant improvements in PASI scores relative to placebo were seen in the CF101 2 mg group at Week 12 (-8.77 vs. -2.17; *P*=0.031 using a 2-sample t-test), as well as at Week 8 (-6.22 vs. -0.99; *P*=0.047) and Week 14 (-9.49 vs. -3.01; *P*=0.048). At other time points, the differences between CF101 2 mg and placebo were not statistically significant, but improvements with CF101 2 mg were greater than those with placebo. No statistically significant differences were seen between either CF101 1 mg or CF101 4 mg and placebo at any time point, but the mean reductions with CF101 4 mg were greater than those with placebo at all time points.

- Summary statistics for the change in PASI scores from baseline showed greater reductions with CF101 1 mg and 2 mg than with placebo at Week 2. All three CF101 groups showed greater mean reductions at Week 4. The CF101 2 mg and 4 mg groups showed greater mean reductions in PASI scores than placebo at Week 12, as well as at Week 8.

- Analysis of the frequency distribution and treatment differences for PGA scores in the ITT population showed no statistically significant differences between the CF101 treatment groups and placebo. However, examination of the results showed that 2 patients in the CF101 1 mg group and 1 patient in the placebo group had Baseline scores of 1 (psoriasis signs and symptoms Slight) and therefore were classified as responders at Baseline. Re-analysis of the data for patients with Baseline scores > 1 (0 and 1 being indicators of response) showed that the PGA success rate was statistically significantly higher for the CF101 2 mg group (23.5%) than in the placebo group (0.0%) (*P*=0.045) at Week 12.

- No treatment group showed a statistically significant difference in PASI 75 or PASI 50 scores, compared with placebo, at any point during the study.

- Through Week 4, no patient in any treatment group showed success for PASI 75. Sporadic successes for PASI 75 were seen with CF101 at Weeks 8 and 12.

- For PASI 50, the CF101 1 mg and 2 mg groups showed a higher percentage of response than placebo at Week 8 (12.5% and 11.8%, respectively, vs 6.7%) and Week 12 (20.8% and 35.3%, respectively, vs 15.8%). The CF101 4 mg group had response rates that were the same as with placebo at both time points.

Safety: No apparent safety concerns of 12 weeks of treatment with CF101 were identified.

Date of the Report: 5 February 2010