ORIGINAL ARTICLE

Treatment of plaque-type psoriasis with oral CF101: data from an exploratory randomized phase 2 clinical trial

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Abstract

Aims CF101 demonstrated a marked anti-inflammatory effect in Phase 2 studies conducted in patients with rheumatoid arthritis and dry eye syndrome. The aim of this study was to evaluate the safety and efficacy of CF101 for the treatment of patients with moderate to severe plaque-type psoriasis.

Materials and methods This was a phase 2, multicentre, randomized, double-blind, dose-ranging, placebo-controlled study. Seventy five patients with moderate to severe plaque-type psoriasis were enrolled, randomized and treated with CF101 (1, 2, or 4 mg) or placebo administered orally twice daily for 12 weeks. Safety and change from base line of Psoriasis Area and Severity Index (PASI) score and physician's global assessment (PGA) score over 12 weeks.

Results In the 2 mg CF101-treated group, a progressive improvement in the mean change from baseline in the PASI score vs. placebo throughout the study period was observed, with a statistically significant difference on weeks 8 and 12 ($P = 0.047$; $P = 0.031$, respectively). In this group, 35.3% of the patients achieved PASI ≥50 response, and 23.5% of the patients achieved a PGA score of 0 or 1. CF101 was safe and well tolerated.

Conclusions CF101 was well tolerated and demonstrated clear evidence of efficacy in patients with moderate to severe plaque psoriasis.

Received: 21 November 2010; Accepted: 24 March 2011

Conflicts of interest

None declared.

Introduction

Psoriasis is a chronic inflammatory skin disease with the potential for multisystem pathology and negative impact on the quality of life of the patients. It is characterized by epidermal hyper proliferation and immature differentiation, as a result of complex interactions between T cells, dendritic cells and keratinocytes.[1,2] Th1 cytokines such as INF-γ, TNF-α, IL-23, Th17 cytokines have shown to play a major role in inducing and maintaining inflammation and epidermal alterations in psoriasis.[3]

Registration number and name of the trial: NCT00428974, Safety and Efficacy Study of CF101 to Treat Psoriasis.

CF101 is an oral anti-inflammatory agent that binds with high affinity and selectivity to the A_3AR, a Gi protein-associated cell surface receptor. The A_3AR is over expressed in inflammatory cells, whereas healthy cells show low or no receptor expression. High A_3AR expression levels have been found in synovial fluid cells and peripheral blood mononuclear cells (PBMCs) derived from patients with rheumatoid arthritis (RA), indicating that circulating cells reflect the receptor status in remote inflammatory tissue.[4–7] Similarly, over-expression of A_3AR has been described in PBMCs of patients with psoriasis and patients with Crohn's Disease, suggesting that this is a general phenomenon in immuno-inflammatory diseases.[7–10]

CF101 induced a marked anti-inflammatory effect in experimental animal models of arthritis, inflammatory bowel disease, osteoarthritis and septic peritonitis.[4,5,11–15] The anti-inflammatory mechanism of action of CF101 entails down-regulation of the NF-κB signalling pathway, resulting in de-regulation of pro-inflammatory cytokines and chemokines, such as of TNF-α and MIP-1α. Furthermore, CF101 inhibits the proliferation of specific auto-reactive T cells and induces apoptosis of inflammatory cells.[4,5,11–15]

The A_3AR is considered today as a validated target to combat inflammation based on proof-of-concept in human clinical trials. In separate Phase 2 studies conducted in patients with RA and keratoconjunctivitis sicca (KCS), treatment with CF101 was safe and well tolerated and resulted in an improvement of disease signs and symptoms as assessed by standard disease outcome criteria.[16,17]

All the above points provided the rationale to study the effects of CF101 in patients with moderate to severe plaque psoriasis.

Methods

Patients

Adult males and females, aged 18–70 years with moderate to severe chronic plaque psoriasis of at least 6 months duration and a PASI score ≥10, were enrolled to the study. Patients were excluded as follows: a diagnosed with erythro dermic, guttate, or pustular psoriasis; history of treatment with systemic retinoids, corticosteroids, or immuno-suppressants within 6 weeks of the baseline visit; treatment with moderate-high potency topical corticosteroids (Class I–III), calcipotriol within 2 weeks of the baseline visit; treatment with phototherapy or Dead Sea climato-therapy within 4 weeks of the Baseline visit; treatment with a biological agent within a period of time equal to five times its circulating half-life, or 30 days, whichever is longer, prior to the baseline visit; history of poor clinical response to methotrexate after an adequate regimen and duration of treatment; pregnancy, planned pregnancy, lactation, or inadequate contraception as judged by the investigator or other conditions which would confound the study evaluations or endanger patient safety. The conduct of this trial was approved by all local Ethics Committees in accordance with the Declaration of Helsinki. Written informed consent was obtained from the patients before inclusion in the study.

Study design

This was a Phase 2, multicentre, randomized, double-blind, dose-ranging, placebo-controlled study. Eligible patients were assigned to one of three sequential dosing cohorts with planned sample sizes of approximately 15 patients each: Cohort 1 (CF101 1 mg q12 hours); cohort 2 (CF101 2 mg q12 hours); or Cohort 3 (CF101 4 mg q12 hours). Within each cohort, patients were randomly assigned to either active drug or matching placebo tablets at a 3 : 1 ratio. Patients were permitted to use emollients along the study period.

A detailed clinical examination, assessment of body surface area of psoriasis involvement and evaluation of Psoriasis Area and Severity Index (PASI) scores were performed in all patients.[18] Clinical laboratory tests included fasting clinical chemistry testing, haematology, urinalysis and serum pregnancy test (women of child bearing potential). A resting 12-lead electrocardiogram was obtained.

A screening period of up to 4 weeks was followed by a 12-weeks treatment period, and then by 2 weeks of follow-up period. Patients were assessed at screening visit, baseline, weeks 2, 4, 8 and 12.

Efficacy and safety assessments

The exploratory efficacy endpoints were: Change from Baseline (CFB) in PASI Scores; proportion of patients achieving 50% and 75% improvement in PASI scores (PASI 50 and PASI 75, respectively); and static physician's global assessment (PGA), which measures the physician's impression of the disease at a single point (graded on a 0–5 scale as follows: 0 = absent, 1 = slight, 2 = mild, 3 = moderate, 4 = marked, 5 = severe).[19] These parameters were calculated at Weeks 2, 4, 8, 12 and 14.

Safety assessments included recording of treatment-emergent adverse events, and changes in vital signs, physical examinations, clinical laboratory tests and electrocardiography findings.

Statistical analysis

Prior to analysis, the most recent recorded value for PASI CFB was utilized in the place of the missing data point. Between-treatment comparisons of each active treatment group to placebo, with respect to PASI CFB, at each visit were performed using student *t*-test analysis. Descriptive statistics for PASI CFB were provided by treatment group.

Missing post-baseline data for PASI 50 and PASI 75 were imputed. Statistical comparisons between placebo and the active treatments with respect to the PASI 50 and PASI 75 rates were performed using the Fisher's exact test. Descriptive statistics were performed for the PASI score for baseline, Weeks 2, 4, 8 and 12, and for the change from baseline.

Safety endpoints were summarized using descriptive statistics. Adverse events were coded using Medical Dictionary for Regulatory Activities endorsed by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (MedDRA, version 9.0).

Results

Patients

A total of 84 patients with moderate to severe plaque psoriasis were screened. Patients who met the inclusion criteria ($n = 75$) were randomized to placebo ($n = 19$), CF101 1 mg ($n = 25$), CF101 2 mg ($n = 17$) or CF101 4 mg ($n = 15$). Most of the patients completed the study ($n = 64$, 84.2%); reasons for withdrawal from the study included: occurrence of an adverse event

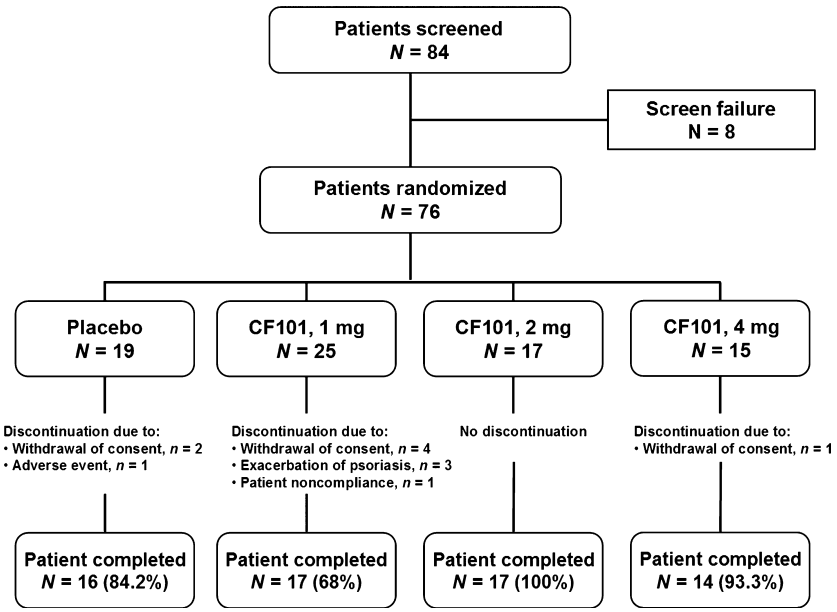

Figure 1 Patients' eligibility, randomization, assignment and discontinuation.

(1), exacerbation of psoriasis (3) and withdrawal of consent (7) (Fig. 1). Summary of demographic data, disease characteristics and PGA data at baseline are shown in Table 1.

Efficacy

Analysis of mean change from baseline in PASI score at week 12 revealed a statistically significant difference between the 2 mg CF101-treated group and the placebo group ($P < 0.001$ vs. baseline and $P = 0.031$ vs. placebo). The 4 mg CF101 dose treatment resulted in lesser improvement than that of the 2 mg dose treatment, and no therapeutic effect was observed in the 1 mg CF101-treated group. Furthermore, in the 2 mg CF101-treated group, a progressive improvement in the mean change from baseline in the PASI score throughout the study period was observed (week 2: 1.64 ± 0.9; week 4: 3.76 ± 1.9; week 8: 6.22 ± 1.9; week 12: 8.77 ± 2.1), with a statistically significant difference from placebo at weeks 8 and 12 ($P = 0.047$ and $P = 0.031$, respectively) (Fig. 2).

In the 2 mg CF101-treated group, 35.3% (6 out of 17) of the patients achieved PASI ≥50 response (Fig. 3). Among this group, 11.8% (2 out of 17) of the patients achieved a response that was very close to PASI 50 (47.7% and 49.9%) at week 12. Furthermore, of those patients achieving PASI 50, one showed PASI improvement of 73%, and one reached PASI 90.

Since there was no entry requirement for a minimum PGA score, analysis of PGA data was performed on patients who entered the trial with a PGA score >1 to avoid confounding by low baseline scores. At week 12, 23.5% of the patients treated with the 2 mg CF101 dose achieved a score of 0 or 1, in comparison with 0% in the placebo group ($P < 0.05$). The percentage of patients presenting only slight or no clinical signs (PGA score 0–1) increased throughout the study period in the 2 mg CF101-treated group (Fig. 4).

Table 1 Patients' baseline characteristics

	Placebo	CF101, 1 mg	CF101, 2 mg	CF101, 4 mg
N	19	24	17	15
Age (years)	51.2 ± 2.4	51.5 ± 2.4	48.4 ± 2.5	45.3 ± 3.1
Weight (kg)	84.2 ± 2.6	82.1 ± 2.4	83.7 ± 2.7	75.1 ± 3.8
Gender (M : F)	14 : 5	19 : 5	15 : 2	10 : 5
Duration of disease (years)	23.5 ± 2.5	18.7 ± 2.3	19.4 ± 2.8	19.1 ± 2.9
Prior treatments used				
Topical therapy	15 (79)	15 (63)	15 (88)	14 (93)
Systemic therapy	9 (47)	17 (71)	10 (59)	8 (53)
Phototherapy	10 (53)	23 (96)	11 (65)	6 (40)
PASI	16.8 ± 1.2	17.3 ± 1.6	22.9 ± 2.3	21.5 ± 2.1
PGA				
Absent-slight (0–1)	1 (5.3)	2 (8.3)	0 (0.0)	0 (0)
Mild (2)	1 (5.3)	6 (25)	3 (17.7)	1 (6.7)
Moderate (3)	8 (42.1)	10 (41.7)	8 (47.1)	3 (20.0)
Marked (4)	8 (42.1	1 (4.2)	3 (17.7)	9 (60.0)
Severe (5)	1 (5.3)	5 (20.8)	3 (17.7)	2 (13.3)

PASI, Psoriasis Area and Severity Index; PGA, physician's global assessment.

A representative photograph of the clinical improvement upon treatment with 2 mg dose CF101 is depicted in Fig. 5.

Safety

Over all, CF101 was found to be safe and well tolerated. The incidence of adverse events was 58.3% in the CF101 1 mg group, 17.6% in the CF101 2 mg group and 13.3% in the CF101 4 mg group; these figures compare to an incidence of 21.1% in the placebo group.

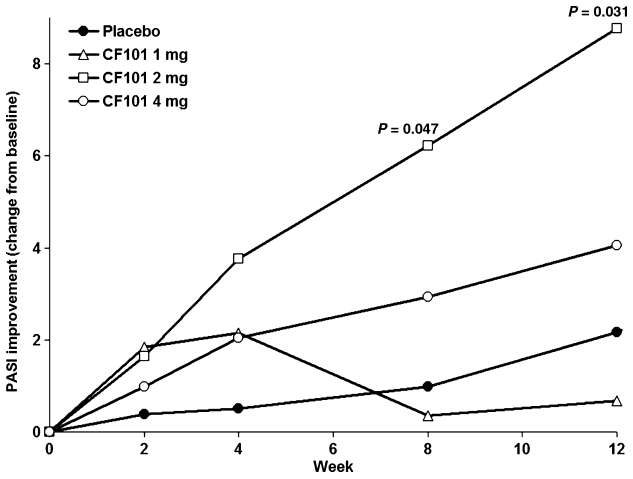

Figure 2 Improvement in mean change from baseline in Psoriasis Area and Severity Index score in the 1, 2 and 4 mg CF101 groups vs. placebo, along study period.

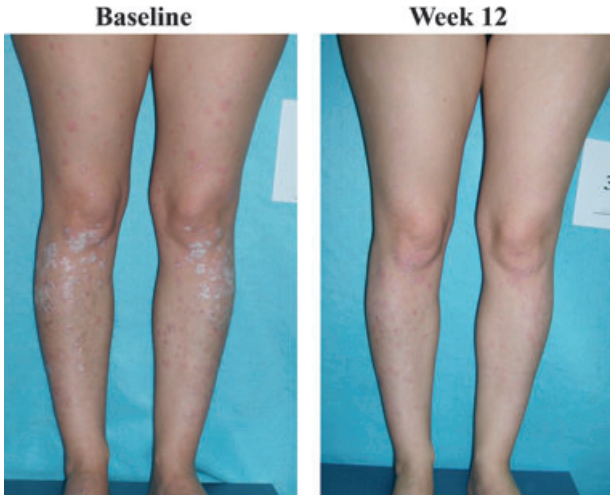

Figure 5 Representative picture of a patient with plaque-type psoriasis on the upper and lower legs treated with 2 mg CF101. A comparison between baseline and week 12.

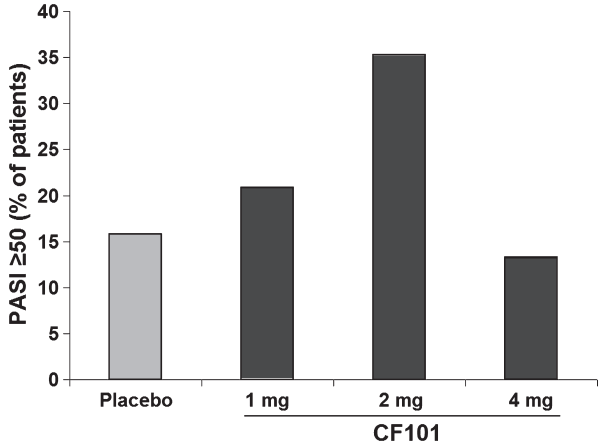

Figure 3 Percentage of patients with Psoriasis Area and Severity Index 50 response at week 12 by treatment group.

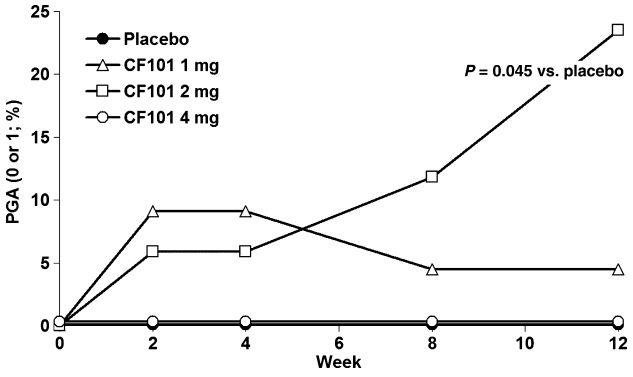

Figure 4 Percentage of patients with PGA >1 at baseline achieving PGA values of 0–1 in the 1, 2 and 4 mg CF101 groups vs. placebo along study period.

Two adverse events were rated as severe, both were in patients receiving CF101 1 mg: pruritus, and skin rash allergic reaction/psoriatic exacerbation. One serious adverse event (moderately severe arrhythmia/atrial fibrillation) occurred during this study in a subject who received placebo, and was not attributed to study medication.

No clear patterns of difference between the CF101 treatment groups and the placebo group were evident for any body system/organ classes.

There were 20 adverse events reported, and 15 of the 20 were adverse events that were possibly related to the study drug; all were mild or moderately severe except for one exacerbation of psoriasis judged to be severe. All adverse events reported are listed in Table 2. Only four patients were withdrawn from the study due to adverse events, including one patient from the placebo group who experienced arrhythmia.

Discussion

The data presented in this exploratory study demonstrate that CF101, a novel small molecule drug, significantly improved the clinical signs of psoriasis, as measured by the PASI score and PGA, in patients treated with CF101 2 mg twice daily for 12 weeks, as compared to patients receiving placebo. Eight of 17 patients had a ≥47% reduction from baseline in the total PASI score and 23.5% achieved a PGA score of 0–1 while no patient in the placebo group achieved a PGA score of 0–1. The onset of therapeutic effect in plaque psoriasis, evidenced by the PASI and the PGA results, was relatively rapid, persistent and increased throughout the study period. This pattern of response is similar to the CF101 effect observed in the RA and KCS clinical studies, both of which were also of 12 weeks duration.[16,17] These data support the hypothesis

Table 2 Summary of all adverse events

Adverse events	No. (%) of patients treated with Placebo *N* = 19	No. (%) of patients treated with 1 mg CF101 *N* = 24	No. (%) of patients treated with 2 mg CF101 *N* = 17	No. (%) of patients treated with 4 mg CF101 *N* = 15
Abdominal discomfort	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Acute tonsillitis	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Alopecia	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Arrhythmia	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Arthralgia	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Arthropathy	0 (0.0)	2 (8.3)	0 (0.0)	0 (0.0)
Back pain	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Calculus urinary	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Chest pain	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)
Chills	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Constipation	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Diarrhoea	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Dizziness	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Erectal dysfunction	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Influenza	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)
Libido decrease	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Liver function test abnormal	1 (5.3)	0 (0.0)	0 (0.0)	0 (0.0)
Oedema Peripheral	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Oesophagitis	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Otitis externa	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)
Pruritus	0 (0.0)	3 (12.5)	0 (0.0)	0 (0.0)
Psoriasis	0 (0.0)	2 (8.3)	0 (0.0)	0 (0.0)
Rhinorrhoea	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Rhinitis	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Sinusitis	0 (0.0)	0 (0.0)	1 (5.9)	0 (0.0)
Skin infection	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Urine oxalate	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)
Uterine haemorrhage	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Viral infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (6.7)
Xerosis	0 (0.0)	1 (4.2)	0 (0.0)	0 (0.0)

that prolonging treatment beyond 12 weeks may result in continued improvement. The drug was safe and well tolerated throughout the study period.

Currently there are only few small molecule orally bioavailable drugs for the treatment of Psoriasis. Among those, is acitretin (a synthetic retinoid) showing comparable efficacy to CF101 but is associated with side-effects and organ toxicity that prevents long-term therapy.[20–23]

CF101 had a bell-shaped dose–response effect, with the highest efficacy at the 2 mg group dose, as manifested by significant improvement in the PASI score. In the 4 mg dose group there was a suggestion of efficacy, which did not reach statistical significance. Our earlier preclinical and clinical data with A_3 adenosine receptor agonists have also demonstrated that the drugs exert a bell-shaped dose–response curve. This phenomenon has already been described in drugs which target G protein-coupled receptors, presumably due to an increase in agonist concentration that may lead to receptor desensitization, resulting in less response to the ligand.[13,24–28] In addition, the lack of dose-dependent response in our study could be a function of the relatively small sample size which will be further investigated in future trials. Nevertheless, it is intriguing that the bell-shaped dose–response pattern of clinical efficacy in the current trial repeats the data seen in our previous Phase 2 study of CF101 in patients with RA.[16]

CF101 is an A_3AR agonist with a proven anti-inflammatory effect. Its efficacy was first proven in a Phase 2 clinical study in RA, demonstrating an improvement in ACR20 (American College of Rheumatology criteria) and DAS (Disease Activity Score).[16] Anti-inflammatory effects have also been recently confirmed in a Phase 2 study in patients with dry eye syndrome.[17]

Chronic plaque psoriasis is an immune-mediated, inflammatory skin disease. The pro-inflammatory cytokine, TNF-α, plays a critical role in the pathogenesis and development of psoriasis. In the last decade, the use of biological anti-TNF-α agents (efalizumab, etanercept, infliximab and adalimumab) has been approved for the treatment of plaque-type psoriasis.[29,30] The

anti-inflammatory effect of CF101 is partially mediated via the inhibition of pro-inflammatory cytokine production, including TNF-α.[4–6,9,10]

Recent data showing over-expression of A_3AR in PBMCs from patients with psoriasis support the utilization of this target in the treatment of this disease and provide the rationale for the current trial. The results of the present study further confirm CF101's anti-inflammatory effect and suggest clinically relevant activity across a range of immuno-inflammatory diseases. Moreover, in a phase 2 clinical study in which CF101 was administered to patients with RA a direct correlation between A_3AR expression levels at base line and patients' responses to the drug was observed, suggesting its utilization as a biomarker to predict clinical response.[16]

This trial further corroborates our previous experience with CF101, demonstrating the excellent tolerability of the drug.[16,17] In a Phase II trial of CF101 in 74 patients with RA receiving twice daily doses of CF101 as high as 4 mg and in a Phase II dry eye syndrome trial in which 43 patients received twice daily 1 mg CF101, the drug was safe and well tolerated. Safety data from the current trial are consistent with those from prior trials in that adverse events associated with CF101 are generally mild in severity, self-limited and only infrequently a cause of discontinuation from treatment. The favourable safety profile of CF101 may be explained by the fact that CF101 has a differential effect on normal and pathological cells due to A_3AR over-expression in inflammatory cells, minimizing the likelihood of clinically important A_3AR-mediated adverse effects.[4–8,31] Furthermore, with its high selectivity for the A_3AR over other adenosine receptors, off-target effects are not anticipated at the dose levels used in this trial.[12,32]

To conclude, the clinical data from this proof-of-concept study support further evaluation of CF101 as a potential treatment for psoriasis. The good safety profile of CF101, as demonstrated in this and other clinical studies, suggest further clinical development of this small molecule drug.

Acknowledgements

The authors thank all the investigators and participants in this study: M Kerner, A Zoabi, B Dimitrov, N Ivanov, M Ralinovska, V Pavlova-Petkovad, H Trau, G Kriger, F Salameh, M Gyurova, M Hitova, A Dancheva-Atanasova, P Kaliasheva-Zaimova, A Mercer, S Fishman, Z Harpaz, M Farbstein and S Bar Yehuda.

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