

Treatment of Plaque-Type Psoriasis With Oral CF101: Data from a Phase II/III Multicenter, Randomized, Controlled Trial

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ABSTRACT

Background: CF101, an adenosine A3 receptor agonist, is an orally bioavailable small molecule drug presenting an anti-psoriatic effect demonstrated in a Phase 2 clinical trial in psoriasis patients.

Objective: To evaluate the safety and efficacy of CF101 treatment in a Phase 2/3 study in patients with moderate to severe plaque-type psoriasis.

Methods: This multicenter, double-blind, 2-segment, placebo-controlled study randomized subjects with moderate to severe plaque psoriasis to CF101 1 or 2 mg, or placebo twice daily. At either week 12 (Segment 1) or 16 (Segment 2), the placebo group crossed over to CF101 BID through week 32 in an open-label fashion. At week 12, following an interim analysis, the CF101 1mg group was discontinued due to futility. The primary endpoint was proportion of patients achieving $\geq 75\%$ improvement in Psoriasis Area Severity Index (PASI 75). Efficacy testing was performed using the Cochran-Mantel Haenszel test, the primary analysis of PASI 75 was performed at the 0.035 significance level.

Results: CF101 had an excellent safety profile at all tested dosages with a profile similar to the placebo group. The most common adverse events were infections and gastrointestinal events, and there was no cumulative intolerance over the 32-week dosing period. The study did not meet the primary endpoint of PASI 75 at week 12 (2 mg: 8.5% vs. placebo: 6.9%, $P=0.621$). However, at week 32, PASI mean percent improvement with CF101 2 mg was 57% ($P<0.001$) compared to baseline, with linear improvement in PASI 50 (63.5%), 75 (35.5%), 90 (24.7%), and 100 (10.6%).

Conclusions: Oral CF101 was found to be safe and very well tolerated, demonstrating evidence of efficacy in patients with moderate to severe plaque psoriasis through 32 weeks of treatment.

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INTRODUCTION

Pсориаз is a chronic inflammatory, systemic immune-mediated disease of that affects the skin and joints and is associated with multiple comorbidities¹. The effect on quality of life is severe with patients reporting social discomfort, embarrassment, reduced mental functioning, and physical pain.^{2,3}

Despite the beneficial effect of the current agents approved for moderate to severe psoriasis, many patients discontinue treatment with biologics or traditional systemic medications because of loss or lack of efficacy, monitoring and safety issues, and lack of tolerance.⁴

The Gi protein-associated A₃ adenosine receptor (A₃AR) has been found to be overexpressed in inflammatory cells, whereas low expression of the receptor is found in normal cells.^{5,6} The high receptor expression is also reflected in the peripheral blood mononuclear cells of psoriasis patients.^{7,8}

CF101 is an orally bioavailable A₃AR agonist inducing anti-inflammatory effect via de-regulation of the Wnt and the nuclear factor kappa-B (NF-κB) signal transduction pathways, leading to the inhibition of tumor necrosis factor-α (TNF-α), interleukin-6 and IL-12, macrophage inflammatory proteins, and receptor activator of NF-κB ligand (RANKL).^{9,10} CF101's anti-inflammatory effect has been demonstrated in Phase 2 studies in patients with rheumatoid arthritis and with psoriasis, showing efficacy and an excellent safety profile.^{11,12} In an earlier Phase 2 placebo controlled study in patients with moderate-to-severe plaque psoriasis, CF101 at a dose of 2 mg BID demonstrated a statistically significant improvement compared to control as evidenced a 35.3% rate of PASI ≥50 response and a 23.5% rate of achieving a PGA score of 0 or 1 at week 12. CF101 was safe and well tolerated at doses as high as 4 mg BID for 12 weeks.¹¹

In the current Phase 2/3 study, CF101 treatment of patients with moderate-to-severe plaque psoriasis has been further investigated, with the demonstration of favorable safety and efficacy through 32 weeks of treatment.

PATIENTS AND METHODS

Patients

Male and female subjects, aged 18-80, diagnosed with moderate-to-severe plaque psoriasis for at least 6 months' duration with Physician's Global Assessment (PGA) ≥3, Psoriasis Area Severity Index (PASI) score ≥10, body surface area involvement ≥10%, who were candidates for systemic treatment or phototherapy, were enrolled into the study.

Main exclusion criteria were: other clinical forms of psoriasis, 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), 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; pregnancy; and severe infections or other conditions that 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 (NCT00428974).

Study Design

This was a Phase 2/3, multicenter, randomized, double-blind, placebo-controlled study performed in 2 segments. In Segment 1, eligible subjects were randomly assigned to parallel dosing groups of orally administered CF101 1 mg, CF101 2 mg, or matching placebo tablets twice daily (BID) in a 1:1:1 ratio for a 12-week blinded placebo-controlled period (BPCP). At week 12, following the completion of Segment 1, an interim analysis was performed including data from 103 subjects (33 subjects in the CF101 1 mg BID dose group, 33 in the CF101 2 mg BID dose group, and 37 in the BID placebo group). Based on efficacy results of the interim analysis, the CF101 1 mg dose group was eliminated for futility. Therefore, only 2 treatment groups remained in the study.

Under the subsequent protocol amendment, which implemented Segment 2 of the trial, an additional 223 patients were enrolled and assigned in 1:1 ratio to placebo or CF101 2 mg taken orally BID for 16 weeks in a BPCP. At the end of 16 weeks, an open label extension (OLE) period started; subjects assigned to CF101 2 mg were continued on CF101 2 mg, while subjects originally assigned to placebo were reassigned to CF101 2 mg BID.

Disease severity during both segments was assessed using PASI and static PGA scores.

Subjects returned for safety and efficacy assessments and for new supply of study medication at weeks 4, 8, 12, 16, 20, 24, and 28, and for final study assessments at week 32.

Efficacy and Safety

The primary efficacy endpoint during Segment 2 of the trial was the proportion of subjects achieving PASI 75 at week 12, and the secondary efficacy endpoints were the proportion of subjects achieving PASI 75 at week 16 and the proportions of subjects achieving PGA of 0 or 1 at weeks 12 and 16. Efficacy for the OLE period was determined by the change in the proportion of subjects who achieved PASI 75 over time within each group.

Safety assessments for both segments, including BPCP and OLE, included treatment-emergent adverse events (TEAEs) and

TABLE 1.**Patients' Baseline Characteristics**

Parameter	Statistic	CF101 2 mg (N=145)	Placebo (N=148)	Total (N=293)
Age (years)	n	145	148	293
	Mean (SD)	48.3 (13.57)	50.0 (13.96)	49.2 (13.77)
	Median	48	51	49
	Min, Max	19, 79	20, 78	19, 79
Weight (kg)	n	145	147	292
	Mean (SD)	83.4 (17.67)	83.3 (17.42)	83.3 (17.51)
	Median	82	80.9	82
	Min, Max	47, 140	45, 138	45, 140
Height (cm)	n	145	147	292
	Mean (SD)	171.3 (9.05)	170.6 (9.26)	171.0 (9.15)
	Median	170	170	170
	Min, Max	150, 200	145, 197	145, 200
BMI (kg/m ²)	n	145	147	292
	Mean (SD)	28.33 (5.143)	28.52 (5.156)	28.43 (5.142)
	Median	27.78	28.33	28.08
	Min, Max	18.0, 47.9	18.0, 44.5	18.0, 47.9
Sex	Male, n (%)	91 (62.8)	95 (64.2)	186 (63.5)
	Female, n (%)	54 (37.2)	53 (35.8)	107 (36.5)
	Total	145	148	293
Origin	White/Caucasian, n (%)	144 (99.3)	146 (98.6)	290 (99.0)
	Black/African, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
	Oriental, n (%)	1 (0.7)	0 (0.0)	1 (0.3)
	Other, n (%)	0 (0.0)	2 (1.4)	2 (0.7)
	Total	145	148	293
PASI	n	141	144	285
	Mean (SD)	21.5 (9.51)	21.5 (10.11)	
	Median	18.2	18.3	
	Min, Max	6, 59	6, 52	
Disease Duration (yrs)	n	145	148	293
	Mean (SD)	11.8 (11.91)	11.3 (10.02)	11.6 (10.98)
	Median	6	8	7
	Min, Max	0, 57	0, 46	0, 57

changes in vital signs, physical examination, clinical laboratory tests (liver, kidney, hematology, chemistry, urinalysis, and pregnancy test for females), and ECG findings.

STATISTICAL ANALYSIS

An interim analysis was performed using data from the first 103 subjects enrolled in between-treatment comparisons of CF101 to placebo with respect to the proportion of subjects achieving PASI 75 at week 12 using the Cochran-Mantel Haenszel (CMH)

test. To adjust for the interim analysis, the primary analysis of PASI 75 at week 12 was performed at the 0.035 significance level.

The secondary efficacy endpoints were the proportion of subjects achieving a PGA of 0 or 1 at weeks 12 and 16. Between-treatment comparisons of CF101 to placebo with respect to each of these variables were performed using the CMH test at the 0.05 level.

TABLE 2.**Adverse Events**

	BPCP				Weeks 0-32	
	CF101 2mg		Placebo		CF101 2mg	
	n (%)	EAIR	n (%)	EAIR	n (%)	EAIR
≥ 1 AE	37/142 26.10%	108.3	28/145 19.30%	76.4	71/247 28.70%	82.8
≥ 1 Severe AE	4 /129	13.1	1 /129	3.1	6/247	7
	3.10%		0.80%		2.40%	
≥ 1 SAE	7 /129	23	2 /129	6.2	8/247	9.3
	5.40%		1.60%		3.20%	
≥ 1 Discontinue med due to AE	6 /130	19.6	1 /128	3.1	5/247	5.8
	4.60%		0.80%		2.00%	
Death due to AE	1 /130	3.3	0	-	1/247	1.2
	0.80%				0.40%	

The between-treatment comparisons with respect to the proportion of subjects achieving PASI 75 for visits other than week 12 using non-responder imputation and for week 12 using multiple imputations were considered ancillary efficacy analyses. Analyses of the proportion of subjects achieving PASI 75 at each visit were also performed using observed data, ie, without data imputation, as ancillary analyses.

All TEAEs were summarized by treatment group for each observed system organ class (SOC) and preferred term. A subject having more than one TEAE with the same preferred term in a given time period was counted only once in the incidence calculation for that preferred term for that time period. Similarly, if a subject had more than one TEAE in the same SOC in a given time period, the subject was counted only once in the total number of subjects with a TEAE for that SOC for that time period. Descriptive statistics were used for vital signs, ECG parameters, physical examination, and laboratory parameters.

RESULTS**Patients**

A total of 293 subjects with moderate to severe plaque psoriasis met the inclusion criteria and randomized into placebo (n=148) and CF101 2 mg (n=145) treated groups. Most of the patients completed the study (n=260, 88.7%), 125 patients (86.2%) in the CF101 2 mg group and 135 patients (91.2%) in the placebo control group. Reasons for withdrawal from the study included patient request (7), lack of efficacy (6), unacceptable concomitant medication or therapy (2), investigator decision in the patient's best interest (5), non-compliance (2), lost to follow up (6), or other (6) (Fig 1). 223 subjects completed the open label extension period (n=112 CF101 and n=111 placebo/CF1010). A summary of demographics and patients' baseline characteristics appears in Table 1.

Efficacy

For the primary endpoint, the difference between treatment groups was not statistically significant at week 12: 12 of 141 subjects in the CF101 2 mg group (8.5%), and 10 of 144 subjects in the placebo group (6.9%) achieved PASI 75 at week 12 ($P=0.621$).

For a secondary efficacy endpoint, the proportion of subjects who achieved PGA of 0 or 1, the difference between treatment groups was not statistically significant at week 12: 9 of 141 subjects in the CF101 2 mg group (6.4%), and 5 of 144 subjects in the placebo group (3.5%) at week 12 ($P=0.256$).

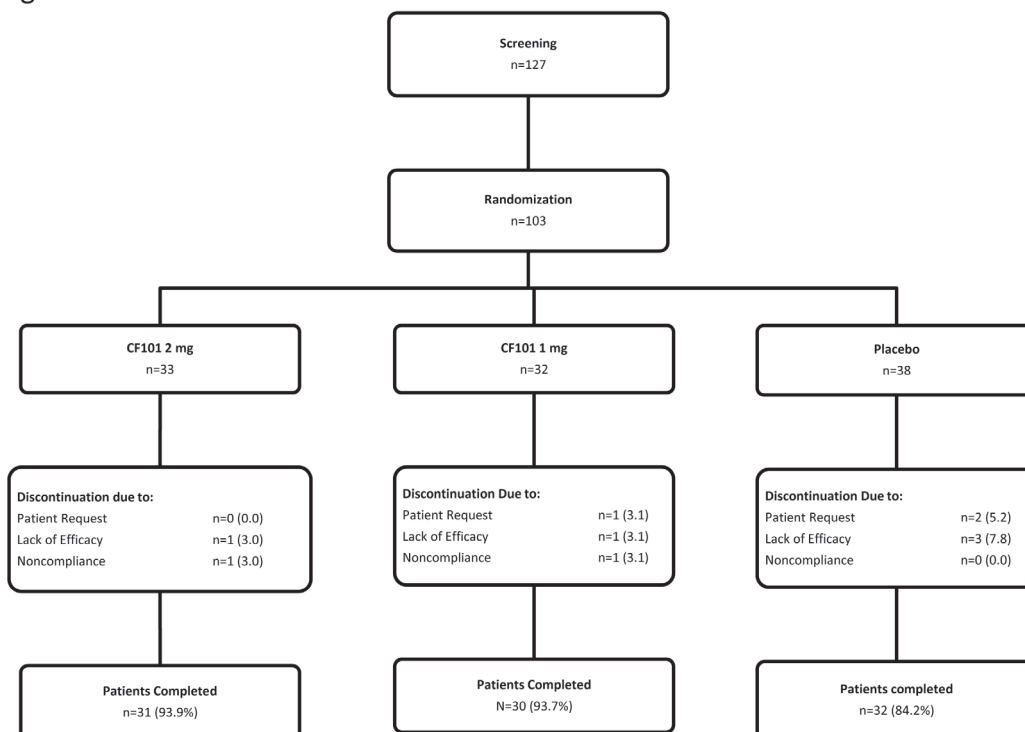
However, positive data were demonstrated at weeks 20 to 32 in the CF101 treatment group, showing linear improvement

TABLE 3.**TEAEs During BPCP With Incidence ≥3% by SOC Safety Population**

MedDRA System Organ Class	CF101 2 mg (N=145)	Placebo (N=148)
Any	37 (25.5)	29 (19.6)
Gastrointestinal disorders	8 (5.5)	3 (2.0)
Infections and infestations	10 (6.9)	13 (8.8)
Musculoskeletal and connective tissue disorders	5 (3.4)	2 (1.4)
Nervous system disorders	6 (4.1)	0 (0.0)
Renal and urinary disorders	5 (3.4)	4 (2.7)

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

Segment 1



Segment 2

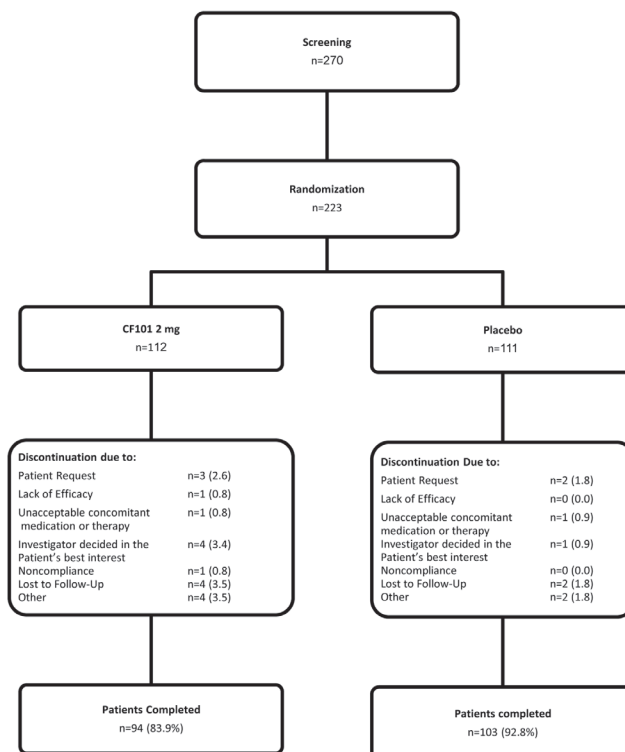
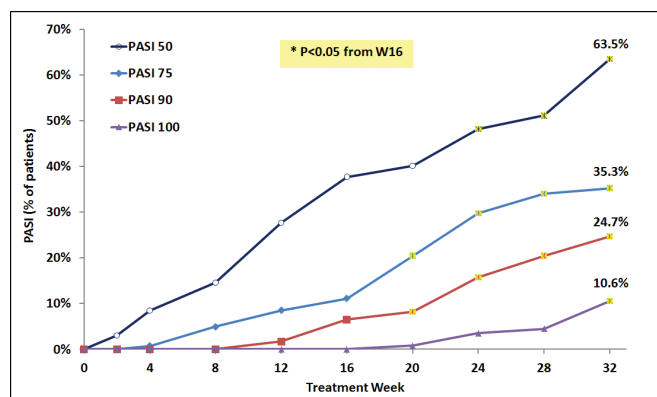


FIGURE 2A. PASI scores through 32 weeks of CF101 treatment.

in PASI 50 (63.5% of patients at week 32), PASI 75 (35.5%), PASI 90 (24.7%), and PASI 100 (10.6%). PASI mean percent improvement was 57% ($P<0.001$) at week 32 (Figure 2a). In addition, comparison made we compared the efficacy of CF101 to published results from a global Phase 3 apremilast trial (18) with those describe in the current study. CF101 efficacy rates continue to increase past 16 weeks of treatment, whereas those for apremilast appear to level off (Figure 3). Statistically significant improvement over time was also observed in proportion of subjects achieving PGA of 0 or 1 at weeks 24, 28, and 32 for

both groups ($P<0.01$ for each time point compared to the rate at 12 or 16 weeks, first cohort and second cohort, respectively (Figure 4). Although not a specific efficacy objective of the trial, cumulative improvement was also observed through week 32 in those subjects who crossed over from placebo to CF101 2 mg after week 16 (Figure 2b).

Safety

CF101 was found to be safe and well tolerated. There were no differences in vital signs, ECG, and clinical laboratory between the CF101 and the placebo.

During both the BPCP and OLE, compliance with dosing was high in both treatment groups (mean of approximately 100%). Duration of dosing was also similar for the groups in both periods (mean of approximately 100 days in both periods).

Thirty-seven of 145 subjects who received CF101 2 mg (25.5%) and 29 of 148 subjects who received placebo (19.6%) experienced at least one TEAE.

TEAEs tended to be distributed evenly between treatment groups. Infections and infestations (10 of 145 CF101 2 mg subjects, 6.9%, and 13 of 148 placebo subjects, 8.8%) were the most frequently reported TEAEs, followed by gastrointestinal

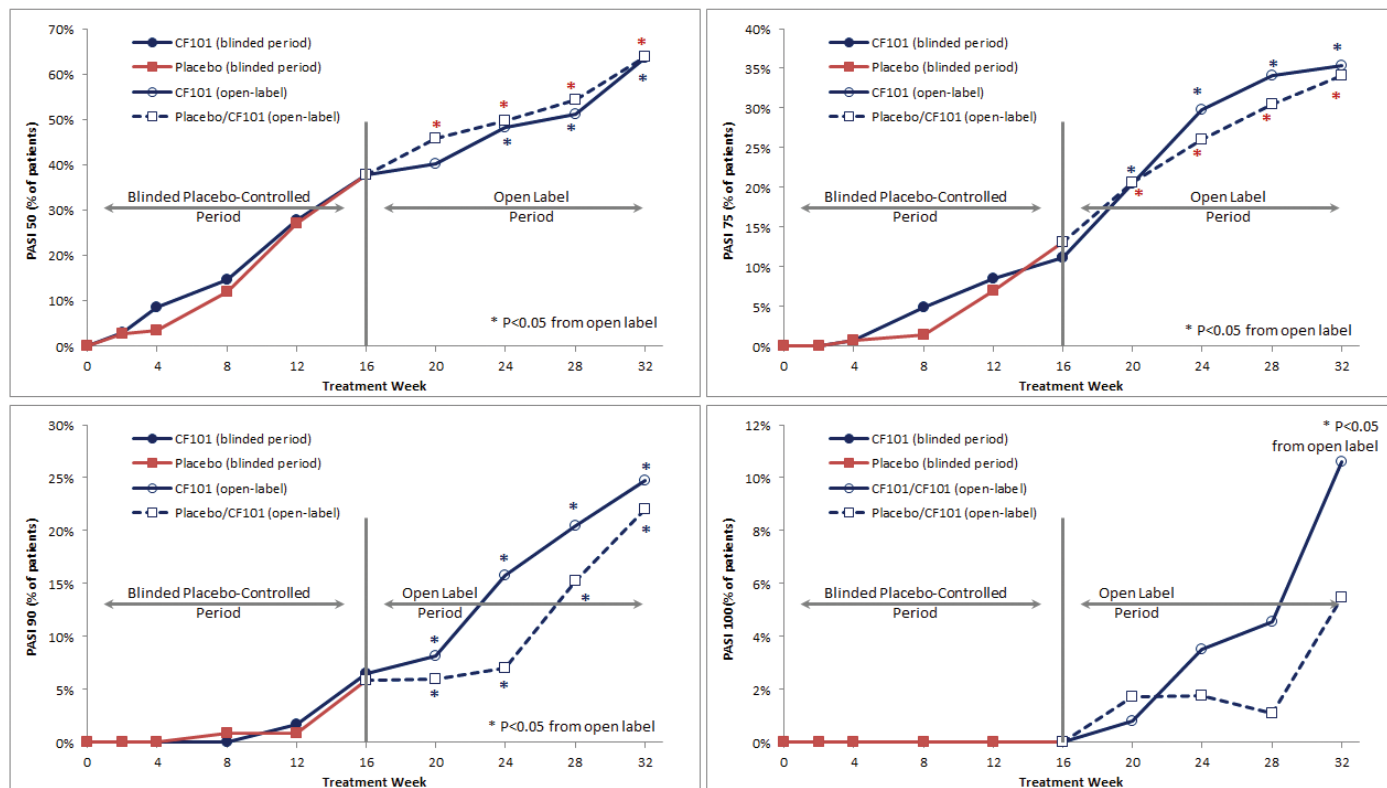
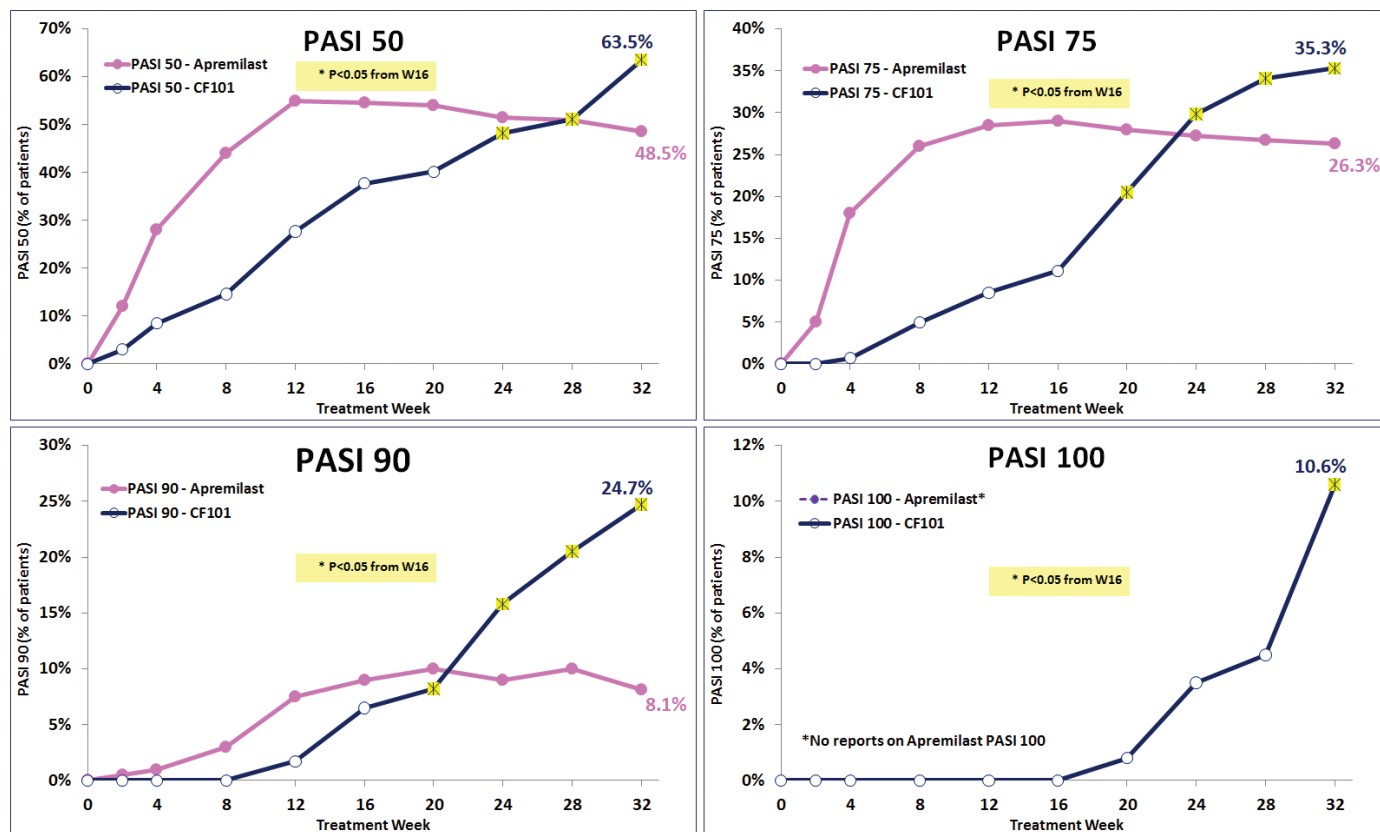
FIGURE 2B. PASI scores through 32 weeks of CF101 treatment.

FIGURE 3. CF101 Compares Favorably to Apremilast.

disorders (8 CF101 2 mg subjects, 5.5%, and 3 placebo subjects, 2%; Table 2 and Table 3). The gastrointestinal events reported in the CF101 group were abdominal pain, diarrhea, dry mouth, and nausea.

The majority of TEAEs were not considered to be related to study medication (18.6% of CF101 2 mg subjects and 14.2% of placebo subjects). There were no TEAEs considered to be definitely related to CF101 2 mg. The majority of TEAEs were mild (25 in CF101 2 mg subjects, 17.2%, and 20 in placebo subjects, 13.5%). Five subjects experienced severe TEAEs: 4 in the CF101 2 mg group and 1 in the placebo group, none of which were related to study drug.

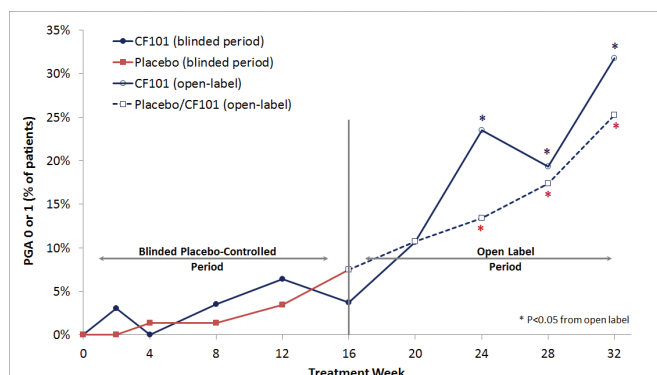
One death occurred during the study in the CF101 group after the visit at week 8. The primary cause of death was unknown and the death was considered by the investigator as not related to the blinded study drug.

During the OLE period of Segment 2, all subjects received CF101 2 mg. Infections and Infestations were the most frequently occurring TEAEs (23 of 275 subjects, 8.4%). The majority of TEAEs were not considered to be related to study drug (41 subjects, 14.9%, vs 5 subjects with possibly related TEAEs, 1.8%). The

majority of TEAEs were mild (31 subjects, 11.3%). Three subjects experienced a severe TEAE, none of which were related to study drug. No change in safety profile and no evidence of cumulative toxicity were seen through 32 weeks.

DISCUSSION

The present study did not achieve the primary efficacy endpoint at week 12. However, at week 32 PASI mean percent improvement was 57% ($P < 0.001$) with cumulative improvement from 16 to 32 weeks.

FIGURE 4. Proportion of subjects achieving PGA of 0 or 1.

PASI 50, 75, 90, and 100 rates were 63.5%, 35.5%, 24.7%, and 10.4%, respectively, in patients with 32 weeks of continuous treatment with CF101 2 mg BID. Historical placebo responses are very rare at PASI 90 and PASI 100, supporting the notion that the effect was CF101-mediated. Moreover, the proportion of subjects achieving PGA of 0 or 1 with CF101 2 mg was significantly increased over time between weeks 24 and 32 ($P < 0.01$ for each time point).

Positive response to CF101 was also described in a recently concluded Phase 2b study in rheumatoid arthritis patients treated with CF101 for 12 weeks.¹² It has been reported that A₃AR levels are highly expressed in inflammatory tissues and PBMCs of patients with RA and psoriasis compared to healthy subjects.^{8,13} Receptor overexpression is attributed to up-regulation of some transcription factors such as NF- κ B and CREB, known to be up-regulated in inflammatory conditions.⁸

CF101 was well-tolerated and there were no severe treatment-emergent adverse events during the study. The drug safety profile in the current study is consistent with the excellent safety profile reflected in previously reported Phase 2 CF101 studies comprising over 1000 patients across different systemic inflammatory diseases.¹¹⁻¹⁴

During the last 2 decades, biological drugs including mainly anti-TNFs, anti-IL17, and anti-IL-23 have been used for the treatment of psoriasis, yielding a marked improvement in disease state. The biological agents are very costly, require parenteral administration, and have been associated with both acute adverse reactions and longer-term sequelae, including serious infectious complications.¹⁵ On average, the median survival for the biologics in psoriasis was 47 months. Indeed, the real life observational data suggest that loss of biologics efficacy occurs in 10-20% of patients annually.¹⁶ 67% of all discontinuations were attributed to loss of efficacy.¹⁷

Thus, despite major recent advances in the treatment of psoriasis, there is still need for convenient, safe, and effective therapies for many patients.

Recently, the small molecule drug Otezla® (Apremilast), a PDE-4 inhibitor, has been approved for the treatment of moderate to severe psoriasis. Although Otezla outperforms CF101 at week 16 on both PASI 50 and PASI 75, its efficacy appears, at best, to plateau beyond that time point¹⁸, while our results indicate that CF101 efficacy continues to improve through 32 weeks.

It therefore seems that although CF101 has a slower efficacy onset, its linear anti-psoriatic effect along the 32 weeks of treatment and good safety profile make it a promising drug candidate.

DISCLOSURES

P. Fishman is an executive of Can-Fite BioPharma, Ltd. and has shares and stock options. Z. Harpaz, S. Fishman, M. Farbstein,

and S. Cohen are employed by Can-Fite and have stock options. M. Silverman is a consultant and has stock options in Can-Fite BioPharma, Ltd.

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