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Efficacy and safety of piclidenoson in plaque psoriasis: Results from a randomized phase 3 clinical trial (COMFORT-1)

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Abstract

Objective: A3 adenosine receptor (A3AR) is overexpressed in the skin and peripheral blood mononuclear cells of psoriasis patients. We investigated the efficacy/safety of piclidenoson (CF101), an orally bioavailable A3AR agonist that inhibits IL-17 and IL-23 production in keratinocytes, in moderate-to-severe plaque psoriasis.

Methods: The randomized, placebo- and active-controlled, double-blind phase 3 COMFORT-1 trial randomized patients (3:3:3:2) to piclidenoson 2 mg BID, piclidenoson 3 mg BID, apremilast 30 mg BID or placebo. At Week 16, patients in the placebo arm were re-randomized (1:1:1) to piclidenoson 2 mg BID, piclidenoson 3 mg BID or apremilast 30 mg BID. The primary end point was the proportion of patients achieving ≥75% improvement in Psoriasis Area and Severity Index (PASI) from baseline (PASI-75) at Week 16 versus placebo.

Results: A total of 529 patients were randomized and received ≥1 dose of study medication (safety population). The efficacy analysis population for the primary end point included 426 patients (piclidenoson 2 mg BID, 127; piclidenoson 3 mg BID, 103; apremilast, 118; placebo, 78). Piclidenoson at 2 and 3 mg BID exhibited similar efficacy. The primary end point was met with the 3 mg BID dose: PASI 75 rate of 9.7% versus 2.6% for piclidenoson versus placebo, $p = 0.037$. The PASI responses with piclidenoson continued to increase throughout the study period in a linear manner. At week 32, analysis in the per-protocol population showed that a greater proportion of patients in the piclidenoson 3 mg BID arm (51/88, 58.0%) achieved improvement from baseline in Psoriasis Disability Index (PDI) compared to apremilast (59/108, 55.1%), and the test for noninferiority trended towards significance ($p = 0.072$). The safety/tolerability profile of piclidenoson was excellent and superior to apremilast.

Conclusions: Piclidenoson demonstrated efficacy responses that increased over time alongside a favourable safety profile. These findings support its continued clinical development as a psoriasis treatment (ClinicalTrials.gov identifier: NCT03168256).

For Affiliation refer page on 8

INTRODUCTION

Psoriasis is an autoimmune inflammatory disease manifested by cutaneous plaques resulting from hyperproliferation of keratinocytes, potentially mediated by their resistance to apoptosis. Cytokines including TNF-α, IL-17 and IL-23 induce the continuous proliferation of keratinocytes, thus playing a key role in disease pathogenesis.[1] Although during the last two decades, biological therapies targeting these key cytokines have been approved as treatments for psoriasis, toxicity/side effects, loss of efficacy, disease recurrence and cost prompt the exploration of novel strategies for psoriasis treatment.[2]

The A3 adenosine receptor (A3AR) is a Gi protein-associated cell surface receptor that belongs to the larger family of adenosine receptors. The uniqueness of this receptor stems from its high expression in inflammatory but not normal cells. The highly selective, orally bioavailable, A3AR agonist piclidenoson (CF101) induces an anti-inflammatory effect by down-regulating the NF-κB signalling pathway, which leads to de-regulation of pro-inflammatory cytokines and chemokines, including IL-1, IL-8, TNF-α and MIP-1α. Piclidenoson also inhibits the proliferation of specific auto-reactive T cells and induces apoptosis of inflammatory cells.[3–11]

Skin biopsies from psoriasis patients are characterized by high A3AR expression levels, whereas low/no A3AR expression is found in normal skin biopsies.[4] Moreover, in the HaCat human keratinocyte cell line derived from a psoriasis patient, piclidenoson induced an anti-proliferative effect through deregulation of the NF-κB signalling pathway, leading to inhibition of IL-17 and IL-23 expression levels, suggesting a therapeutic role for piclidenoson in psoriasis.[4,12]

In phase 2 and 2/3 trials evaluating piclidenoson in moderate-to-severe plaque psoriasis, piclidenoson had a safety profile similar to placebo.[13,14] In the first study, 2 mg BID piclidenoson demonstrated clinical benefit versus placebo at several timepoints as measured by the Psoriasis Area and Severity Index (PASI) and the Physician's Global Assessment (PGA). In the second study, although the proportion of patients achieving ≥75% improvement in PASI from baseline (PASI 75) was greater in the 2 mg BID piclidenoson group compared with placebo, the difference was not statistically significant (18.2% vs. 5.4%, respectively, $p = 0.096$).[13] Nonetheless, significant differences between piclidenoson 2 mg BID and placebo were found during the extension period, and an ad hoc analysis of PASI 90 and PASI 100 over time found that the proportion of piclidenoson-treated patients achieving both measures increased over time, with a statistically significant increase in PASI 100 at Week 32 (vs. Week 16).[14] Thus, the results supported the continued clinical development of piclidenoson for psoriasis.

The current phase 3 trial (COMFORT-1) evaluated the efficacy and safety of 2 and 3 mg BID piclidenoson versus placebo and an active comparator (apremilast [Otezla®, Amgen Inc., Thousand Oaks, CA]). The study also evaluated the pharmacokinetics (PK) of piclidenoson.

MATERIALS AND METHODS

Study design

The COMFORT-1 study was a phase 3 multicentre (sites in Bosnia, Bulgaria, Canada, Israel, Moldova, Poland, Romania and Serbia) randomized, double-blind, controlled clinical trial in moderate-to-severe plaque psoriasis (ClinicalTrials.gov identifier: NCT03168256, Protocol available in the Appendices S1 and S2). The trial including screening, randomization and monitoring, was managed through a contract-research organization (Biorasi LLC). The trial had two segments (Figure 1). The first (Weeks 0–16) included four treatment arms: Two with piclidenoson (2 or 3 mg BID), one with matching apremilast (the active comparator, dose-titrated over 6 days to 30 mg BID, according to the label) and a matching placebo arm. Eligible patients were randomly assigned to these arms in a 3:3:3:2 ratio using block randomization, and a block size of 11. Blinding was maintained using a double-dummy technique. The second segment (Weeks 17–32) included 3 treatment arms, as at Week 16, the patients in the placebo arm were re-randomized to piclidenoson 2 mg BID, piclidenoson 3 mg BID, or apremilast (dose-titrated over 6 days to 30 mg BID) in a 1:1:1 ratio and treated through Week 32. Those originally assigned to piclidenoson or apremilast remained on their initially assigned blinded treatment through Week 32. All investigators, study personnel, medical/clinical monitors and patients remained blinded to treatment assignment throughout the study. Patients were evaluated every 2 weeks for efficacy and safety. The primary efficacy end point was assessed at Week 16, and the secondary end points were assessed at Weeks 16 and 32. PK sampling was performed at Weeks 0, 8 and 16.

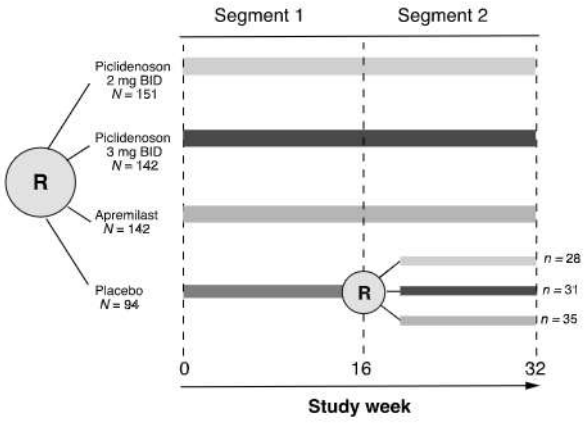

FIGURE 1 Study design.

In 2020, the protocol was modified due to challenges arising from the COVID-19 pandemic that impacted the conduct/monitoring of the trial. Most notably, after 189 of 307 enrolled patients completed Week 16, enrolment was paused for an interim analysis of all data through Week 16. An Independent Data Monitoring Committee reviewed the interim analysis results and recommended continued enrolment.

This study was approved by all relevant national regulatory authorities and local Ethics Committees/Institutional Review Boards. This study was conducted in accordance with the Declaration of Helsinki and written informed consent was obtained from all patients.

Study patients

The study population included male and female patients aged 18–80 years with a moderate-to-severe chronic plaque psoriasis and a body surface area involvement ≥10% who were candidates for systemic treatment or phototherapy. Main inclusion criteria were a PASI score ≥12, a static PGA ≥3 and having psoriasis for ≥6 months. Key exclusion criteria included prior treatment with apremilast within 4 weeks of the baseline (BL) visit, or contraindication to apremilast, certain prior/concomitant treatment such as systemic retinoids, corticosteroids, tofacitinib or immunosuppressive agents within 4 weeks of the BL visit; an approved/investigational biological agent within 30 days or 5 half-lives, whichever was longer; high potency dermatological corticosteroids (Class I–III in the United States, Class III–IV in Europe), vitamin D analogues, keratolytics or coal tar (other than on the scalp, palms, groin and/or soles) within 2 weeks of the BL visit; ultraviolet/Dead Sea therapy within 4 weeks of the BL visit, or anticipated need for these therapies during the study period. Renal or hepatic dysfunction, uncontrolled concomitant illness and pregnancy or lactation.

Assessment

The primary end points included PASI 75 rates for the piclidenoson 2 and 3 mg BID arms versus placebo at Week 16 (superiority) and safety. Secondary end points at Week 16 compared the piclidenoson arms to placebo and included PASI 50 rates and the proportion of patients achieving a score of PGA2 score of 0–1. PGA2 was the average of the PASI erythema, infiltration and desquamation scores.[15] Another secondary end point was the proportion of patients experiencing an improvement from BL in Psoriasis Disability Index (PDI). Other secondary end points, the proportion of patients achieving PASI 75, PASI 50, PGA2 of 0–1 and the proportion of patients experiencing an improvement from BL in PDI, were evaluated at Week 32 comparing the piclidenoson arms to apremilast. PK analysis (C_{max}, exposure) was conducted for Weeks 0, 8 and 16.

Safety assessments included treatment-emergent adverse events (TEAEs) and changes in vital signs, physical examination, clinical laboratory tests (liver, kidney, haematology, chemistry and urinalysis) and electrocardiography findings.

Statistical analysis

Power calculation determined that a sample size of 111 patients for each piclidenoson dose and 74 patients for placebo provided a power ≥80% to reject at least one null hypothesis of equality of the probability of response for piclidenoson versus placebo. Assuming the probability of achieving PASI 75 at Week 32 was 35% for the less effective piclidenoson dose and 28% for apremilast, a sample size of 111 patients per active treatment group provided power of ≥69% for exhibiting the noninferiority of at least one dose of piclidenoson to apremilast with a noninferiority margin of 10% at Week 32.

Four analysis populations were defined: The safety population included all patients who received ≥1 dose of study medication; the intention-to-treat (ITT) population included all those in the safety population with at least one PASI score recorded post-BL and excluded patients who withdrew prior to Week 16 due to COVID-19-related study suspension; the modified ITT (mITT) population, which was used for the Week 16 efficacy analyses, included all ITT patients except one in the placebo arm who was excluded due to major protocol violations found after discussion with the site that were not captured in the original data (Supplemental Statistical Analysis Plan v3.0, 18 Nov 2022, available in the Appendix S2); and the per protocol (PP) population, which was used for the Week 32 analyses, and included all ITT patients with no major protocol violations on or before Week 16 who completed Week 16 of the study (Figure 2). Exclusion from the PP population was finalized prior to any unblinded analyses. The analyses conducted for Week 32 were performed separately for patients who were initially randomized to piclidenoson or apremilast and for those initially randomized to placebo.

Descriptive statistics were used to summarize patient characteristics and safety. TEAEs were reported by treatment group for each System Organ Class (SOC) and Preferred Term (PT), as defined in the Medical Dictionary for Regulatory Activities (MedDRA), version 23.0. If a patient had more than one TEAE with the same PT, the patient was counted once.

For the primary and secondary efficacy analyses, missing values due to discontinuation were considered a non-response post-discontinuation and were referred to as Non-Responder Imputation (NRI); intermediate missing values were imputed using Last Observation Carried Forward (LOCF). *p* values for the primary efficacy analysis and the secondary analyses comparing piclidenoson to placebo were determined with the normal approximation for comparing two binomial proportions (NAB). Secondary

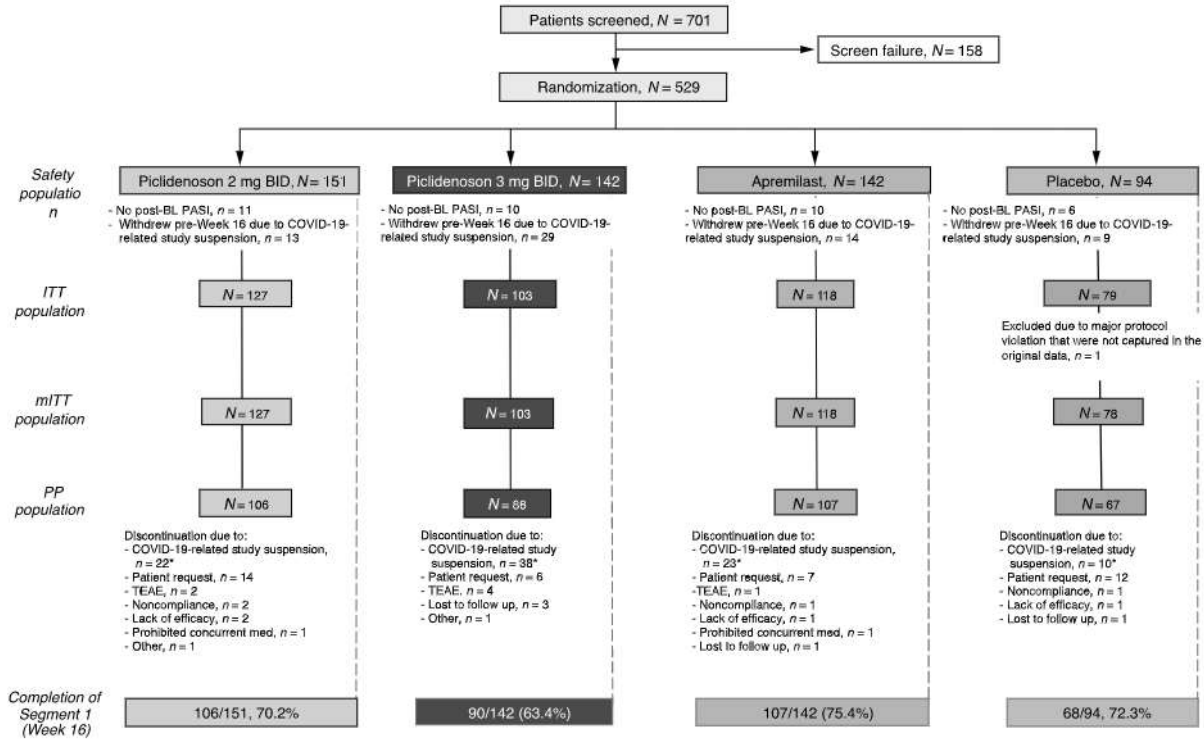

FIGURE 2 Patient disposition through Week 16 showing all patient populations used in the analyses of the study.

analyses comparing piclidenoson to apremilast were non-inferiority analyses with a noninferiority margin of 10% using NAB. Data are presented as proportions/means ± SE. All statistical tests were two-sided and $p < 0.05$ was considered statistically significant. Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC).

RESULTS

Patients

Between August 2018 and September 2021, 701 patients with moderate-to-severe plaque psoriasis were screened and enrolled. Patients who met the eligibility criteria ($N = 529$) were randomized to piclidenoson 2 mg BID ($N = 151$), piclidenoson 3 mg BID ($N = 142$), apremilast ($N = 142$) or placebo ($N = 94$) (Figure 2).

Nearly a third of all patients ($n = 158$, 29.9%) across all treatment arms discontinued treatment in the first segment of the study (Weeks 0–16), largely due to the COVID-19-related study suspension in 2020 ($n = 93$ across all arms, 17.6%). Additional reasons for discontinuation included patients' requests ($n = 39$, 7.4%) and TEAEs ($n = 7$, 1.3%) (Figure 2).

The baseline patient/disease characteristics of the study safety population by treatment are presented in Table 1, demonstrating balanced distribution across the study arms. The median age for the entire study population was 49 (range: 19–81) years, 62% were male and all but one were White. The median duration of disease for all patients was 12 (range: 0–67) years and was similar between the treatment arms.

Efficacy versus placebo (Week 16)

The primary end point was met. Piclidenoson 3 mg BID demonstrated superior efficacy versus placebo at Week 16 in the mITT population with a statistically significantly higher PASI 75 rate (9.7% ± 1.8% vs. 2.6% ± 1.8%, $p = 0.037$; Figure 3). For the 2 mg BID arm, the PASI 75 rate was higher than placebo (7.9% ± 2.4%); however, the difference was not statistically significant ($p = 0.075$). For both doses, PASI 75 rates improved linearly over time (Figure 3).

For the secondary end point of the proportion of patients achieving PGA2 of 0–1 at Week 16 in the mITT population (Figure 4), greater proportions of patients treated with 3 mg BID (10.7% ± 3.0%) or 2 mg BID (11.8% ± 2.8%) achieved versus placebo (3.8% ± 2.2%). The observed difference between piclidenoson 3 mg BID and placebo trended towards statistical significance ($p = 0.068$) and was significant for the 2 mg BID dose ($p = 0.027$).

Other secondary end points evaluated at Week 16 on the mITT population, including the PASI 50 rate and the proportion of patients with improvement from BL in PDI did not demonstrate statistically significant superiority of either piclidenoson dose over placebo. The PASI 50 rates were 19.4%, 26.0% and 15.4% for piclidenoson 3 mg BID,

TABLE 1 Baseline patient and disease characteristics.

	Piclidenoson 2 mg BID	Piclidenoson 3 mg BID	Apremilast	Placebo
	N = 151	N = 142	N = 142	N = 94
Male, n (%)	85 (56.3%)	94 (66.2%)	95 (66.9%)	55 (58.5%)
Age, median (range), years	50 (20–78)	49 (19–74)	47.5 (19–81)	47 (19–77)
Weight, median (range), kg	82 (45–135)	82 (46–141)	83 (53–136)	82 (41–135)
BMI, median (range), kg/m^2	28.3 (19.0–51.9)	27.9 (16.5–41.9)	27.6 (18.4–42.1)	27.5 (16.2–43.1)
Race, n (%)				
White/Caucasian	150 (99.3%)	142 (100.0%)	142 (100.0%)	94 (100.0%)
Other	1 (0.7%)	0 (0.0)	0 (0.0)	0 (0.0)
Ethnicity, n (%)				
Hispanic/Latino	1 (0.7%)	1 (0.7%)	2 (1.4%)	0 (0.0)
Not Hispanic/Latino	150 (99.3%)	141 (99.3%)	140 (98.6%)	94 (100.0%)
Duration of disease, median (range), years	12 (0–61)	10 (1–47)	13 (0–67)	11.5 (1–45)

Abbreviations: BID, twice a day; BMI, body mass index; SD, standard deviation.

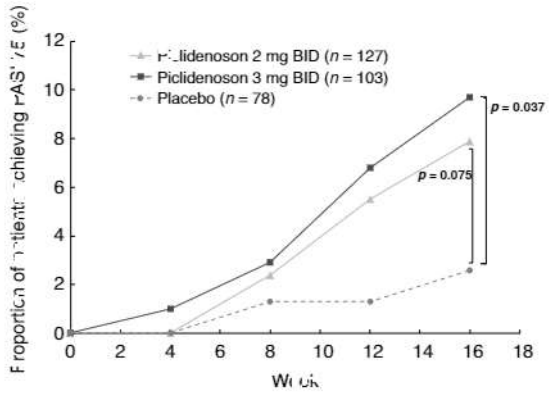

FIGURE 3 Proportion of patients achieving PASI 75 by treatment arm over time (mITT population).

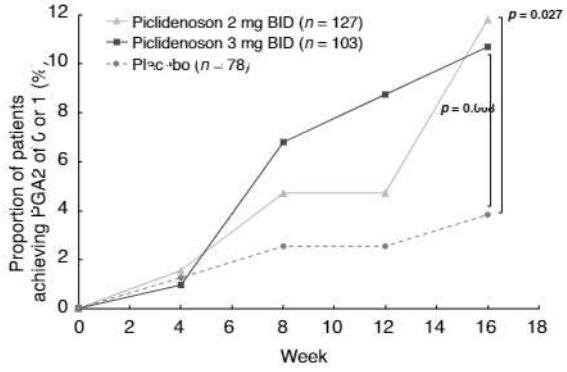

FIGURE 4 Proportion of patients achieving PGA2 of 0 or 1 by treatment arm over time (mITT population).

2 mg BID and placebo respectively ($p = 0.48$ and $p = 0.060$ for the respective comparisons vs. placebo). The proportions of patients achieving PDI improvement from BL were 58.3%, 63.3% and 60.3% for the 3 mg BID, 2 mg BID and placebo respectively ($p > 0.99$ and $p = 0.70$ for the respective comparisons vs. placebo).

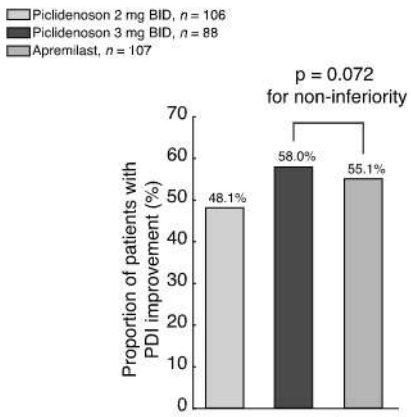

FIGURE 5 The proportions of patients with improvements from BL in PDI at Week 32 by study arm (PP population).

Efficacy versus apremilast (Week 32)

Noninferiority of piclidenoson versus apremilast was evaluated at Week 32 on the PP population and included the patients who were initially randomized to active treatment. For the PASI 75 rates, noninferiority was not established for 3 mg or 2 mg BID versus apremilast (17.0%, 20.8% and 26.2% respectively; $p = 0.88$ and $p = 0.43$ for the respective comparisons vs. apremilast). The PASI 50 rates were lower with both piclidenoson doses compared to apremilast, and noninferiority was not established (19.3%, 17.0% and 25.2% for piclidenoson 3 mg BID, 2 mg BID and apremilast respectively; $p = 0.49$ and $p = 0.75$ for the respective comparisons vs. apremilast). Similarly, the proportions of patients with PGA2 of 0–1 were also lower (both doses) compared to apremilast, and noninferiority was not established (15.9%, 18.9% and 24.3% for piclidenoson 3 mg BID, 2 mg BID and apremilast respectively; $p = 0.78$ and $p = 0.42$ for the comparisons vs. apremilast respectively).

A greater proportion of patients in the piclidenoson 3 mg BID arm achieved improvement from BL in PDI compared to apremilast (58.0% vs. 55.1%). The test for noninferiority trended towards significance ($p = 0.072$, Figure 5). The corresponding proportion in the 2 mg BID was 48.1%, and noninferiority versus apremilast was not established ($p = 0.66$).

Safety

Both piclidenoson doses were well tolerated throughout the 32-week study period, with no dose-related differences in TEAE incidence (Table 2). The safety profile of the two doses was generally comparable to that of placebo, which was used only from Week 0 through Week 16. Furthermore, piclidenoson safety profile was more favourable than that of apremilast, which was associated with a higher frequency of nervous system disorders (9.6% for apremilast vs. 1.7% for each piclidenoson dose) and gastrointestinal disorders (7.3% for apremilast vs. 2.8% for piclidenoson 2 mg BID and 1.2% for piclidenoson 3 mg BID). The only TEAEs occurring in >2% of patients in the piclidenoson arms were nasopharyngitis (2.2% and 2.9% in the 2 and 3 mg BID arms respectively) and urinary tract infection (3.4% in the 2 mg BID

TABLE 2 Incidence of TEAE during Weeks 0–32 in the safety population[a].

MedDRA system organ class and preferred term	Piclidenoson 2 mg BID $N = 179$[b]	Piclidenoson 3 mg BID $N = 173$[c]	Apremilast $N = 177$[d]	Placebo $N = 94$[e]
Any, *n* (%)	50 (27.9%)	41 (23.7%)	55 (31.1%)	32 (34.0%)
Cardiac disorders				
Any	3 (1.7%)	2 (1.2%)	2 (1.1%)	2 (2.1%)
Gastrointestinal disorders, *n* (%)				
Any	5 (2.8%)	2 (1.2%)	13 (7.3%)	1 (1.1%)
Diarrhoea	1 (0.6%)	1 (0.6%)	5 (2.8%)	0 (0.0)
Nausea	1 (0.6%)	0 (0.0)	4 (2.3%)	1 (1.1%)
General disorders and administration site conditions, *n* (%)				
Any	4 (2.2%)	5 (2.9%)	4 (2.3%)	4 (4.3%)
Infections and infestations, *n* (%)				
Any	20 (11.2%)	14 (8.1%)	19 (10.7%)	15 (16.0%)
Nasopharyngitis	4 (2.2%)	5 (2.9%)	2 (1.1%)	7 (7.4%)
Urinary tract infection	6 (3.4%)	0 (0.0)	3 (1.7%)	1 (1.1%)
Investigations, *n* (%)				
Any	5 (2.8%)	10 (5.8%)	13 (7.3%)	7 (7.4%)
Weight decreased	1 (0.6%)	2 (1.2%)	5 (2.8%)	2 (2.1%)
Metabolism and nutrition disorders, *n* (%)				
Any	4 (2.2%)	1 (0.6%)	5 (2.8%)	1 (1.1%)
Musculoskeletal and connective tissue disorders, *n* (%)				
Any	2 (1.1%)	4 (2.3%)	2 (1.1%)	2 (2.1%)
Nervous system disorders, *n* (%)				
Any	3 (1.7%)	3 (1.7%)	17 (9.6%)	4 (4.3%)
Headache	2 (1.1%)	1 (0.6%)	15 (8.5%)	3 (3.2%)
Psychiatric disorders, *n* (%)				
Any	3 (1.7%)	0 (0.0%)	2 (1.1%)	2 (2.1%)
Renal and urinary disorders, *n* (%)				
Any	1 (0.6%)	2 (1.2%)	1 (0.6%)	2 (2.1%)
Skin and subcutaneous tissue disorders, *n* (%)				
Any	5 (2.8%)	7 (4.0%)	6 (3.4%)	7 (7.4%)
Pruritus	1 (0.6%)	2 (1.2%)	4 (2.3%)	2 (2.1%)

Abbreviations: BID, twice a day; PT, preferred term; SOC, System Organ Class; TEAE, treatment-emergent adverse event.

[a]Includes instances where the incidence in the MedRA SOC was >2%.

[b]Includes 151 patients who received piclidenoson 2 mg BID in Segment 1 of the study plus 28 patients who received placebo in Segment 1 and were re-randomized to piclidenoson 2 mg BID at Week 16.

[c]Includes 142 patients who received piclidenoson 3 mg BID in Segment 1 of the study plus 31 patients who received placebo in Segment 1 and were re-randomized to piclidenoson 3 mg BID at Week 16.

[d]Includes 142 patients who received apremilast 3 in Segment 1 of the study plus 35 patients who received placebo in Segment 1 and were re-randomized to apremilast at Week 16.

[e]Patients received placebo for 16 weeks only before re-randomization to an active treatment.

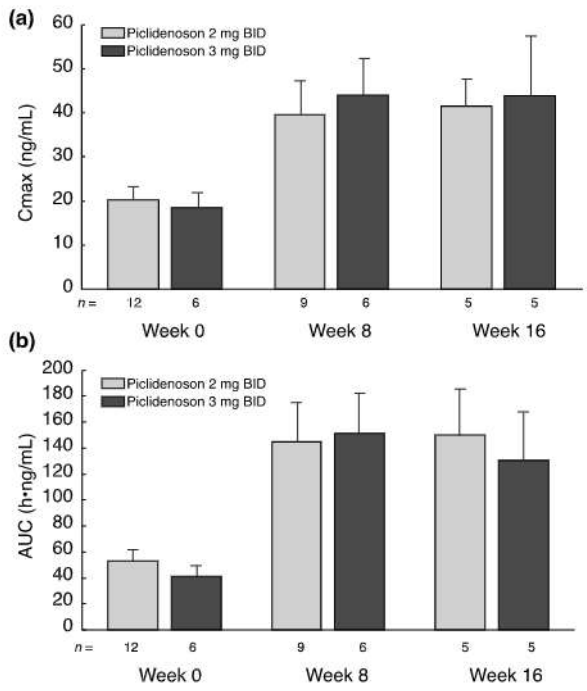

FIGURE 6 C_{max} (a) and AUC (b) for piclidenoson 2 and 3 mg BID over time. Error bars represent SE.

arm) (Table 2). No cumulative risk with piclidenoson was observed upon treatment beyond Week 16, when all patients received active treatment.

Overall, there were three serious TEAE in patients receiving active treatment including one in the piclidenoson 2 mg BID arm (arterial embolism), one in the piclidenoson 3 mg BID arm (osteomyelitis) and one in the apremilast arm (pneumonia); none were considered drug-related by the investigator. Nine patients withdrew from the study due to 10 TEAEs (seven in Weeks 0–16 and two in Weeks 17–32), including one each in the placebo and apremilast arms, two in the piclidenoson 2 mg BID arm and five in the piclidenoson 3 mg BID arm. None of the events were considered drug-related. Electrocardiography showed no clinically significant drug effects on QTcF or other parameters across all arms. No other safety events of note occurred, and no deaths were reported throughout the study period.

Pharmacokinetics

Pharmacokinetics data demonstrated that the exposure to piclidenoson as measured by C_{max} and AUC was similar in the 2 mg and 3 mg BID arms (Figure 6).

DISCUSSION

This phase 3 trial investigating piclidenoson as a treatment for moderate-to-severe plaque psoriasis met the primary end point for the 3 mg BID dose (superiority over placebo in PASI 75 at Week 16), with response to piclidenoson demonstrating linear improvement over time. Noninferiority versus apremilast, which was a secondary end point, was shown for PASI 75 with 2 mg BID at Week 32, and a trend towards significance was shown for piclidenoson 3 mg BID for the proportion of patients achieving PDI improvement from BL. Piclidenoson was safe/well tolerated with a safety profile that was comparable to placebo, and better than apremilast. The two piclidenoson dosages were overall similar with respect to safety, PK and efficacy; however, the primary efficacy end point was achieved only by the 3 mg BID dose.

The efficacy results observed in this trial are aligned with the previous phase 2 and 2/3 studies which demonstrated clinical benefit for piclidenoson in moderate-to-severe plaque psoriasis.[13,14] The excellent safety profile observed with piclidenoson is consistent with the phase 2 and 2/3 studies where 201 patients received piclidenoson,[13,14] as well as with studies evaluating piclidenoson for other diseases (e.g. rheumatoid arthritis, dry eye disease) where a total of >1500 subjects received piclidenoson.[16]

In clinical practice, systemic nonbiological therapies (methotrexate, cyclosporin), targeted therapies (apremilast, an oral PDE4 inhibitor) and biological therapies (TNF-α, IL 12/23, IL-17 or IL-23 inhibitors) are commonly used for moderate-to-severe psoriasis. The emergence of biologics and oral-targeted therapies such as apremilast constitutes a marked advance in the care of patients with moderate-to-severe psoriasis.[17,18] Biologics therapies are costly, administered parenterally, require regular monitoring and are associated with short- and long-term adverse events, including increased risk for serious infections.[2,17,18] Drug survival studies that reflect real-life performance (e.g. effectiveness, safety and patients' preference) of biologics vary in their findings, with some studies showing 1-year discontinuation rates of up to approximately 20%.[19–23] The most common reason cited for discontinuing treatment with a biological agent was lack/loss of efficacy.[24,25] Survival studies on apremilast were generally smaller, and suggested lower survival rates relative to biologics, with 1-year discontinuation rates reaching and even exceeding half of all patients in some studies, mainly due to lack/loss of efficacy.[26–29] Hence, the need for a convenient, cost-effective, safe and efficacious treatment for moderate-to-severe psoriasis still exists. Given that psoriasis is a chronic disease that often requires lifelong therapy, the safety profile of piclidenoson, along with its documented efficacy, characterized by a linear cumulative effect, may address an important unmet need in this population.

The main limitation of this trial was a COVID-19-related study suspension which caused an unusually high withdrawal rate.

In conclusion, the findings of this phase 3 placebo- and apremilast-controlled trial, although limited by the high withdrawal rate stemming from a COVID-19-related study suspension, support the continued clinical development of piclidenoson as a psoriasis treatment.

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CONFLICT OF INTEREST STATEMENT

K.A Papp and A. Bareket-Samish are consultant for Can-Fite BioPharma; Z. Harpaz, M. Farbstein, M.H. Silverman and P. Fishman are employed by Can-Fite BioPharma. Z. Harpaz, M. Farbstein and P. Fishman hold Can-Fite stock. All other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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