EA DV CONGRESS
BERLIN 11-14 OCTOBER 2023
EUROPEAN ACADEMY OF DERMATOLOGY AND VENEREOLOGY

Abstract N°: 2332

Efficacy and safety of a small molecule with innovative inhibition of TNFR1 signalling in plaque psoriasis: A double-blind, randomized, placebo-controlled study

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Introduction & Objectives: Tumor necrosis factor (TNF) is an inflammatory cytokine involved in the pathogenesis of psoriasis. SAR441566 is an orally administrated small molecule that selectively inhibits TNF signaling through the TNF receptor 1 (TNFR1). In contrast to injectable TNF inhibitors, SAR441566 preserves signalling through TNF receptor 2 (TNFR2), a pathway that plays a role in immune homeostasis, regulatory T- cell expansion and function, tissue regeneration, and host defence against pathogens. This proof of mechanism study in adults with mild-to-moderate plaque psoriasis evaluated the safety, tolerability, and clinical response of SAR441566 compared to placebo through 4-weeks of treatment.

Materials & Methods: This phase 1, double-blind, placebo-controlled study evaluated male participants with chronic mild-to-moderate plaque psoriasis with at least two lesions of a Target Lesion Severity Score (TLSS) >4 at baseline. Patients were randomized 2:1 to SAR441566 200 mg twice a day (BID) or placebo for 4 weeks. Clinical efficacy was evaluated using the percent change from baseline to Week 4 in Psoriasis Area and Severity Index (PASI) and TLSS.

Results: A total of 38 male participants with comparable demographic characteristics were randomized; 26 participants received oral SAR441566 and 12 received placebo (**Table 1**). Patients who received SAR441566 had a statistically significant improvement from baseline in PASI compared to those who received placebo at Week 2 (17.73% versus 4.12%, p= 0.005) and Week 4 (35.09% versus 15.71%, p=0.009) (adjusted mean % improvement from baseline, p-value for one-sided test at 5% significance level) (**Figure 1**). Consistent with these findings, patients who had received SAR441566 also had a significant improvement in TLSS compared to placebo at Week 2 (17.06% versus 6.29%, p= 0.032) and Week 4 (38.18% versus 20.44%, p= 0.012) (**Figure 1**). Furthermore, separate analyses of patients with mild (PASI<10) or moderate psoriasis (PASI≥10 and <16) at baseline demonstrated improvement for SAR441566 versus placebo at Week 2 (mild: 20.9% vs 8.5%; moderate: 10.9% vs 0%) and Week 4 (mild: 37.0% vs 22.3%; moderate: 39.7% vs 15.0%), despite disease severity. Treatment with 200 mg BID of SAR441566 over 28 days was safe and well-tolerated, with no serious adverse events (AEs), severe treatment emergent AEs or AE of special interest (AESI) being reported.

Conclusion: SAR441566, a specific inhibitor of TNFR1 signalling, demonstrated clinical efficacy in mild-to-moderate psoriasis over a 4-week treatment period. This novel oral therapy was safe and well-tolerated. The results support the mechanism of action of SAR441566, a small molecule inhibitor of TNFR1 signalling and warrants further clinical evaluation in psoriasis. **Keywords:** psoriasis, TNF inhibitor, TNF, Clinical trial

Table 1: Demographics and Baseline Characteristics

Baseline Characteristics	Placebo (n=12)	SAR441566 (n=26)
Age, mean (±SD), years	40.5 (12.5)	44.2 (9.7)
BMI, mean (±SD), kg/m^2	25.98 (2.92)	26.45 (2.97)
TLSS, mean (±SD)	7.42 (1.40)	6.83 (1.60)
PASI, mean (±SD)	7.86 (2.53)	8.91 (3.73)
PASI score, n (%)		
< 10 (mild psoriasis)	8 (66.7)	17 (65.4)
≥ 10 and <16 (moderate psoriasis)	4 (33.3)	9 (34.6)

Figure 1: PASI and TLSS improvement from baseline to week 2 and 4.

Adjusted mean % improvement from baseline using a Mixed Model with Repeated Measurement with SE and p-value. p-value for one sided test comparing the adjusted means of the two groups, SE=standard error, PASI=Psoriasis Area and Severity Index, TLSS=Target Lesion Severity score