Efficacy and Safety of a Small Molecule with Innovative Inhibition of TNFR1 Signal in Plaque Psoriasis: A Double-Blinded, Randomized, Placebo Controlled Study

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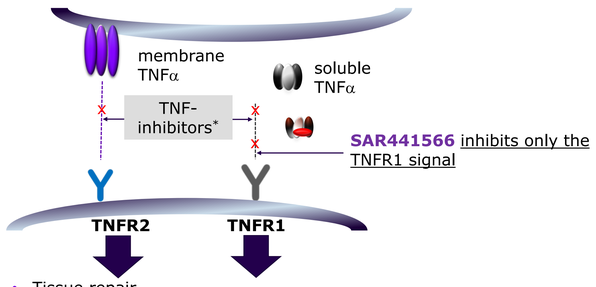
Introduction

- Tumor necrosis factor (TNF) alpha, an inflammatory cytokine, is a key driver in the pathogenesis of psoriasis, and regulates signalling via engagement with TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2)[1,2]

SAR441566: Mechanism of Action

- SAR441566 is an oral small molecule that selectively inhibits TNFR1 signal by preventing the soluble TNF (sTNF) from activating TNFR1[3–5], but allows membrane TNF to bind to TNFR2



Potential benefits of targeting TNFR1 with small molecules[2,6–8]

Oral route of administration
- No injection site reactions

Small molecule
- No anti-drug antibodies; leading to long-term efficacy maintenance

*SAR441566 binds to sTNFα and prevents sTNFα from binding to TNFR1, resulting in inhibition of TNFR1 signal.

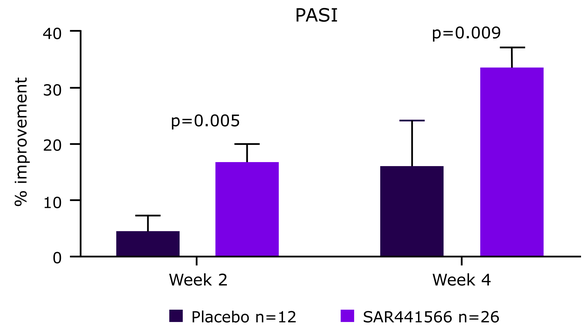
Results

Baseline Demographics and Clinical Characteristics	Placebo (N=12)	SAR441566 200 mg BID (N=26)	All (N=38)
Age (years)	40.5 (12.5)	44.2 (9.7)	43.0 (10.6)
Gender (male), n (%)	12 (100)	26 (100)	38 (100)
Race, n (%)§			
White	11 (91.7)	25 (96.2)	36 (94.7)
Asian	1 (8.3)	1 (3.8)	2 (5.3)
Asian Indian	1 (8.3)	1 (3.8)	2 (5.3)
Smoking status, n (%)			
Smokers	5 (41.7)	11 (42.3)	16 (42.1)
Non-Smokers	7 (58.3)	15 (57.7)	22 (57.9)
Baseline Weight (kg)	81.49 (12.03)	86.97 (11.15)	85.24 (11.56)
Baseline BMI (kg/m²)	25.98 (2.92)	26.45 (2.97)	26.30 (2.92)
Baseline BMI by category (kg/m²), n (%)			
18.5 to <25	5 (41.7)	7 (26.9)	12 (31.6)
25 to <30	6 (50.0)	15 (57.7)	21 (55.3)
≥30	1 (8.3)	4 (15.4)	5 (13.2)
Baseline TLSS	7.42 (1.40)	6.83 (1.60)	7.01 (1.54)
Baseline PASI	7.86 (2.53)	8.91 (3.73)	8.58 (3.40)
Baseline PASI by category, n (%)			
<10	8 (66.7)	17 (65.4)	25 (65.8)
≥10	4 (33.3)	9 (34.6)	13 (34.3)
Baseline hs-CRP (mg/L)	1.28 (0.86)	1.76 (2.25)	1.61 (1.92)

§Race was reported by the patients on a questionnaire at screening or baseline; Values presented in mean with standard deviation. BMI, body mass index; hs-CRP, high-sensitivity C-reactive protein; SD, standard deviation; sIGA, static Investigator Global Assessment of Psoriasis.

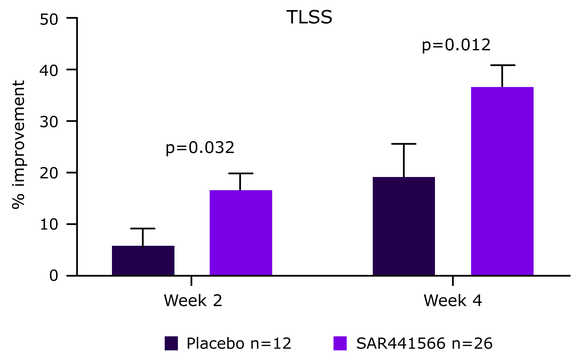
- Sub-group analyses of patients with mild (PASI<10) or moderate psoriasis (PASI≥10 and ≤16) at baseline demonstrated % mean improvement from baseline in the TLSS score for SAR441566 versus placebo at Week 2 (mild: 20.9% vs 8.5%; moderate: 10.9% vs 0%) and Week 4 (mild: 37.0% vs 22.3%; moderate: 39.7% vs 15.0%), despite disease severity

- SAR441566 vs placebo statistically significantly improved PASI from baseline to Week 2 and 4



Values presented in %adjusted mean with standard error (SE), p-value for one-sided test. PASI, Psoriasis Area Severity Index.

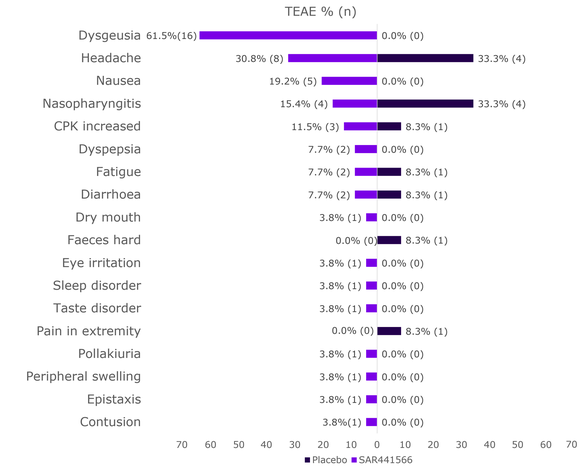
- SAR441566 vs placebo statistically significantly improved TLSS from baseline to Week 2 and 4



Values presented in %adjusted mean with standard error (SE), p-value for one-sided test. TLSS, Target Lesion Severity.

Safety

- 24 (92.3%) participants in the SAR441566 group and 7 (58.3%) in the placebo group experienced at least one TEAE. 51% of AEs related to tolerability may be improved in future studies with coating of the tablets
- Treatment with SAR441566 over Week 4 was safe and well-tolerated, with no serious AEs, severe TEAEs or AESI



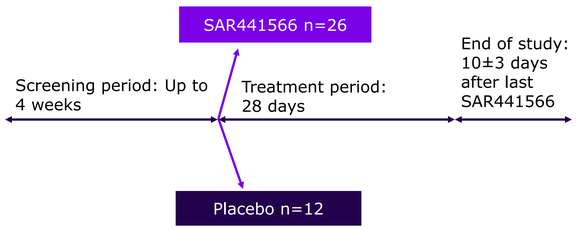
Conclusion

- SAR441566, the first oral targeting TNF-receptor mediated signalling, to enter phase 1 clinical trials, demonstrated clinical efficacy in mild-to-moderate psoriasis over a 4-week treatment period and was safe and well-tolerated
- Results of this study supports the mechanism of action of SAR441566, a small molecule inhibitor of TNFR1 signal

Methods

Study Design

- Phase 1b, double-blind, placebo-controlled, single center, parallel, 4-week study for the treatment of 38 adult patients with mild-to-moderate psoriasis that were randomized (2:1) to either SAR441566 200 mg twice daily or placebo



Objective

- Evaluate clinical response, safety, and tolerability of SAR441566 compared to placebo

Study Outcomes

- *Efficacy Assessments:* percent change in the PASI and TLSS from baseline to Weeks 2 and 4
- *Safety and Tolerability Assessments:* incidence of adverse events (AEs) / treatment-emergent adverse events (TEAEs) including serious adverse events (SAEs) and adverse events of special interest (AESI), safety laboratory parameters, vital signs, electrocardiogram result, and physical examination

Inclusion Criteria

- Age 18–65 years
- Confirmed diagnosis of mild-to-moderate plaque psoriasis for at least 6 months prior to screening, defined as PASI≤16
- At least two lesions with TLSS≥4

Exclusion Criteria

- Patients with any pre-existing signs of skin atrophy, telangiectasia or striae in the affected area, current evidence of non-plaque forms of psoriasis, psoriatic arthritis or drug-induced psoriasis
- Previous treatment with biological agents, systemic non-biologic psoriasis therapies, other systemic immunosuppressive drugs within 4 weeks of baseline
- Topical corticosteroids or other topical preparations with immunomodulatory properties within 2 weeks of baseline

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Disclosures

Tiago R. Matos, Mai Anh Nguyen, Nassr Nassr, Ohn A. Chow, Anna Fishbein, Markus Kohlmann, Laurent Perrin: Employees of Sanofi and may hold stock/stock options in the company. **Wagner Frank-Dietrich:** Have no conflicts of interest

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