Abstract N°: 1189

The novel, first-in-class IL-1R3 Antagonist SAR445399 Reduces Skin Inflammation in an Innovative Proof-of-Mechanism Study with Dual Immune Challenge Models and Comparator Drugs

Anouk Meijs[1], Cecilia Deantonio[2], Caroline Dreis[3], Paul Aubel[4], Sarah Suard[5], Manon Bouet[6], Tobias Paehler[3], Christian Asbrand[3], Ben Lin[2], Fabienne Schumacher[3], Tessa van der Kolk[1], Matthijs Moerland[1], Joachim Tillner[3]

[1]Centre for Human Drug Research, Leiden, Netherlands
[2]Sanofi, Cambridge, United States
[3]Sanofi, Frankfurt, Germany
[4]Orange Cyberdefense, Vitry-Sur-Seine, France
[5]Aixial, Montpellier, France
[6]Sanofi, Montpellier, France

Introduction & Objectives:

SAR445399 is a first-in-class IgG4 mAb binding to IL-1R3, a co-receptor required for signaling of IL-1, IL-33, and IL-36. This study was designed to evaluate the effect of SAR445399 on dermal inflammation induced by imiquimod (IMQ) and lipopolysaccharide (LPS) which trigger a local skin reaction via IL-36 and IL-1 pathways. The IL-1 antagonist canakinumab and the IL-36R inhibitor spesolimab served as comparators. The primary objective was to quantify the effect of SAR445399 on IMQ/LPS induced skin reaction compared to placebo.

Materials & Methods:

Randomized, 5-arms (SAR445399 high & low dose, placebo, canakinumab, spesolimab) single doses, in healthy participants with LPS (ID)/IMQ (topical) challenges on separate locations. Skin reaction was quantified by laser speckle contrast and multispectral imaging up to 72 hours post challenge. Parameters assessed were skin blood perfusion (SBP, primary) and erythema (secondary) change from baseline. Blood was collected for PK of SAR445399 and ex vivo stimulation assays (TruCultureTM) in which inhibition of cytokine release was analyzed with IL-6 as a reporter for IL-1β stimulation, and IFNγ for IL-33/ IL-12 stimulation. Skin biopsies at challenge sites were collected for transcriptomic analysis. Suction blisters were induced at site of LPS, exudate was collected for proteomic analysis (Olink).

Results:

50 participants completed the study (10 per arm). Increases of SBP and erythema (not shown) were detected in the placebo group after both challenges (Fig. 1 a/b & Table 1 a/b). Canakinumab suppressed SBP and erythema for both challenges. Spesolimab suppressed SBP and erythema for IMQ only, while the effect on SBP for LPS was negligible. Reduction of SBP and erythema was observed for both SAR445399 doses after both challenges. Low and high doses were comparable for LPS while low dose was more effective for IMQ.

Upon IL-1β stimulation, SAR445399 and canakinumab inhibited IL-6 release in the ex vivo assay, spesolimab and placebo demonstrated negligible IL-6 reduction. Upon IL-33/ IL-12 stimulation, SAR445399 showed sustained IFNγ inhibition, which was more pronounced in the high dose group. Neither placebo nor comparator arms had any effect on IFNγ inhibition.

A significant reduction of IL-6 in suction blister fluid was observed in both SAR445399 arms compared to placebo, with a comparable effect seen for canakinumab. Spesolimab showed no effect on IL-6 levels. Relevant changes

were also observed for IL-33, IL-1β, IL-17F, and IL-17C.

Conclusion:

In this innovative study SAR445399 demonstrated significant inhibition of skin inflammation after LPS and IMQ challenges via the IL-1 and IL-36 pathways. Canakinumab also inhibited LPS and IMQ induced skin inflammation while spesolimab was effective in the IMQ model only. Results are in line with scientific literature describing IL-1 contribution to the LPS and IL-1/ IL-36 contribution to the IMQ driven skin inflammation. Comparator results validate the models to assess inhibition of IL-1 and IL-36 pathway and confirm IL-1 and IL-36 target engagement for SAR445399.

Ex-vivo assay results confirm SAR445399 to inhibit the IL-1 and IL-33 pathways. Proteomic results show SAR445399 effects at skin level (decrease in IL-6 levels), confirming impact on key soluble cytokines (IL-33 and IL-1β) related to the IL-1R3 pathway, and suggesting synergistic effects on key inflammatory pathways (IL-17F).

Figure 1a: Skin blood perfusion (SBP) after LPS challenge – Raw data

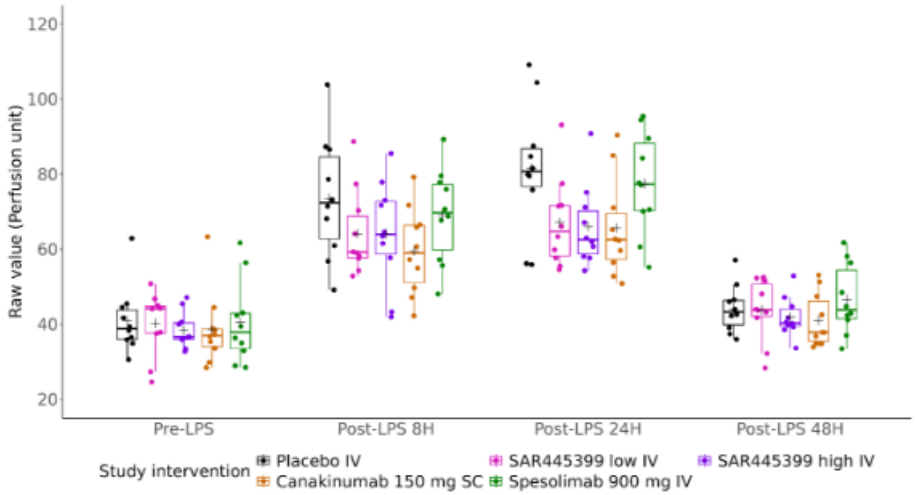

Figure 1b: Skin blood perfusion (SBP) after IMQ challenge – Raw data

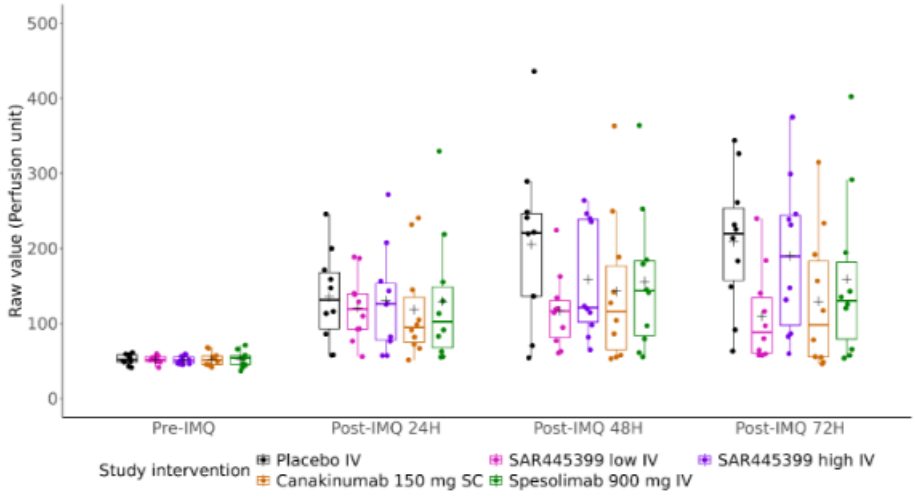

Table 1a: Comparators - SBP after LPS and IMQ challenge (change from baseline [LS mean, 90% CI] and difference vs. placebo)

	Placebo	Canakinumab			Spesolimab		
LPS							
Time-point*	CfBL	CfBL	△	% change estimate	CfBL	△	% change estimate
8h	33.18 (26.69,39.68)	20.32 (13.83,26.82)	-12.86 (-22.05,-3.67)	-38.75	28.92 (22.43,35.42)	-4.26 (-13.44,4.92)	-12.83
24h	41.04 (34.35,47.72)	26.44 (19.76,33.12)	-14.60 (-24.06,-5.14)	-35.57	37.34 (30.66,44.02)	-3.70 (-13.15,5.75)	-9.02
48h	3.74 (0.76,6.72)	1.87 (-1.11,4.84)	-1.87 (-6.09,2.35)	-50.05	6.50 (3.53,9.48)	2.77 (-1.44,6.97)	73.99
IMQ							
24h	83.28 (47.43,119.13)	65.62 (29.76,101.48)	-17.66 (-68.37,33.04)	-21.21	76.35 (40.47,112.23)	-6.93 (-57.65,43.79)	-8.32
48h	153.22 (105.50,200.93)	89.92 (42.20,137.64)	-63.30 (-130.78,4.19)	-41.31	102.97 (55.23,150.70)	-50.25 (-117.7,17.24)	-32.80
72h	156.75 (107.09,206.41)	76.99 (27.32,126.65)	-79.76 (-150.00,-9.53)	-50.89	105.85 (56.17,155.53)	-50.90 (-121.14,19.34)	-32.47

**post LPS/IMQ challenge*

Table 1b: SAR445399 - SBP after LPS and IMQ challenge (change from baseline [LS mean, 90% CI] and difference vs. placebo)

	Placebo	SAR445399 low dose			SAR445399 high dose		
LPS							
Time-point*	CfBL	CfBL	△	% change estimate	CfBL	△	% change estimate
8h	33.18 (26.69,39.68)	24.14 (17.65,30.63)	-9.04 (-18.22,0.14)	-27.25	24.95 (18.45,31.45)	-8.23 (-17.42,0.96)	-24.81
24h	41.04 (34.35,47.72)	27.04 (20.35,33.72)	-14.00 (-23.45,-4.55)	-34.12	26.88 (20.19,33.56)	-14.16 (-23.62,-4.70)	-34.50
48h	3.74 (0.76,6.72)	3.73 (0.76,6.70)	-0.01 (-4.21,4.20)	-0.22	2.75 (-0.23,5.73)	-0.99 (-5.21,3.23)	-26.44
IMQ							
24h	83.28 (47.43,119.13)	68.97 (33.12,104.81)	-14.31 (-65.01,36.38)	-17.19	79.77 (43.85,115.69)	-3.51 (-54.25,47.23)	-4.22
48h	153.22 (105.50,200.93)	64.85 (17.14,112.57)	-88.36 (-155.84,-20.89)	-57.67	108.01 (60.24,155.78)	-45.20 (-112.72,22.31)	-29.50
72h	156.75 (107.09,206.41)	57.53 (7.87,107.19)	-99.22 (-169.44,-28.99)	-63.30	139.12 (89.41,188.83)	-17.63 (-87.89,52.63)	-11.25