Abstract N°: LBA-54

Balinatunfib, the first oral selective inhibitor of TNFR1 signalling, in plaque psoriasis: A double-blind, randomized, placebo-controlled Phase 2b study

Fernando Valenzuela[1, 2], Kim A. Papp[3, 4], Andreas Pinter[5], Markus Kohlmann[6], Xiaomei Liao[7], Mai Anh Nguyen[6], Rui Wang[8], Maria Wiekowski[7], Andrea Szegedi[9], Mark Lebwohl[10], tiago matos[11, 12]

[1] Dermatology Department, Universidad de los Andes, Santiago, Chile
[2] Probity Medical Research, Santiago, Chile
[3] Division of Dermatology, Temerty Faculty of Medicine,, University of Toronto, Ontario, Canada
[4] Probity Medical Research, Ontario, Canada
[5] Department of Dermatology, Venereology and Allergology, University Hospital Frankfurt, Frankfurt, Germany
[6] Sanofi`, Frankfurt, Germany
[7] Sanofi, Morristown, United States
[8] Sanofi, Cambridge, United States
[9] Department of Dermatology, University of Debrecen,, Debrecen, Hungary
[10] Icahn School of Medicine at Mount Sinai, New York, United States
[11] Sanofi, Amsterdam, Netherlands
[12] Amsterdam University Medical Centers, University of Amsterdam, Amsterdam, Netherlands

Introduction

Balinatunfib is a novel, oral, small molecule selective inhibitor of tumor necrosis factor (TNF) signaling through the TNF receptor 1 (TNFR1) while preserving signalling through the TNF receptor 2 (TNFR2) mediated pathway that plays a role in immune homeostasis, regulatory T-cell function, tissue regeneration, and host defence against pathogens. Excessive production of TNF has been implicated in psoriasis pathogenesis and its inhibition is a clinically validated treatment.

Materials and Methods

This phase 2b, double-blind, placebo-controlled, dose-ranging study evaluated efficacy and safety of balinatunfib vs placebo in adult participants with moderate-to-severe plaque psoriasis and included both patients naïve to and experienced to advanced therapies. Participants were randomized to receive balinatunfib 200 mg twice-daily (BID), 100 mg BID, 200 mg once daily (QD), 100 mg QD, or 50 mg QD or matching placebo orally for 12 weeks. The primary endpoint was the proportion of patients achieving PASI75 at week 12 (W12) in the advanced therapy-naive cohort. A pre-defined hierarchy of testing of primary endpoint followed the order of 200 mg BID->100 mg BID->200 mg QD.

Results

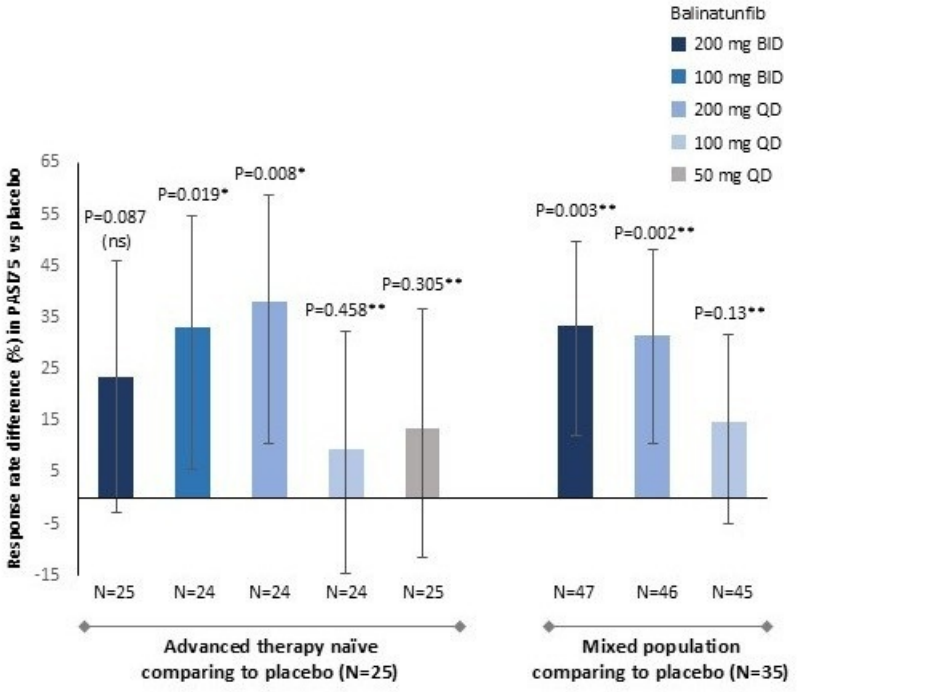
A total of 221 participants with comparable demographic characteristics were randomized to receive balinatunfib

or placebo. An analysis of the primary endpoint showed clinically meaningful efficacy with a numerically higher proportion of patients receiving 200 mg BID balinatunfib in the advanced therapy-naïve population achieving PASI75 vs.placebo at W12 (response rate difference (RRD): 23.43% [95% CI: (-2.74%, 45.98%); P=0.087]). A higher proportion of patients achieved PASI75 with 100 mg BID (RRD: 33.08% [95% CI: 5.71%, 54.83%]; nominal P=0.019), and 200 mg QD, (RRD: 38.02% [10.62%, 58.84%]; nominal P=0.008) in the advanced therapy-naïve patients vs. placebo (Figure). In the mixed study population, comprising both advanced therapy naïve and experienced participants, strong differences were observed in RRD (95% CI) vs. placebo at W12 for PASI75; 33.29% (11.97%, 49.86%) in the 200 mg BID group, 31.62% (10.39%, 48.32%) in the 200 mg QD group (nominal P<0.01 for all) but not in the 100 mg QD group (14.64% [-4.99%, 31.54%]; nominal P=0.13) (Figure). A greater proportion of patients in the mixed population treated with balinatunfib 200 mg QD (41.3%) achieved sPGA 0/1 vs placebo (17.1%) at W12 (nominal P=0.006). Levels of IL-17A, IL-17F, IL-22 and IL-19 were significantly lower in the balinatunfib 200 mg QD group at W4 and W12 vs placebo (nominal P≤0.05). Balinatunfib was generally well tolerated across all tested doses, with no deaths reported and steady-state plasma exposure was maintained until end of treatment. Adverse events were more commonly reported in the 200 mg BID and 200 mg QD groups compared to other doses and placebo. Most frequently reported AEs were nasopharyngitis, dysgeusia and arthralgia.

Conclusion

Balinatunfib, an oral selective inhibitor of TNFR1 signalling, was generally well-tolerated. While the highest balinatunfib dose (200 mg BID) group did not meet statistical significance vs placebo for the primary endpoint (PASI75 at W12) in the naïve population, clinically meaningful and numerically larger (nominal p< 0.05) improvements at W12 were observed with other dose groups vs placebo in both advanced therapy-naïve and experienced patients. Inhibition of TNFR1 signal by balinatunfib was associated with reduction in biomarkers of Th17/Th22-mediated inflammation.

Figure: Response rate difference in PASI75 vs placebo in advanced therapy naïve and mixed population cohorts at Week 12



Error bars represent 95% CI;
*Statistical significance cannot be claimed due to non-significance of 200mg BID dose in the Type-I error multiplicity control plan;
**These comparisons are not under Type-I error multiplicity control, hence p-values are all nominal;
BID, twice daily; CI, confidence interval; ns, non-significant; QD, once daily