A randomized, placebo-controlled study of the tolerability, pharmacokinetics, and pharmacodynamics of the oral JAK2 inhibitor SAR302503 in healthy volunteers

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Disclosures
Zhang, M., Xu, C.R., Liu, F., Yin, J., Maltzke, L.L., Smith, W.B. have received personal fees from Tavelli.

Introduction
SAR302503 (Figure 1) is an orally administered JAK2-selective inhibitor under clinical development for the treatment of myelofibrosis.1–3

Methods
Trial design and participants
• This was a Phase I, double-blind, placebo-controlled, sequential ascending-dose study.
• Subjects were male, aged 18–45 years, and healthy (certified by a comprehensive clinical assessment), having normal or non-clinically significant laboratory parameters and vital signs.
• Subjects were randomized to receive a single dose of either placebo or SAR302503 ranging from 10 mg to 680 mg under fasted conditions (Figure 2).

Pharmacokinetic assessments
• Plasma concentrations were determined using a validated liquid chromatography with tandem mass spectrometry method with a lower limit of quantification of 1 ng/mL.
• Dose proportionality was assessed using an empirical power model for log-transformed Cₚ,max, AUC₀–∞, and t₁/2z. Dose effect was analyzed using a linear fixed-effect model for log-transformed t₁/2z.

Pharmacodynamic assessments
• Whole blood samples were extracted into vpn with glacial acetic acid (10%; v/v) and leukocytes were isolated after lysis of red blood cells. The levels of pSTAT3 in total leukocytes were assessed using Phospho-JAK2/STAT3 (Cell Signaling Technology, Danvers, MA) after normalization to total STAT3 measured by PathScan® Total STAT3 (Zymed Laboratories, South San Francisco, CA).
• The relationship between pSTAT3 suppression and SAR302503 dose was modeled using an empirical power model for log-transformed t₁/2z.

Results
Patient disposition
• A total of 56 subjects were treated, with 42 randomized to SAR302503 and 14 to placebo.
• The dose groups were generally well balanced demographically (Table 1).

Safety
• All adverse events (AEs) were of mild intensity (MedDRA v15.0).
• The most common AEs were gastrointestinal disorders (Table 3).
• Nausea and vomiting were the most frequent events (24%) treated with placebo.

Pharmacokinetics
• SAR302503 exposure increased in a greater than dose-proportional manner: a doubling of SAR302503 dose resulted in an estimated 90% (97% CI: 84–100%) increase in Cₚ,max and AUC₀–∞, of 475 (95% CI: 76–710)-fold and 689 (83–1030)-fold, respectively (Table 2, Figure 3).
• The relationship between SAR302503 plasma concentrations and remaining pSTAT3 levels was described by an inhibitory effect sigmoid maximum effect E₄₅₀ model (Figure 6).

Pharmacodynamics
• pSTAT3 levels were reduced below that of pre-dose and placebo at 3 hours and 4 hours post-dose in the 500 and 680 mg dose groups; the reduction was dose-related (Figure 5).

Conclusions
• The tolerability, safety, and efficacy of SAR302503 were evaluated in healthy male subjects across a study dose range of 10 to 680 mg.
• SAR302503 was absorbed with a mean t₁/2z of 29–53 hours, with the geometric mean (90% CI) of pooled t₁/2z as 66.9 hours and the median t₁/2z of 29–53 hours.
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• An increase in t₁/2z with dose was most prominent at doses 300 mg and above.
• The mean terminal half-life (t₁/2z) of SAR302503 at 300 mg to 680 mg single dose was 34–2.5 hours, compared with 61.7±16.8 hours at doses of 300–680 mg.
• SAR302503 was well tolerated with mild AEs.

References

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