Evaluation of Changes in Laboratory Parameters from a Phase 2b Trial of Zasocitinib (TAK-279), an Oral, Selective TYK2 Inhibitor, in Patients with Moderate-to-Severe Plaque Psoriasis

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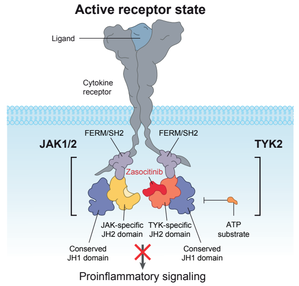
Synopsis

- TYK2 mediates the activation of cytokines involved in the proinflammatory pathways of several immune-mediated inflammatory diseases, including psoriasis.[1]
- Zasocitinib (TAK-279) is a potent and selective, allosteric, oral TYK2 inhibitor (**Figure 1**).[2]
- In a phase 2b trial of patients with moderate-to-severe plaque psoriasis (NCT04999839), more patients in the zasocitinib groups achieved a ≥ 75% improvement in PASI at Week 12 (primary efficacy endpoint) than those in the placebo group (zasocitinib 15 mg QD, 68%; zasocitinib 30 mg QD, 67%; placebo, 6%; $p < 0.001$).[3]
  - Approximately one-third of patients in the zasocitinib 30 mg QD group achieved skin clearance at Week 12 (PASI 100).
  - Zasocitinib had an acceptable safety profile and was generally well tolerated at all doses examined.[3]

Figure 1. Zasocitinib binds with high specificity to the JH2 domain of TYK2 but not to JAK family members, blocking downstream proinflammatory signaling.[2,4]



Objective

- To compare the clinical laboratory parameters from the phase 2b study of zasocitinib versus placebo in patients with moderate-to-severe plaque psoriasis.

Methods

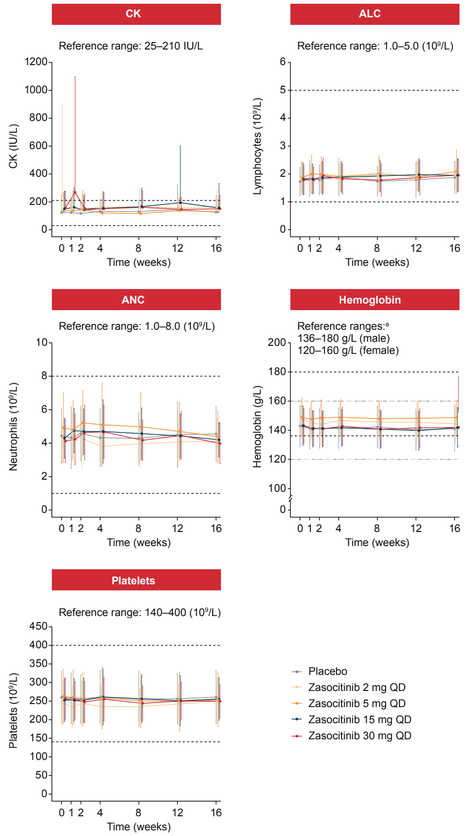
- In this randomized, multicenter, double-blind, placebo-controlled trial, adults with moderate-to-severe plaque psoriasis were randomized (1:1:1:1:1) to receive oral zasocitinib (2 mg, 5 mg, 15 mg or 30 mg) or placebo QD for 12 weeks.
- All patients who received ≥ 1 dose of assigned study treatment were included in the safety analysis set.
- Laboratory parameters assessed throughout the trial included CK, as well as hematological (lymphocytes, neutrophils, hemoglobin, platelets), lipid (cholesterol, triglycerides), and hepatic and renal (ALT, AST, bilirubin, creatinine, eGFR) parameters. Summaries are based on observed data only.

Scan the QR code to see the supplementary material for further details of the study design (**Figure S1**).

Results

Demographic and baseline clinical characteristics were generally similar between treatment groups (**Table S1**).

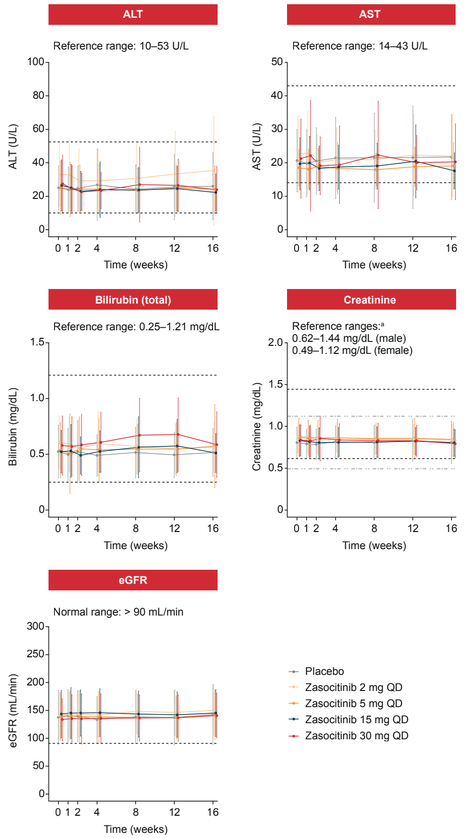
Figure 2. Longitudinal changes in hematological parameters were generally similar in the placebo and zasocitinib groups, with no dose dependency observed. Some CK elevation was observed; however, elevations were transient or reversible. Most mean values remained within normal ranges during the study.[3]



Data are presented as mean ± SD. Owing to the large variability in the CK values, one-sided error bars are shown for this parameter. Dashed lines represent upper and lower limits of the normal range for each parameter; [a]where a graph has four dashed lines, the black lines (- - -) represent the male limits and the gray lines (- - -) represent the female limits.

Scan the QR code to see patient numbers (**Table S2**).

Figure 3. Longitudinal changes in hepatic and renal parameters were generally similar in the placebo and zasocitinib groups, with no dose dependency observed. Mean values remained within normal ranges during the study.[3]



Data are presented as mean ± SD. Dashed lines represent upper and lower limits of the normal range for each parameter; [a]where a graph has four dashed lines, the black lines (- - -) represent the male limits and the gray lines (- - -) represent the female limits.

Scan the QR code to see patient numbers (**Table S3**).

There was no link observed between zasocitinib treatment and occurrence of cytopenias (**Table S4**).

Table 1. Some CK elevations were observed in the placebo and zasocitinib groups; however, most were CTCAE Grade 1 or 2 and elevations were similar between groups. CK elevations were transient or reversible and not associated with rhabdomyolysis. Grade ≥ 2 events were similar between groups.

	Placebo (n = 52)	Zasocitinib 2 mg QD (n = 50)	Zasocitinib 5 mg QD (n = 52)	Zasocitinib 15 mg QD (n = 53)	Zasocitinib 30 mg QD (n = 52)
CK increased CTCAE Grade ≥ 2, n (%)[a]	2 (3.8)	2 (4.1)	6 (11.5)	4 (7.8)	3 (5.8)

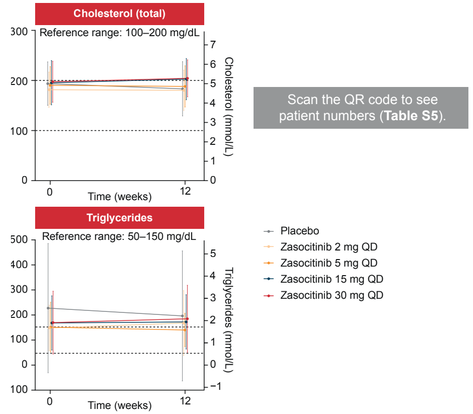
Maximum post-baseline CTCAE Grades ≥ 2 are presented. Percentages are based on the number of patients with non-missing CTCAE grade for the laboratory parameter of interest at baseline and post-baseline.
[a]Zasocitinib 2 mg QD (n = 49), zasocitinib 15 mg QD (n = 51).

Table 2. Laboratory parameter CTCAEs Grade ≥ 3 were infrequently reported in the placebo and zasocitinib groups.

Laboratory parameter CTCAE Grade ≥ 3, n (%)	Placebo (n = 52)	Zasocitinib 2 mg QD (n = 50)	Zasocitinib 5 mg QD (n = 52)	Zasocitinib 15 mg QD (n = 53)	Zasocitinib 30 mg QD (n = 52)
CK increased[a]	1 (1.9)	0 (0.0)	0 (0.0)	1 (2.0)	1 (1.9)
Creatinine increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholesterol increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Triglycerides increased[b]	2 (4.3)	2 (4.8)	1 (2.2)	1 (2.1)	2 (4.2)
ALT increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
AST increased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neutrophil count decreased[c]	1 (1.9)	1 (2.0)	0 (0.0)	0 (0.0)	1 (1.9)
Lymphocyte count decreased[d]	1 (1.9)	1 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hemoglobin decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Platelet count decreased	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Maximum post-baseline CTCAE Grades ≥ 3 are presented. Percentages are based on the number of patients with non-missing CTCAE grade for the laboratory parameter of interest at baseline and post-baseline.
[a]Zasocitinib 15 mg QD (n = 51); [b]placebo (n = 46), zasocitinib 2 mg QD (n = 42), zasocitinib 5 mg QD (n = 45), zasocitinib 15 mg QD (n = 47), zasocitinib 30 mg QD (n = 48); [c]zasocitinib 2 mg QD (n = 49).

Figure 4. Longitudinal changes in lipid parameters were generally similar in the placebo and zasocitinib groups. Mean triglyceride values were slightly higher than normal ranges at baseline and Week 12 in most treatment groups, but these presented as mainly asymptomatic, mild-to-moderate elevations. These changes were not accompanied by increases in serum cholesterol levels.[3]



Data are presented as mean ± SD. Dashed lines represent upper and lower limits of the normal range for each parameter.

Scan the QR code to see patient numbers (**Table S5**).

Scan the QR code to view the longitudinal changes in HDL-C and LDL-C (**Figure S2**).

Conclusions

Over the study period, zasocitinib did not result in any dose-dependent changes in laboratory parameters investigated; no consistent differences were observed between placebo and treatment arms.

Laboratory changes characteristic of JAK inhibitors were not observed.[5]

Phase 3 studies of zasocitinib in patients with moderate-to-severe plaque psoriasis are ongoing (NCT06088043; NCT06108544).

Abbreviations: ALC, absolute lymphocyte count; ALT, alanine aminotransferase; ANC, absolute neutrophil count; AST, aspartate aminotransferase; ATP, adenosine triphosphate; CK, creatine kinase; CTCAE, Common Terminology Criteria for Adverse Events; eGFR, estimated glomerular filtration rate; FERM, band-4.1, erzin, radixin, moesin; HDL-C, high-density lipoprotein cholesterol; JAK, Janus kinase; JH, Janus homology; LDL-C, low-density lipoprotein cholesterol; PASI, Psoriasis Area and Severity Index; QD, once daily; SD, standard deviation; SH, Src homology; TYK2, tyrosine kinase 2.

Disclosures: MG: investigator, speaker and/or advisor for AbbVie, Akros, Amgen, AnaptysBio, Apogee, Arcutis Biotherapeutics, Aristea, Bausch Health, Boehringer Ingelheim, Bristol Myers Squibb, Dermavant, Dermira, Eli Lilly, Galderma, GSK, Incyte, Inmagene, JAMP, Janssen Pharmaceuticals, Kyowa Kirin, LEO Pharma, MedImmune, Meiji, MoonLake Immunotherapeutics, Nimbus,* Novartis, Pfizer, Regeneron, Sanofi (Genzyme), Sun Pharma, Takeda, Tarsus Pharmaceuticals, UCB, Union Therapeutics, Ventyx Biosciences and VYNE Therapeutics. **CB:** investigator, consultant and/or received fees for being a speaker for AbbVie, Almirall, Apogee, Arcutis Biotherapeutics, Allergan, Connect Biopharma, Daiichi Sankyo, Eli Lilly, EPI Health/Novan, Incyte, LEO Pharma, Novartis, Ortho Dermatologics, Palvella Therapeutics, Pfizer, Regeneron, Sanofi (Genzyme), Sun Pharma, Takeda, Timber Pharmaceuticals and UCB. **LHK:** speaker, investigator, consultant and/or advisory board member for Abbott Laboratories, AbbVie, Allergan, Almirall, Amgen, Arcutis Biotherapeutics, Biogen Idec, Boehringer Ingelheim, Breckinridge Pharma, Bristol Myers Squibb, Celgene, Centocor, Cipher, Combinatrix, Connetics, Coria, Dermavant, Dermira, Dow Pharmaceutical Sciences, Dr. Reddy's Laboratories, Eli Lilly, Galderma, Genentech, GSK, Idera, Innovation Pharmaceuticals (Cellceutix), Johnson & Johnson, LEO Pharma, Maruho, Medicis Pharmaceutical, Merck, Merck Serono, Nimbus,* Novartis, Pfizer, Pharmaderm, Promius, Stiefel Laboratories, Sun Pharma, Taro Pharmaceuticals, UCB, Valeant Pharmaceuticals, Ventyx Biosciences and XenoPort. **CL:** speaker, principal investigator and/or consultant for AbbVie, Acelyrin, Akros, Altius, Amgen, Aralez Pharmaceuticals, Arcutis Biotherapeutics, Avillion, Bausch Health, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Cipher, Concert Pharmaceuticals, Dermavant, Devonian Health Group, Eli Lilly, Evelo, Fresenius Kabi, Galderma, GSK, Incyte, Innovaderm, Intega Skin Sciences, Janssen Pharmaceuticals, Kyowa Kirin, La Roche-Posay, LEO Pharma, L'Oreal, Medexus Pharmaceuticals, MedX, Merck, MoonLake Immunotherapeutics, Nimbus,* Novartis, Pediapharm, Pfizer, Procter & Gamble, Regeneron, Roche, Sandoz, Sanofi (Genzyme), Sentrex Health Solutions, Sun Pharma, TEVA, Tribute, UCB, Valeant Pharmaceuticals, Viatris and Volo Health. **LS:** investigator, speaker and/or advisor for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Galderma, Incyte, Janssen Pharmaceuticals, LEO Pharma, Novartis, Novo Nordisk, Pfizer, Sanofi (Genzyme), Takeda and UCB. **JB, WZ, JU** and **WW:** employees and equity holders of Takeda. **DT:** advisor, speaker or consultant for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Celtrion, Galderma, Janssen Pharmaceuticals, Kyowa Kirin, L'Oréal, LEO Pharma, Eli Lilly, NewBridge, Novartis, Pfizer, Regeneron, Sanofi (Genzyme), Target RWE, UCB and Vichy Laboratories.

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*Nimbus refers to the group of entities including Nimbus Therapeutics LLC, Nimbus Discovery, Inc., and Nimbus Lakshmi, Inc. (NB: Nimbus Lakshmi, Inc., was acquired by Takeda Pharmaceuticals in February 2023).

This poster is intended for healthcare professionals

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Previous presentations: This poster was previously presented at the European Academy of Dermatology and Venereology (EADV) 2024 Congress. Gooderham M *et al.* Presented at EADV 2024.