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Efficacy and safety of HS-10374 in patients with moderate-to-severe plaque psoriasis: Results from a randomized, double-blind, placebo-controlled phase 2 trial

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Introduction & Objectives:

Tyrosine kinase 2 (TYK2) is essential for signaling of interleukin (IL)-12 and IL-23, which are key cytokines involved in psoriasis pathogenesis. HS-10374 is an oral, selective, allosteric TYK2 inhibitor. This phase 2 trial was to assess the efficacy and safety of HS-10374 in patients with moderate-to-severe plaque psoriasis.

Materials & Methods:

In this phase 2, randomized, double-blind, placebo-controlled trial (NCT06077331), patients with moderate-to-severe plaque psoriasis were randomized 1:1:1 to receive HS-10374 6 mg, 12 mg or placebo (PBO) orally once daily (QD), stratified by previous biologics use (yes/no). The treatment period was 12 weeks, followed by a 4-week follow-up period for safety monitoring. The primary efficacy endpoint was PASI 75 response rate at Week 12. Additional efficacy outcomes and safety were evaluated.

Results:

Of 125 Chinese patients enrolled, 42 were assigned to receive HS-10374 6 mg, 43 to receive HS-10374 12 mg, and 40 to receive PBO. One hundred and fifteen patients (92%) completed 12 weeks of treatment.

Efficacy: At Week 12, the primary endpoint was met, with significantly greater proportion of patients in HS-10374 6 mg and 12 mg groups achieving PASI 75 responses compared with PBO (PBO: 7.5%; HS-10374 6 mg: 28.6%, $P=0.013$; HS-10374 12 mg: 72.1%, $P<0.001$). At Week 12, additional efficacy endpoints were met as well, including significantly higher sPGA 0/1, PASI 50 and PASI 90 response rates compared with PBO in HS-10374 12 mg group, and significantly higher sPGA 0/1 and PASI 50 response rates in HS-10374 6mg group. (Figure 1).

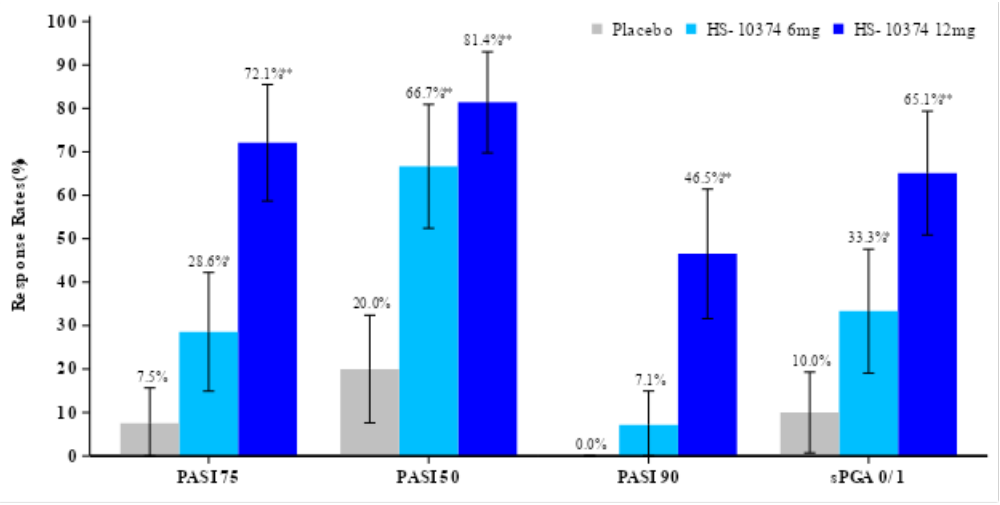

Figure 1. Proportions of patients achieving PASI 50/75/90 response and sPGA 0/1 response.
* $P<0.05$, ** $P<0.001$

Safety: AE rates of HS-10374 groups were slightly higher than PBO group, while rates of treatment-related AEs (TRAEs), serious AEs (SAEs), and AEs leading to discontinuation of trial regimen were comparable across the three treatment groups. One patient in the 6 mg group experienced SAE of limb traumatic amputation that was considered unrelated to treatment, and the only patient with treatment-related SAE (gastrointestinal haemorrhage) was from PBO group. No death occurred. AEs under the SOC "infections and infestations" were most commonly reported, with the majority being graded as CTCAE 1-2 except for one patient receiving intravenous antibiotics. In contrast to the relative higher incidence of skin-related adverse events for some other TYK2 inhibitors, AEs under "skin and subcutaneous disorders" in this study were more commonly reported in PBO group (detailed in Table 1). Treatment with HS-10374 did not result in significant changes from baseline in mean values of blood counts, hepatic and renal parameters, or lipids.

Table 1. Summary of Adverse Events through Week 16

	PBO (N=40) n(%)	HS-10374 6 mg (N=42) n(%)	HS-10374 12 mg (N=43) n(%)
AEs	28(70.0)	32(76.2)	38(88.4)
TRAEs	22(55.0)	19(45.2)	25(58.1)
SAEs	1(2.5)	1(2.4)	0
Treatment-related SAE	1(2.5)	0	0
AEs leading to discontinuation of trial regimen	1(2.5)	0	1(2.3)
Infections and infestations *	9(22.5)	9(21.4)	17(39.5)
Skin and subcutaneous disorders	5(12.5)	3(7.1)	4(9.3)

* Most frequently reported. Events elicited by laboratory testing not included.

Exploratory exposure-response analysis: A relationship between exposure and primary efficacy endpoint (PASI 75 response rate at Week 12) was adequately described by a logistic regression model. PASI 75 response rate increased with increasing steady state average concentration and reached a plateau at the exposure level of 12 mg QD dosage.

Conclusion:

HS-10374 showed significant clinical efficacy versus PBO in PASI 75 response rate and sPGA 0/1 response rate at oral doses ≥ 6 mg in patients with moderate-to-severe plaque psoriasis. The overall safety profile was similar to other TYK2 inhibitors with less risk of skin toxicity. Trials of longer treatment duration with a larger population are required to further confirm the efficacy and safety of HS-10374 in such patients.