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Safety, Tolerability and Pharmacokinetics of GT20029 Gel and GT20029 Solution in Healthy Subjects

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Introduction & Objectives:

The interaction of dihydrotestosterone (DHT) and the androgen receptors (AR) is one of the pathophysiologies of Androgenetic Alopecia (AGA) and Acne. GT20029 is a topical AR-Proteolysis Targeting Chimera (PROTAC), which recruits AR in proximity to an E3 ubiquitin ligases to initiate AR ubiquitination and subsequent degradation. In preclinical studies, GT20029 can promote hair growth significantly in dihydrotestosterone (DHT)-induced AGA mouse model and inhibit testosterone propionate (TP)-induced flank organ enlargement with statistically significance in hamster flank organ acne model. Therefore, it showed potential treatment efficacy in promoting hair growth and inhibiting sebaceous gland development. GT20029 also exhibited low systemic exposure and a good safety profile. In light of the above, this phase I clinical trial to evaluate GT20029 gel and solution safety, tolerability and pharmacokinetics (PK) in healthy volunteers (HV) was initiated at China.

Materials & Methods:

This was a single-center, randomized, double-blinded, placebo-controlled, parallel group, dose escalation study with two stages. Stage 1: HVs were treated with GT20029 gel or placebo. 28 HVs were planned to enter single ascending dose (SAD) group with 4 different doses, and 40 HVs to multiple ascending dose (MAD) group, of whom can be recruited from SAD cohorts (after 14 days wash out period) or from other sources. Stage 2: HVs were treated with GT20029 solution or placebo. 24 HVs were planned to enter MAD group with 3 different doses. All drugs/placebo were topically administrated to the subjects on a fixed 8cmX 8cm area of the back. The study design and dose assignement table are in Figure 1. PK blood samples were collected regularly. Safety assessment included monitoring of adverse events (AEs), vital signs, laboratory findings, electrocardiogram, physical exams and assessment of the application site skin. Study endpoints included evaluation of safety and recommended phase II dose (primary) , PK characters and systemic exposure (secondary) of GT20029.

Results:

From July2021 to Aug2022, 95 subjects were randomly enrolled, including 69 in stage 1 and 26 in Stage 2 (Figure 2). HVs' baseline demographics is listed in Table 1.

Total 92 HVs were included in the safey analysis set, treatment emergent AEs (TEAEs) were reported in 68 subjects (73.9%), of whom 64 and 4 subject's TEAEs were grade 1 and grade 2, respectively. 64 subjects' AEs were deemed as drug-related AEs (DRAEs). The most reported DRAEs (≥10%) were rash, skin exfoliation, and pruritus. Less DRAEs incidences were observed in Stage 2 compared to that treated with gel (Table 2). No DRAEs were ≥ grade 3 nor led to cessation of treatment or death.

There was no systemic exposure after single dose of gel application. Since blood concentrations were Below

Limit of Quantification (1pg/ml) at the most points, PK showed linear characteristics after multi-dose application of gel/solution in the range of 2-10 mg and 5-20 mg, respectively.

Conclusion:

Overall, HVs who received a single application of GT20029 gel (1, 2, 5 and 10 mg) or 14-days topical GT20029 gel (2 mg QD, 2mg BID, 5mg QD, 5mg BID, 10 mg QD) or solution (5mg QD, 10mg QD and 20 mg QD) showed low system exposure and good safety. Combined with the obtained PK characteristics and overall safety data, it is recommended to explore the safety and efficacy of multi-dose application of GT20029 solution (5 mg 0.5% QD, 10 mg 1.0% QD) in follow-up studies.

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