Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Multiple Ascending Doses of TAK-935 in Healthy Subjects

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Introduction

TAK-935 is a potent and selective inhibitor of cholesterol 24-hydroxylase (CH24H), which is responsible for the biosynthesis of 24-hydroxycholesterol (24-OHCh) from cholesterol. The safety, tolerability, and pharmacokinetics (PK) and pharmacodynamics (PD) of TAK-935 were evaluated in multiple ascending doses in healthy subjects. The study was conducted to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of TAK-935 and its metabolite, M-I, and PD parameters were derived using available PK data from the preceding cohort.

Methods

Study Design

This was a phase 1, randomized, double-blind, placebo-controlled, multiple-dose study conducted in healthy subjects.

A total of 20 healthy male and female subjects aged 18 to 45 years were randomized to the study with 10 subjects in the TAK-935 group and 10 subjects in the placebo group for each of the 5 doses: 100 mg qd (cohort 1), 300 mg qd (cohort 2), 400 mg qd (cohort 3), 300 mg bid (cohort 4), and 400 mg qd (cohort 5).

The subjects were started on the target dose in this MRD study without up-titration. In order to simulate the clinical setting, all the patients were treated with the drug in the same manner, with the dose escalation based on the safety and tolerability of the previous cohort.

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The exposure of M-I was comparable between day 1 and day 14 after 100, 300, and 400 mg qd dosing. Over the 4-fold dose range of 100 to 400 mg qd after multiple-dose administration, mean metabolic ratio, based on AUC(∞), generally decreased with increasing dose, ranging from 0.33 to 0.53 across the dose range investigated.

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Statistical Methods

The safety analysis set consisted of all subjects who received and analyzed study drug. The PD analysis set consisted of all subjects who were in the safety set and had at least 2 measurable 2004 plasma concentrations or at least 1 solid lipid nanoparticle (SLN) concentration. In the case of discontinuation of the study drug, the last observation carried forward was used to evaluate safety endpoints between day 1 and day 14 for Cmax and AUCs.

Results

PK Results (Tables 1 and 2; Figures 1 and 2)

- Mean (CV%) values were presented for Cmax, AUC, and t1/2 values across the dose range.
- AUC(∞) values were compared with day 1, whereas 300 mg qd for 14 days showed an approximately 1.74- and 1.25-fold increase of Cmax and AUC(τ) on day 14, respectively.
- The exposure of M-I was comparable between day 1 and day 14 for Cmax and AUCs.

PK Results (Tables 1 and 2; Figures 1 and 2)

- TD-935 was safe and well tolerated after once-daily doses up to 400 mg for 14 days in healthy subjects.
- There were a total of 45 treatment-emergent AEs (TEAEs) reported in 14 of the 30 TAK-935–treated subjects. The majority of the TEAEs were considered unrelated to TAK-935, and 14 were considered unrelated. The majority of the TEAEs reported in this study were unrelated to the study drug.

Safety Results

- No deaths or other serious adverse events occurred in this study.
- There were 2 cases of QT and 1 case of diastolic hypertension.
- The trial was designed to be a randomized, double-blind, placebo-controlled, multiple-dose study conducted in healthy subjects.

Conclusions

- TAK-935 was safe and well tolerated after once-daily doses up to 400 mg for 14 days in healthy subjects.
- The results were consistent with the target dose in the MRD study with no additional safety signals observed.

Acknowledgments

The authors would like to thank Takeda, Inc., for access to the medical writing support services.

This study was funded by Takeda Pharmaceuticals.

Please see the American Society of Clinical Oncology, Annual Meeting, December 1-5, 2023, Washington, D.C.