Phase 1 Single and Multiple Ascending Dose Study to Assess the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of AG-946 in Healthy Volunteers

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BACKGROUND

AG-946, an oral, highly potent PK activator, was well tolerated in healthy volunteers following single dose administrations up to 60 mg and multiple dose administrations up to 10 mg QD. Enrollment into additional SAD (100 mg) and MAD (10 mg QD) cohorts is ongoing and will be followed by an open-label phase in subjects with SCD.

METHODS

In the phase 1, randomized, double-blind, placebo-controlled study, single ascending doses (SAD) or multiple ascending doses (MAD) of AG-946 or placebo were administered under fasting conditions to healthy men and women (18-55 years of age) in sequence cohorts (Figure 1).

RESULTS

As of 24 June 2021, 47 subjects (median age: 30 years; 39 male in SAD cohorts and 25 subjects [median age: 35 years; 25 male] in MAD cohorts received AG-946 or placebo. Demographic and baseline characteristics were balanced across the SAD and MAD cohorts (Table 1 and Table 2). Baseline characteristics of MAD cohorts are provided in Table 2.

There were 6 (SAD cohorts, n = 5; MAD cohorts, n = 1) early discontinuations; all were unrelated to study treatment (Table 3 and Table 4).

Pharmacokinetics

In both SAD and MAD cohorts, AG-946 exhibited rapid absorption with median time to maximum concentration (Tmax) ranging from 0.5 to 1 hour. Following SAD, dose-normalized AG-946 exposures increased as a result of a dose proportional increase in exposure over the dose range tested (Figure 2A and 2B).

Safety

In SAD cohorts, 4/7 (57.1%) subjects experienced 1 treatment-emergent adverse event (TEAE); all TEAEs were assessed as grade 1 and unrelated to study treatment.

In MAD cohorts, 2/5 (40.0%) subjects experienced 1 TEAE; all TEAEs except for rhabdomyolysis were mild (grade 1), and all were considered unrelated to study treatment.

CONCLUSIONS

AG-946, an oral, potent PK activator, was well tolerated in healthy volunteers following single dose administrations up to 60 mg and multiple dose administrations up to 10 mg QD.

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REFERENCES


