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 converts brain cholesterol to 24S-hydroxycholesterol (24HC), a positive allosteric modulator at the *N*-methyl-D-aspartate (NMDA) receptor. 24HC can drive glutamatergic overactivation by modulation via NMDA channel activity, which implies a potential role in central nervous system diseases such as epilepsy. TAK-935 is currently under development for the treatment of patients with rare epilepsies.
- In nonclinical studies, TAK-935 protected neurons from glutamate excitotoxicity. In the pentylenetetrazol-induced mouse kindling model of epilepsy, TAK-935 delayed seizure onset and severity in a dose-dependent manner.
- The antiepileptic effect of TAK-935 was associated with a reduction of 24HC levels in mice, which supports an effective in vivo targeting of CH24H.
- This study was conducted to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of TAK-935 when administered as multiple doses of oral solution at escalating dose levels to healthy subjects.

Methods

Study Design

- This was a phase I, randomized, double-blind, placebo-controlled, multiple-rising-dose study conducted in healthy subjects.
- A total of 40 healthy male and female subjects aged 19 to 54 years were enrolled in the study, with 8 subjects (6 on TAK-935, 2 on placebo) per cohort receiving TAK-935 once daily (qd) or twice daily (bid) orally for 10 to 14 days.
- The 5 dose groups included 100 mg qd (cohort 1), 300 mg qd (cohort 2), 300 mg bid (cohort 3), 600 mg qd (cohort 4), and 400 mg qd (cohort 5).
- The decision to escalate to the next dose was made after a full review of the blinded safety and tolerability and available PK data from the preceding cohort.

PK and PD Evaluation

- Serial plasma and urine samples were collected at prespecified time points up to 24 hours post dose on day 1 and day 14 to measure concentrations of TAK-935 and its major identified metabolite, M-I, using high-performance liquid chromatography with tandem mass spectrometry detection.
- PK parameters of TAK-935 and its metabolite, M-I, and PD parameters were derived using noncompartmental analysis methods with Phoenix WinNonlin, version 6.3 (Certara USA, Inc., Princeton, NJ). Actual sampling times were used for plasma PK and PD analysis, and nominal sampling times were used for urine PK analysis.

Safety Evaluation

- Safety evaluations included adverse events (AEs); physical examinations (including eye examinations); weight, height, and body mass index; vital signs; clinical laboratory tests; and psychiatric assessments.

Statistical Methods

- The safety analysis set consisted of all subjects who enrolled and received study drug.
- The PK set consisted of all subjects in the safety set who had at least 1 measurable plasma or urine concentration.
- The PD set consisted of all subjects who were in the safety set and had at least 1 measurable 24HC plasma concentration or at least 1 valid Cogstate battery result (Cogstate Ltd., New Haven, CT) at baseline and post dose.
- For subjects who received once-daily administration of study drug, dose proportionality was assessed using the power model for day 1 and day 14 plasma exposures (maximum observed plasma drug concentration [C_{max}] and area under the concentration-time curve [AUC]). AUC_{∞} was assessed on day 1, and AUC_{τ} was assessed on day 14.
- For the once-daily cohorts, an analysis of variance model was used to assess the time dependency between day 1 and day 14 for C_{max} and AUCs.

Results

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

- TAK-935 C_{max} was reached rapidly at 0.33 to 0.5 hours across the dose-range studies (**Table 1**).
- Over the 6-fold dose range of 100 to 600 mg after a single-dose administration, mean TAK-935 C_{max} and AUC_{∞} on day 1 increased 6.55- and 9.35-fold, respectively (**Table 1**).
- Mean TAK-935 $t_{1/2z}$ (terminal elimination half-life) was similar between day 1 and day 14, ranging from 3.49 to 4.83 hours across the 100- to 600-mg dose range (**Table 1**).
- Over the 4-fold dose range of 100 to 400 mg qd after multiple-dose administration, mean TAK-935 C_{max} and AUC_{τ} on day 14 increased 6.08- and 6.12-fold, respectively (**Table 1**).
- Doses of 100 or 400 mg qd for 14 days did not show apparent exposure accumulation on day 14 compared with day 1, whereas 300 mg qd for 14 days showed an approximately 1.74- and 1.42-fold increase of C_{max} and AUC_{τ} on day 14, respectively (**Figure 3**).
- Approximately 0.08% to 0.25% of the administered TAK-935 dose was excreted in urine across all dose groups after single and multiple oral doses.
- M-I metabolite showed median t_{max} values (time to reach C_{max}) that ranged from 0.5 to 1.0 hours across the dose range studied (**Table 2**).
- Mean $t_{1/2z}$ values for M-I ranged from 2.32 to 3.88 hours (**Table 2**).
- The exposure of M-I was comparable between day 1 and day 14 after 100, 300, and 400 mg qd of TAK-935 for 14 days (**Table 2** and **Figure 2**).
- Mean metabolic ratio, based on AUC_{τ}, generally decreased with increasing dose, ranging from 0.56 to 0.31 after a single dose (100 to 600 mg) and from 0.44 to 0.26 after multiple doses (100 to 400 mg).
- The TAK-935 PK/PD profile supports advancement to clinical trials.

Table 1. Plasma PK Parameter Estimates of TAK-935 on Day 1 and Day 14 After Single and Multiple Doses of TAK-935

	TAK-935 100 mg qd		TAK-935 300 mg qd		TAK-935 400 mg qd		TAK-935 300 mg bid[a,b]	TAK-935 600 mg qd[a]
PK Parameters	**D1**	**D14**	**D1**	**D14**	**D1**	**D14**	**D1**	**D1**
C_{max} (ng/mL)								
Mean (CV%)	467.50 (50.0)	481.17 (25.3)	2015.17 (61.7)	3098.33 (41.1)	2630.00 (50.6)	2925.00 (40.3)	1328.17 (37.5)	3060.00 (70.2)
t_{max} (h)								
Median (range)	0.42 (0.33-0.53)	0.42 (0.25-0.50)	0.42 (0.33-1.05)	0.33 (0.17-0.33)	0.33 (0.25-0.50)	0.33 (0.33-0.50)	0.44 (0.33-1.00)	0.50 (0.50-1.00)
AUC_{∞} (h*ng/mL)								
Mean (CV%)	440.41 (29.8)	451.85 (29.5)	2027.05 (55.7)	2685.68 (40.0)	2496.21 (48.8)	2801.92 (40.4)	1324.02 (38.5)	4180.86 (59.7)
AUC_{τ} (h*ng/mL)								
Mean (CV%)	451.35 (36.7)	508.85 (24.8)	2043.92 (55.3)	2841.47 (40.1)	2521.87 (48.1)	3093.66 (32.8)	1512.12 (48.0)	4219.26 (59.4)
AUC_{τ} (h*ng/mL)[c]								
Mean (CV%)	445.81 (37.1)	458.23 (28.4)	2030.80 (55.7)	2686.56 (40.0)	2497.57 (48.8)	2804.98 (40.3)	1464.53 (49.7)	4184.69 (59.6)
$t_{1/2z}$ (h)								
Mean (CV%)	3.91 (20.7)	3.83 (14.2)	4.44 (19.8)	4.22 (23.4)	4.67 (38.1)	3.66 (42.4)	3.49 (59.2)	4.83 (20.9)
CL/F (L/h)								
Mean (CV%)	247.96 (40.4)	234.14 (29.6)	184.67 (47.6)	129.92 (43.9)	186.70 (38.8)	166.15 (44.4)	232.22 (47.3)	194.05 (57.5)
V_z/F (L)								
Mean (CV%)	1321.98 (21.1)	1138.38 (24.2)	1184.04 (48.1)	732.14 (43.3)	1328.13 (56.5)	713.18 (38.0)	1364.42 (101.4)	1318.90 (61.4)

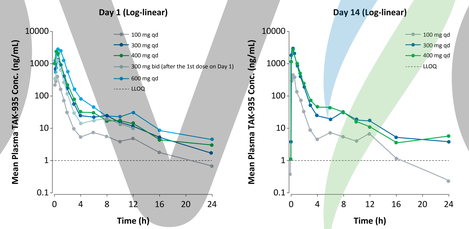
N=6 per group. AUC_{∞}, area under the concentration-time curve (AUC) from time zero to infinity; AUC_{τ}, AUC from time zero to time of last measurable concentration; AUC_{τ}, AUC for dosing interval; CL/F, apparent clearance after extravascular administration; C_{max}, maximum observed plasma concentration; CV%, coefficient of variation percentage; PK, pharmacokinetics; t_{max}, time to reach C_{max}; $t_{1/2z}$, terminal elimination half-life; V_z/F, apparent volume of distribution during terminal disposition phase after extravascular administration.
(a) Dosing for the 300 mg bid and 600 mg qd groups was discontinued after day 10; therefore, plasma and urine TAK-935 PK parameters on day 14 were not available for these groups.
(b) TAK-935 PK parameters were derived using plasma and urine concentration data after the first dose on day 1.
(c) AUC_{τ} = AUC_{∞} for qd dosing, AUC_{τ} = AUC_{0t} for bid dosing.

Table 2. Plasma PK Parameter Estimates of M-I on Day 1 and Day 14 After Single and Multiple Doses of TAK-935

	TAK-935 100 mg qd		TAK-935 300 mg qd		TAK-935 400 mg qd		TAK-935 300 mg bid[a,b]	TAK-935 600 mg qd[a]
PK Parameters	**D1**	**D14**	**D1**	**D14**	**D1**	**D14**	**D1**	**D1**
C_{max} (ng/mL)								
Mean (CV%)	105.17 (16.7)	105.75 (23.5)	398.33 (35.2)	449.00 (33.9)	369.17 (28.3)	383.00 (24.8)	302.00 (18.8)	407.17 (17.4)
t_{max} (h)								
Median (range)	0.51 (0.33-1.00)	0.50 (0.33-0.53)	0.50 (0.50-1.05)	0.50 (0.33-0.50)	0.50 (0.33-1.00)	0.50 (0.33-0.50)	0.50 (0.37-1.00)	1.00 (0.50-1.50)
AUC_{∞} (h*ng/mL)								
Mean (CV%)	240.79 (20.6)	239.35 (19.6)	777.92 (35.8)	852.35 (37.4)	721.96 (32.3)	736.17 (31.7)	589.30 (29.2)	1169.64 (23.9)
AUC_{τ} (h*ng/mL)								
Mean (CV%)	257.52 (18.6)	245.05 (19.8)	787.65 (35.3)	828.67 (41.9)	730.71 (31.8)	794.50 (27.6)	601.21 (29.4)	1181.25 (23.8)
AUC_{τ} (h*ng/mL)[c]								
Mean (CV%)	255.02 (18.5)	242.74 (19.7)	784.30 (35.5)	857.73 (37.3)	725.97 (32.1)	740.58 (31.8)	589.56 (29.2)	1173.53 (23.7)
$t_{1/2z}$ (h)								
Mean (CV%)	2.34 (23.3)	2.32 (5.3)	3.15 (44.4)	2.50 (28.5)	3.43 (53.1)	2.42 (21.2)	2.40 (15.8)	3.88 (32.1)

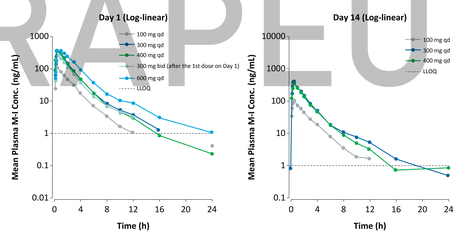
N=6 per group. AUC_{∞}, area under the concentration-time curve (AUC) from time zero to infinity; AUC_{∞}, AUC from time zero to time of last measurable concentration; AUC_{τ}, AUC for dosing interval; C_{max}, maximum observed plasma concentration; CV%, coefficient of variation percentage; PK, pharmacokinetics; t_{max}, time to reach C_{max}; $t_{1/2z}$, terminal elimination half-life.
(a) Dosing for 300 mg bid and 600 mg qd groups was discontinued after day 10; therefore, plasma and urine TAK-935 PK parameters on day 14 were not available for these groups.
(b) TAK-935 PK parameters were derived using plasma and urine concentration data after the first dose on day 1.
(c) AUC_{τ} = AUC_{∞} for qd dosing, AUC_{τ} = AUC_{0t} for bid dosing.

Figure 1. Mean Plasma Concentration-Time Profiles of TAK-935 After Single and Multiple Dose Administrations



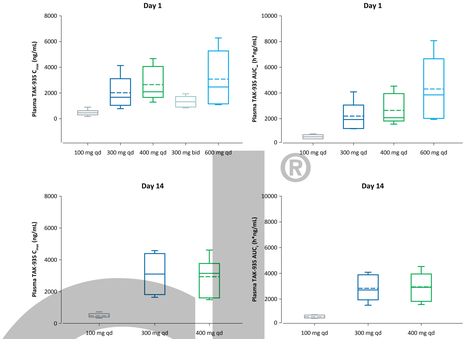
bid, twice daily; conc., concentration; LLOQ, lower limit of quantification; qd, once daily.

Figure 2. Mean Plasma Concentration-Time Profiles of M-I After Single and Multiple Dose Administrations



bid, twice daily; conc., concentration; LLOQ, lower limit of quantification; qd, once daily.

Figure 3. C_{max} and AUC of TAK-935 After Single and Multiple Dose Administrations

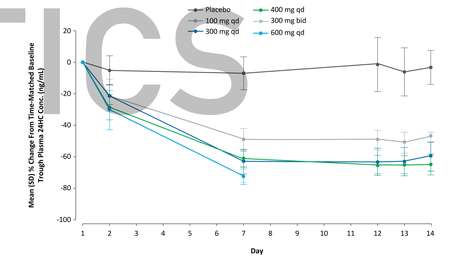


AUC_{τ}, area under the plasma concentration-time curve to infinity; AUC_{τ}, area under the plasma concentration-time curve for dosing interval; bid, twice daily; C_{max}, maximum observed plasma drug concentration; qd, once daily.

PD Results

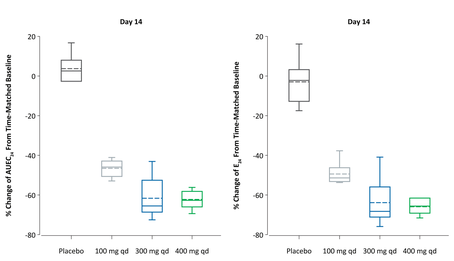
- After multiple-dose administrations of 100 mg qd, 300 mg qd, 400 mg qd, 300 mg bid, and 600 mg qd of TAK-935, a generally dose-dependent decrease in plasma 24HC concentrations was observed, with more profound decreases at higher doses (**Figure 4**).
- Plasma 24HC inhibition appeared to approach steady state on day 7 after multiple-dose treatment.
- Time-matched percent change in 24HC $AUEC_{24}$ (area under the effect-time curve from time 0 to 24 hours) and E_{24} (observed effect at 24 hours) showed a decreasing trend on day 14, ranging from 46.82% to 62.66% for $AUEC_{24}$ and from 49.11% to 65.59% for E_{24} across the doses of 100 to 400 mg qd (**Figure 5**).

Figure 4. Mean Time-Matched Percent Change From Baseline in Trough Plasma 24HC Concentration-Time Profiles of TAK-935 After Multiple Dose Administrations



24HC, 24S-hydroxycholesterol; bid, twice daily; conc., concentration; qd, once daily; SD, standard deviation.

Figure 5. Time-Matched Percent Change From Baseline in $AUEC_{24}$ and E_{24} After Multiple Dose Administrations



$AUEC_{24}$, area under the effect-time curve from time 0 to 24 hours; bid, twice daily; E_{24}, observed effect at 24 hours; qd, once daily.

Safety Results

- Multiple rising doses of TAK-935 up to 400 mg qd for 14 days were generally safe and well tolerated.
- There were a total of 45 treatment-emergent AEs (TEAEs) reported in 14 of the 30 TAK-935–dosed subjects (46.7%). Thirty-one of the events reported in 13 subjects (43.3%) were considered related to TAK-935, and 14 were considered unrelated. The majority of the TAK-935–related TEAEs were reported in the nervous system disorder SOC and the psychiatric disorders SOC (MedDRA system organ classes). The majority of TEAEs were of mild intensity and were reported in 12 TAK-935–dosed subjects.
- All reported TEAEs during the entire study resolved without treatment before study exit on day 15.
- No deaths or other serious AEs occurred in this study.
- There were 2 AEs in 2 subjects that led to study drug discontinuation.
  - The first TEAE that led to study drug discontinuation was an event of mental confusion of mild intensity that occurred in a subject receiving TAK-935 300 mg bid.
  - The second TEAE that led to study drug discontinuation was an event of acute psychosis of severe intensity that occurred in a subject receiving TAK-935 600 mg qd.
  - As a result, dosing in the remaining subjects in the TAK-935 600 mg qd cohort and the TAK-935 300 mg bid cohort was stopped on day 11. The subsequent cohort completed the planned dosing through study day 15 at a lower dosing of 400 mg qd and with the implementation of additional safety monitoring measures and stopping rules.

Conclusions

- TAK-935 was safe and well tolerated after once-daily doses up to 400 mg for 14 days in healthy subjects.
- The subjects were started on the target dose in this MRD study without up-titration. In order to maximize safety and tolerability, patients will be up-titrated to the target dose in future studies.
- Exposure to TAK-935 showed a slightly greater than dose-proportional increase over the dose range of 100 to 400 mg qd.
- Plasma 24HC concentrations generally decreased with increasing TAK-935 doses.

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