- **EudraCT ID**: 2020-000777-24
- **Takeda Study ID**: TAK-994-1501
- **Product**: TAK-994
- **Protocol Title**: A Randomized, Double-Blind, Placebo-Controlled, Multiple Rising Oral Dose Study to Evaluate the Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of TAK-994 in Patients With Narcolepsy With or Without Cataplexy (Narcolepsy Type 1 or Narcolepsy Type 2)
- **Trial Status**: Prematurely Ended
- **Rationale**: A safety signal emerged in Phase 2 studies of TAK-994. As an immediate precautionary measure, Takeda has suspended dosing of patients and has decided to stop Phase 2 studies early.
- **Actual enrolled**: Part A: 58; Part B: 154; Part C: 2; Part D: 37
- **Subject Disposition**

In Part A, a total of 58 subjects signed the informed consent form; 36 were not randomized due to screen failure. Fourteen subjects failed screening because of the HLA genotype or OX-1 level not being acceptable to qualify for Part A. Other reasons for screen failures included: liver enzyme levels higher than permissible, high BP, abnormal vital sign parameters, failed urine drug and alcohol test, history of cancer, a medical disorder other than narcolepsy associated with EDS, bleeding disorder, subject not willing to discontinue NT1 medications or other excluded medication, poor peripheral venous access, withheld consent, compliance issue about smoking, and not having confirmed diagnosis of NT1 per ICSD-3 criteria.

In Part A, a total of 22 subjects were randomized and received at least 1 dose of study drug. A total of 7 subjects received placebo, 7 subjects received TAK-994 low dose BID, and 8 subjects received TAK-994 high dose BID.

In Part B, a total of 154 subjects signed the informed consent form; 81 subjects were not randomized due to screen failure. The most frequent reasons for screen failure were not meeting the eligibility criteria and termination of the study by the sponsor.

In Part C, a total of 2 subjects were randomized and received at least 1 dose of study drug. Both subjects received TAK-994 High dose twice daily, and no subjects received placebo. No subjects completed Part C of the study. One subject was discontinued from study drug on Day 2 due to BP increase that met the discontinuation criteria of the protocol. The other subject discontinued on Day 18 due to the study prematurely ending.

For Part D, a total of 37 subjects signed the informed consent form; 9 subjects were not randomized due to screen failure. The most frequent reason for screen failure was not meeting the eligibility criteria.

A total of 28 subjects were randomized and received at least 1 dose of study drug in Part D: 11 subjects received placebo, 7 subjects received TAK-994 low dose BID, and 10 subjects received TAK-994 High dose BID.

- **Baseline Characteristics**

For Part A, overall mean age was 34.2 years; there were 11 men and 11 women. All subjects were non-Hispanic; among those, 11 were white, 4 were Black or African American, 6 were Asian (Japanese), and 1 was not reported. Overall median height was 169.60 cm, weight was 79.00 kg, and BMI was 28.00 kg/m^2. Overall, mean average sleep latency was 3.45 minutes, ESS score was 18.0, and WCR was 16.8.

In Part B, the overall mean age was 30.8 years; there were 31 males and 42 females. Sixty-eight subjects were non-Hispanic, 2 were Hispanic or Latino, 1 was unknown, and 2 were not reported. Of the 73 total subjects, 41 were white, 16 were Asian, 8 were Black or African American, 2 were multiracial, and 6 were not reported. Overall median height was 170.70 cm, weight was 78.60 kg, and BMI was 27.00 kg/$m^{2.}$ Overall, mean average sleep latency was 5.8 minutes, ESS score was 17.5, and WCR was 14.40.

Part C included one male, aged 52, and one female, aged 25. Both subjects in the China-specific study were Asian. In Part D, the overall mean age was 31.4 years; there were 7 males and 21 females. Twenty-five subjects were non-Hispanic and 3 were Hispanic or Latino. Nineteen subjects were white, 4 were Asian, 4 were Black or African American, and 1 was not reported. Overall median height was 167.70 cm, weight was 66.65 kg, and BMI was 23.60 kg/$m^{2.}$ Overall, mean average sleep latency was 6.5 minutes and ESS score was 17.6.

- **Full Data Analysis**

Due to long-term follow-up of patients with serious hepatic safety events, database lock and full data analyses were significantly delayed. Analysis of the totality of data continues as does investigation of contributing factors to safety events and benefit/risk analysis of TAK-994. To allow the totality of the safety and efficacy data to be evaluated, and avoid any impact to its scientific integrity, full data will be posted by November 2023.

Update November 2023:

Due to the early termination of the study, the prespecified sample size at week 4 was not reached, therefore the pre-planned analyses cannot be adequately interpreted.