Evaluation of Cardiac Safety Profile of ALKS 2680 in Healthy Participants: Concentration-QTc Relationship of ALKS 2680

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INTRODUCTION

- ALKS 2680 is a highly potent, oral, selective orexin 2 receptor agonist being developed as a once-daily treatment for narcolepsy and idiopathic hypersomnia (IH)[1,2]
- In a phase 1 study, ALKS 2680 increased mean sleep latency in patients with narcolepsy type 1, narcolepsy type 2, and IH and was generally well tolerated in these patients and non-sleep–deprived healthy volunteers[3,4]
- Cardiac safety is an important consideration for drugs in clinical development[5] and is particularly important for patients with narcolepsy, who are known to have greater cardiovascular comorbidities than those without narcolepsy[6,7]
- New drugs are evaluated for their effects on the heart rate (HR)-corrected QT interval (QTc),[8,9] as prolongation of the QT interval increases the risk of torsades de pointes, a potentially life-threatening arrhythmia.[10] The QT risk may be evaluated by concentration-QTc (C-QTc) analysis[11]

OBJECTIVES

- To assess the effects of ALKS 2680 on the QTc interval using the Fridericia method (QTcF)
- To assess the effects of ALKS 2680 on other electrocardiogram (ECG) parameters, including HR and cardiac conduction (PR and QRS intervals)

METHODS

STUDY DESIGN

- The cardiac profile of ALKS 2680 was evaluated in a phase 1, randomized, double-blind, placebo-controlled study that enrolled adults aged 18-65 years
  - In the single ascending dose (SAD) regimen, 56 healthy participants were enrolled (6 treated with ALKS 2680 and 2 treated with placebo in each of 7 dose cohorts); doses ranged from 1-50 mg powder-in-capsule (PIC) and nanosuspension formulations
  - In the multiple ascending dose (MAD) regimen, 32 healthy participants were enrolled (6 treated with ALKS 2680 and 2 treated with placebo in each of 4 dose cohorts); doses ranged from 3-25 mg PIC formulations
    - One participant enrolled in the MAD regimen discontinued the trial after Day 1 treatment and was not included in the ECG analysis
- Up to 10 replicate 12-lead ECGs were extracted from Holter recordings[12] and paired with time-matched pharmacokinetic data collected in the SAD regimen and the double-blinded cohorts of the MAD regimen
  - Early precision QT analysis[13] was performed on all analyzable beats in the ECG replicates

ENDPOINTS

- Primary: Model-derived placebo-corrected change-from-baseline (ΔΔ) QTcF
- Secondary:
  - ΔΔQTcF from the by-time-point analysis
  - Change-from-baseline (Δ) HR, PR, and QRS intervals, which were used as the dependent variables for the calculation of model-derived ΔΔHR, ΔΔPR, and ΔΔQRS, respectively, for the by-time-point analysis
  - Categorical outliers for QTcF, HR, PR, and QRS

DATA ANALYSIS

- For all continuous ECG parameters, baseline was defined as the average of the measured ECG intervals from the 3 ECG time points recorded pre-dose (-45, -30, and -15 minutes) on Day 1 for SAD and MAD, separately
- The QT interval was corrected for HR using Fridericia's correction (RR = RR interval of the ECG):
  - $QTcF\ (ms) = QT\ (ms)/[RR\ (ms)/1000]^{1/3}$
- ECG parameters
  - Δ for ECG parameters (including QTcF, HR, PR, and QRS): difference between the post-baseline value and its corresponding baseline value
  - ΔΔ for ECG parameters: difference in ΔECG values between active dose regimen and placebo
- By-time-point analysis:
  - Descriptive analysis and statistical modeling (using a linear mixed-effects model) on the ΔQTcF interval were used to calculate least squares (LS) mean and 2-sided 90% CI for each active dose and pooled placebo at each post-baseline time point
  - LS mean difference of ΔQTcF between each active group and placebo (ie, ΔΔQTcF), with 2-sided 90% CI, was also calculated at each post-baseline time point
- C-QTc analysis
  - ΔΔQTcF was used for the model-predicted effect across concentrations at a population level
  - The relationship between ΔQTcF and plasma concentrations of ALKS 2680 was quantified using a linear mixed-effects modeling approach
    - Dependent variable: ΔQTcF
    - Explanatory variable: plasma concentrations of ALKS 2680 (0 for placebo)
    - Fixed effects: study treatment (active = 1 or placebo = 0) and time (ie, post-baseline time point)
    - Additional covariate: centered baseline QTcF (ie, baseline QTcF for an individual participant minus the population mean baseline QTcF for all participants)

RESULTS

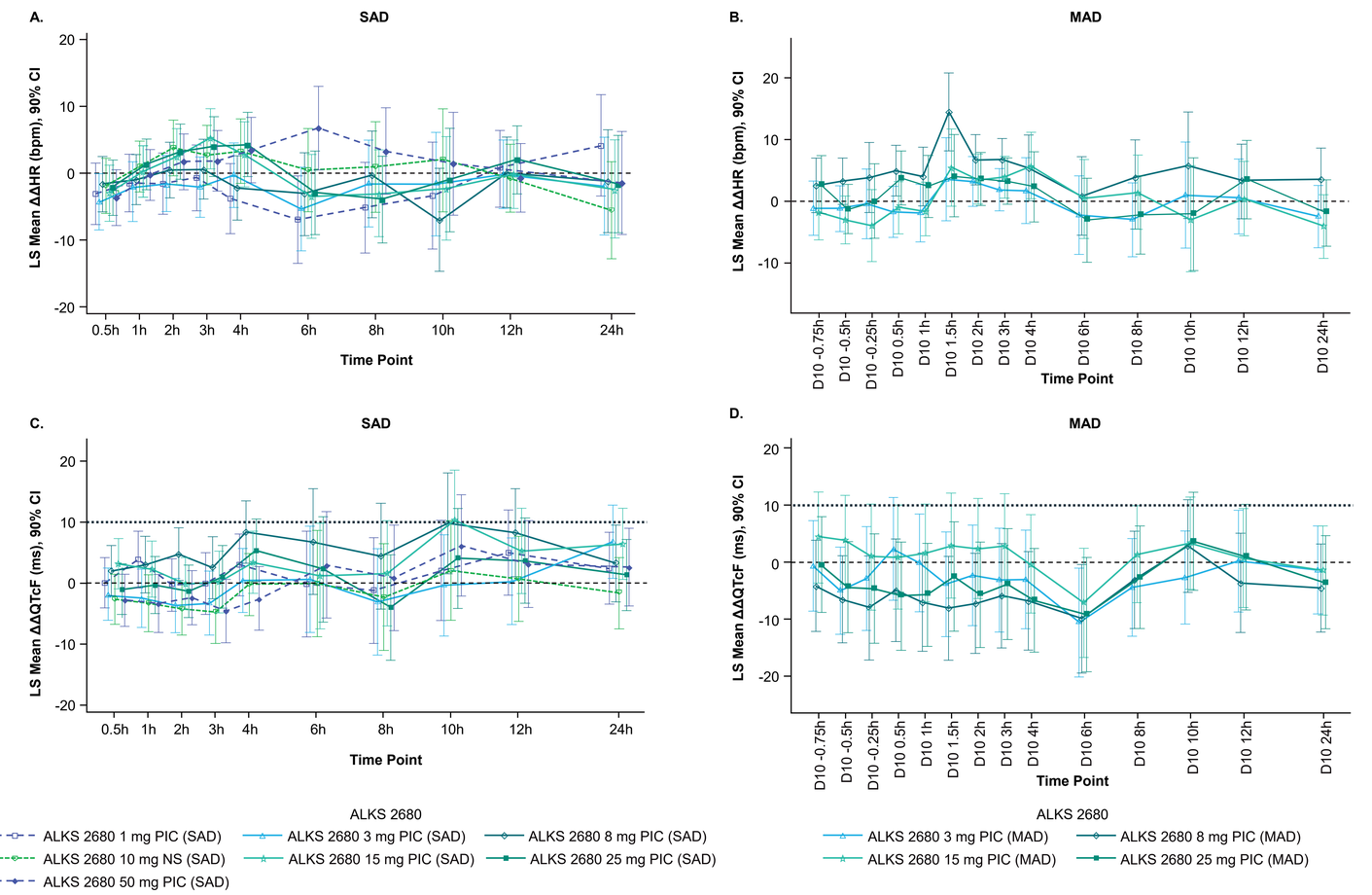
TABLE 1: By-Time-Point Analysis for ΔΔHR and ΔΔQTcF[a]

	SAD (10 mg NS)	MAD (25 mg PIC)
ΔΔHR, bpm	-5.5 to 3.8[b]	-3.0 to 4.2[c]
ΔΔQTcF, ms	-4.8 to 2.1[d]	-9.2 to 3.6[e]

[a]Dose groups included are those with the highest plasma concentration for each dose regimen. [b]Minimum at 24 hours post-dose, maximum at 2 hours post-dose. [c]Minimum at 6 hours post-dose, maximum at 1.5 hours post-dose. [d]Minimum at 3 hours post-dose, maximum at 10 hours post-dose. [e]Minimum at 6 hours post-dose, maximum at 10 hours post-dose.
ΔΔ = placebo-corrected change-from-baseline; bpm = beats per minute; HR = heart rate; MAD = multiple ascending dose; NS = nanosuspension; PIC = powder-in-capsule; QTcF = corrected QT interval using Fridericia's formula; SAD = single ascending dose.

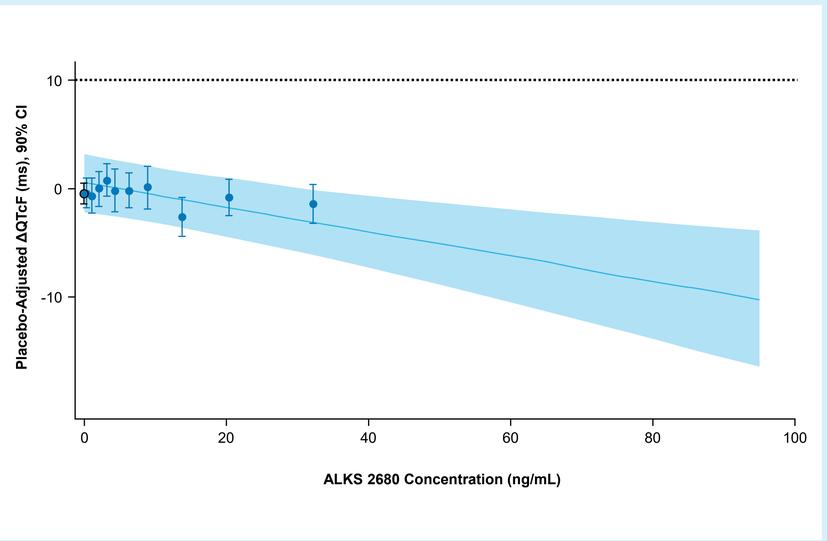
- In the analysis of data pooled from SAD and MAD, the C-QTc relationship was slightly negative at -0.113 ms per ng/mL (90% CI, -0.179 to -0.047; **Figure 2**)
- An effect on ΔΔQTcF exceeding 10 ms can be excluded up to a plasma concentration of ~94.4 ng/mL (**Figure 2**)
- At the studied doses, ALKS 2680 did not have a clinically relevant effect on cardiac conduction
  - No clinically relevant effects on ΔΔPR and ΔΔQRS intervals were observed in the by-time-point analysis

FIGURE 1: LS Mean ΔΔHR (A, B) and LS Mean ΔΔQTcF (C, D)[a] at Each Time Point for SAD and MAD Cohorts



LS mean ΔΔHR and LS mean ΔΔQTcF with 90% CIs for each were based on a linear mixed-effects model: ΔHR = Treatment + Time + Treatment × Time + Baseline HR. ΔQTcF = Treatment + Time + Treatment × Time + Baseline QTcF. An unstructured covariance structure was used to specify the repeated measures (time within participant).
[a]A ΔΔQTcF of less than 10 ms indicates an absence of a clinically meaningful increase in the ΔΔQTcF.
ΔΔ = placebo-corrected change-from-baseline; bpm = beats per minute; HR = heart rate; LS = least squares; MAD = multiple ascending dose; NS = nanosuspension; PIC = powder-in-capsule; QTcF = corrected QT interval using Fridericia's formula; SAD = single ascending dose.

FIGURE 2: Model-Predicted ΔΔQTcF (Mean and 90% CI) and Estimated Placebo-Adjusted ΔQTcF[a] (Mean and 90% CI) Across ALKS 2680 Plasma Concentrations (SAD and MAD Pooled Data)



Individually estimated placebo-adjusted $\Delta QTcF_{i,k}$ equals the individual $\Delta QTcF_{i,k}$ for participant $_i$ administered with ALKS 2680 at time point $_k$ minus the estimation of time effect at time point $_k$. The black circle with vertical bars denotes the mean placebo-adjusted ΔQTcF with 90% CI for placebo at a concentration of 0. The blue-filled circles with vertical bars denote the estimated mean placebo-adjusted ΔQTcF with 90% CI displayed at the associated median plasma concentration within each decile for ALKS 2680. The solid blue line with blue shaded area denotes the model-predicted mean ΔΔQTcF with 90% CI.
[a]A ΔΔQTcF of less than 10 ms indicates an absence of a clinically meaningful increase in ΔΔQTcF .
Δ = change-from-baseline; ΔΔ = placebo-corrected change-from-baseline; MAD = multiple ascending dose; QTcF = corrected QT interval using Fridericia's formula; SAD = single ascending dose.

CONCLUSIONS

- In healthy participants, the high-precision QT analysis confirmed no signal of QT prolongation for ALKS 2680 (up to 50 mg), including supratherapeutic exposures (~3-fold relative to the highest tested dose in phase 2)
- ALKS 2680 did not have a clinically relevant effect on HR or cardiac conduction in healthy participants

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Disclosures

JK, **AL**, **HC**, **BR**, and **IL** are employees and shareholders of Alkermes. **SY** was an employee of Alkermes during this study. **BD** is a consultant for and shareholder of Clario. **HX** is an employee of Clario.

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