2. SYNOPSIS

Name of Sponsor/ Company: Alkermes, Inc. **Name of Finished Product:** ALKS 6610 **Name of Active Ingredient:** selective, μ-opioid receptor partial agonist	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Study Title: A Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose (SAD) Study to Assess the Safety, Tolerability, Pharmacokinetics (PK), and Pharmacodynamics (PD) of ALKS 6610 with a Pilot Evaluation of Food Effect in Healthy Adult Subjects		
Study Center: This study was conducted at a single center in the Netherlands.		
Publications: As of the date of this clinical study report, the data from this study have not been published.		
Study Period: First subject's first visit: 21 Jan 2020 Last subject's last visit: 23 Oct 2020	**Phase of Development:** 1	

Primary Objective:

To evaluate the safety, tolerability, and PK of ALKS 6610 after single ascending oral doses in healthy adult subjects

Secondary Objectives:

- To evaluate the effects of ALKS 6610 on pupil diameter and the relationship between ALKS 6610 exposure and pupil diameter after single ascending doses
- To evaluate the PK/safety relationship between ALKS 6610 plasma concentrations and changes in blood pressure, heart rate, body temperature, and percent oxygen saturation or end-tidal carbon dioxide measurements
- To evaluate the PK/PD relationships with QTc interval changes, if any, following single oral doses of ALKS 6610
- To obtain preliminary information on the effect of a high-fat meal on ALKS 6610 PK after single oral doses in fed and fasted conditions

Exploratory Objectives:

- To explore the role of DNA sequence variability of P-glycoprotein (P-gp) and/or other genes on PK, safety, and PD.

Criteria for Evaluation:

Pharmacokinetics

The following PK endpoints were determined in plasma and urine for ALKS 6610 and its metabolite RDC-059525:

- The maximum plasma concentration observed (C_{max})
- Time to reach C_{max} (t_{max})

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- Time until first quantifiable concentration (t_{lag})
- The last quantifiable plasma concentration (C_t)
- The area under the concentration–time curve from zero time to 12 hours after dosing (AUC_{0-12})
- The area under the concentration–time curve from zero time to 24 hours after dosing (AUC_{0-24})
- The area under the concentration–time curve from zero time to time of last quantifiable concentration (AUC_t)
- The area under the concentration–time curve from zero time extrapolated to infinite time ($AUC_\infty = AUC_t + C_t / \lambda_z$)
- Terminal elimination rate constant (λ_z) with the respective half-life ($t_{½} = Ln(2) / \lambda_z$)
- The apparent total clearance following oral administration (for ALKS 6610 only) (CL/F)
- The apparent volume of distribution at terminal phase (for ALKS 6610 only) (V_z/F)
- The metabolite ratio (%) calculated as ratio of plasma AUC_∞ of metabolite (RDC-059525) to parent following molar correction
- The cumulative amount of ALKS 6610 excreted in urine up to 96 hours post-dose (A_e)
- Renal clearance of ALKS 6610 (CL_R)
- Percentage (%) of administered dose ALKS 6610 excreted in urine (f_e)
- The metabolite ratio (%) calculated as ratio of A_e of metabolite (RDC-059525) to parent following molar correction (MR_u)

Pharmacodynamics: Pupillometry was performed at the time points specified in the Schedule of Assessments.

Safety: Safety was assessed based on adverse event (AE) reports, vital signs measurements (systolic and diastolic blood pressures, pulse rate, respiratory rate, and temperature), pulse oximetry, capnometry, weight and height, physical examination findings, electrocardiography (ECG), continuous cardiac Holter monitoring, clinical laboratory parameters, the Columbia-Suicide Severity Rating Scale (C-SSRS), visual analog scales (VAS; alertness, mood, calmness), and the Pasero Opioid Induced Sedation Scale (POSS).

Methodology: Using a SAD design, the PK/PD part of the study employed 7 inpatient cohorts to administer the planned starting dose of 25 mg and a high dose of 1200 mg. In each cohort, 6 subjects received ALKS 6610 and 2 received placebo. At time points specified in the Schedule of Assessments, blood and urine samples were collected after each dose, and used to calculate the plasma and urine PK parameters specified above in the Criteria for Evaluation section.

Serial pupil/iris ratio measurements were done on Day 1 pre-dose, and after each dose of ALKS 6610.

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Before escalating to a higher dose level, a Safety Review Team assessed blinded safety, tolerability, PK (up to 24 hours plasma concentration data), and available PD data at the current dose.

In a separate part of the study, subjects enrolled in Cohort 3 (n=8) participated in a pilot food effect evaluation following at least a 7-day washout period after dosing in the SAD portion of the study

Number of Subjects: Fifty-six healthy volunteers were planned in 7 dose cohorts of 8 each (6 drug and two placebo in each cohort).

Safety Population: A total of 42 subjects received at least one dose of ALKS 6610, and 13 subjects received placebo.

PK Population: A total of 42 subjects received at least one dose of ALKS 6610.

Food Interaction Study Population: The PK population of the food interaction evaluation consisted of 6 subjects randomized to Cohort 3 who received at least 1 dose of study drug (ALKS 6610) and had sufficient PK data to derive at least one PK parameter.

Main Criteria for Subject Inclusion: Healthy males or females age ≥18 years and ≤60 years old at the time of informed consent, with body mass index ≥18 and <30 kg/m2 at Screening.

Study Treatment (Including Dose, Mode of Administration): Study drug was orally administered using capsule shells filled with ALKS 6610 drug substance with no additional excipients. Doses administered were 25, 75, 150, 225, 450, 825, and 750 mg. The capsules were filled by weighing the ALKS 6610 drug substance into the capsules prior to dosing. In total, 4 fill weights (25 mg, 75 mg, 150 mg, and 300 mg) of ALKS 6610 were manufactured, and the top three dose strengths were administered as multiple capsules of the highest fill weight.

Matching placebo was provided as capsules containing microcrystalline cellulose, identical in appearance to the study drug, but without the active ingredient (ALKS 6610).

Duration of Study: Including the Screening period, the duration of participation for each subject in Cohorts 1, 2, 4, 5, 6, and 7 was approximately 6 weeks. For Cohort 3 (the food effect cohort), the duration was approximately 7 weeks.

STATISTICAL METHODS

Descriptive statistics were provided for continuous variables including the N, mean, standard deviation (SD), median, minimum, and maximum. PK summaries also included geometric mean, and percent coefficient of variation (%CV, percentages to the mean and to the geometric mean where applicable). Descriptive statistics provided for categorical variables included subject counts and percentages. Data were summarized by dose group.

PK and/or PD: Pharmacokinetic parameters were calculated using a noncompartmental model and summarized using descriptive statistics by dose group. Dose proportionality of ALKS 6610 and RDC-059525 was assessed using the power model for AUC_{∞}, AUC_t, and C_{max} over the studied dose range (excluding the food effect cohort). The estimate (standard error) of intercept and slope and associated 90% and 95% confidence intervals (Cis) were reported. Dose effect on $t_{½}$ and t_{max} was assessed through a linear regression model and histogram, respectively. Point estimate and 90% CI for

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the geometric mean of $t_{½}$ were provided. For Cohort 3, a mixed effects model was used to evaluate the effect of a high-fat, high-calorie meal on the plasma PK of ALKS 6610 and RDC-059525. All individual subject-level data were presented as data listings.

Safety: Safety was evaluated based on the incidence of treatment-emergent AEs (TEAEs), including the incidence of serious AEs (SAEs) and TEAEs leading to discontinuation; clinical laboratory test (chemistry, hematology, coagulation, and urinalysis) results; vital signs measurements, including assessment for orthostatic hypotension; ECG findings; pulse oximetry and capnometry; clinical and self-reported questionnaires; and the C-SSRS.

The PK-safety relationship for capnometry ($etCO_2$) and pulse oximetry (SpO_2%) was assessed by integrating data across dose cohorts.

The PK/QT interval analysis was performed to explore the relationship between ALKS 6610 plasma concentrations and QT interval.

Sample Size Considerations: The sample size per dose level was not based on a formal statistical analysis. The sample size planned for this study (n=8 per cohort, including 6 active and 2 placebo) was consistent with the number of subjects typically enrolled in first-in-human dose-escalation study designs to evaluate initial safety, PK, and PD effects. For the food effect evaluation, 8 subjects (6 active, 2 placebo) were employed.

RESULTS SUMMARY

Subject Disposition and Baseline Characteristics: In total, 56 subjects were randomized. One subject who was randomized to the placebo group withdrew consent prior to dosing, and is not included in the Safety Population. A total of 55 subjects were randomized and received study drug in this study: 13 received placebo and 42 received ALKS 6610 (referred to as the All ALKS 6610 Group, and included 6 subjects in each of the 7 ALKS 6610 dose groups: 25 mg (Cohort 1), 75 mg (Cohort 2), 150 mg (Cohort 3), 225 mg (Cohort 4), 450 mg (Cohort 5), 750 mg (Cohort 7), and 825 mg (Cohort 6)). All 55 subjects completed the study.

SAFETY

- Overall ALKS 6610 was generally tolerated at all dose levels up to 750 mg, with mostly mild gastrointestinal TEAEs (Nausea and Vomiting). The highest dose tested of 825 mg was assessed as not tolerated, with 100% (6/6) of subjects experienced Nausea, and 66.7% (4/6) of subjects experienced Vomiting; 2 subjects in this cohort experienced moderate Vomiting. These events were considered dose-dependent.
- There were no SAEs, TEAEs leading to study discontinuation, or deaths in the study.
- TEAEs were reported in 53.8% (7/13) of subjects who received Placebo and 73.8% (31/42) of subjects who received ALKS 6610.
- All TEAEs were mild or moderate in severity; no TEAEs were assessed as severe.
- Most of the drug-related TEAEs that occurred in ≥2 subjects were experienced by a higher percentage of subjects in the All ALKS 6610 Group than subjects in the Overall Placebo Group. Drug-related TEAEs that occurred in ≥10% of subjects in the All ALKS 6610 Group included Nausea, Vomiting, Constipation, Dizziness, and Somnolence.
- TEAEs reported in the highest percentages of subjects in the All ALKS 6610 Group were Nausea (40.5%, 17/42) and Vomiting (26.2%, 11/42), followed by Somnolence (23.8%, 10/42), Dizziness and Headache (14.3% [6/42] each). No subjects experienced any of these TEAEs in the Overall Placebo Group.
- No clinically relevant trends were observed across ALKS 6610 treatment groups or between the All ALKS 6610 Group and the Overall Placebo Group in chemistry, hematology, and urinalysis laboratory values, and in vital sign parameters.
- There were no respiratory effects as assessed by SpO_2% and $etCO_2$.
- A possible dose-dependent mean increase from baseline in QTcF was observed, which was more apparent at the two highest doses, 750mg and 825mg, starting at about 1 hour post-dose until about 10 hours post-dose, and then returned to baseline values within 24 hours. The maximum mean QTcF change from baseline to 10 hours post dose was a 12.3 msec increase (at 3 hours postdose) in the 750 mg dose group, and a22.7 msec increase (at 10 hours postdose) in the 825 mg dose group.
- There were no clinically meaningful differences in sedation level across ALKS 6610 treatment groups and between the All ALKS 6610 and Placebo Groups, as assessed by the POSS. No clinically meaningful trends were observed in VAS Bond & Lader, as assessed by change from baseline across ALKS 6610 treatment groups, and between the All ALKS 6610 Group and the Overall Placebo Group.

PHARMACOKINETICS

- Following oral administration, ALKS 6610 was rapidly absorbed with a median t_{max} ranging from 2.250 to 3.500 hours. The metabolite RDC-059525 levels gradually reached peak concentrations at median t_{max} range of 4.000 to 6.000 hours.

- Dose proportional increases in both C_{max} and AUCs were observed for ALKS 6610 and RDC-059525 between 25 mg to 750 mg. No further increase in exposure was observed between 750 mg and 825 mg doses.
- ALKS 6610 was eliminated with a mean $t_{1/2}$ range of 9.785 to 15.940 hours and RDC-059525 was eliminated with a mean $t_{1/2}$ ranging from 8.900 hours to 13.294 hours (between 25 to 450 mg).
- High fat food reduced exposure of ALKS 6610 (powder-in-capsule formulation) by approximately 40%.
- The renal clearance of ALKS 6610 (fasted doses) was estimated to range from 20.646 L/h to 23.823 L/h. The % recovery was estimated to be 24.840% to 33.795%, suggesting renal elimination may be one of the prominent clearance pathways.

PHARMACODYNAMICS

- Dose-related and post-dose time-dependent changes in pupillometry parameters were observed at doses up to 450 mg.
- Doses higher than 450 mg did not produce additional changes in pupillometry parameters.

OVERALL CONCLUSIONS

Overall, ALKS 6610 was generally tolerated at 750 mg, with mostly mild gastrointestinal TEAEs (Nausea and Vomiting). The highest dose tested of 825 mg was assessed as not tolerated, with subjects experiencing TEAEs of Nausea and Vomiting; 2 subjects in this cohort experienced moderate Vomiting. These events were considered dose-dependent. There were no SAEs, TEAEs leading to study discontinuation, or deaths in the study.

TEAEs were reported in a greater proportion of subjects in the ALKS 6610 Group than in the Placebo Group. All TEAEs were mild or moderate in severity. Most of the drug-related TEAEs that occurred in ≥2 subjects were experienced by a higher percentage of subjects in the All ALKS 6610 than subjects in the Overall Placebo Group. Drug-related TEAEs that occurred in ≥10% of subjects in the All ALKS 6610 Group comprised Nausea, Vomiting, Constipation, Dizziness, and Somnolence.

No clinically relevant trends were observed across ALKS 6610 treatment groups or between the All ALKS 6610 Group and the Overall Placebo Group in chemistry, hematology, and urinalysis laboratory values, and in vital sign parameters. There were no respiratory effects as assessed by SpO2% and et CO_2. A possible dose-dependent mean increase from baseline in QTcF was observed, which was more apparent at the two highest doses, 750mg and 825mg, starting at about 1 hour post-dose until about 10 hours post-dose, and then returned to baseline values within 24 hours. The maximum mean QTcF change from baseline to 10 hours post dose was a 12.3 msec increase (at 3 hours postdose) in the 750 mg dose group, and a22.7 msec increase (at 10 hours postdose) in the 825 mg dose group.

There were no clinically meaningful differences in sedation levels, as assessed by the POSS. No clinically meaningful trends were observed in VAS Bond & Lader.

Following oral administration, ALKS 6610 was rapidly absorbed with a median t_{max} ranging from 2.250 to 3.500 hours, which remained similar across tested dose range. The metabolite RDC-059525 levels gradually reached peak concentrations at median t_{max} range of 4.000 to 6.000 hours.

Dose proportional increases in both C_{max} and AUCs were observed for ALKS 6610 and RDC-059525 between 25 mg to 750 mg. No further increase in exposure was observed between 750 mg and 825 mg doses potentially suggesting saturation of absorption process. ALKS 6610 was eliminated with a $t_{½}$ range of 9.785 to 15.940 hours, which remained comparable between 25 mg and 450 mg, suggesting non-saturation of elimination pathways over this dose range. Also, the observed $t_{½}$ of ALKS 6610 supports potential for once daily dosing. At 750 mg and 825 mg dose-levels, a mean $t_{½}$ of 27.223 and 23.891 hours, respectively, was observed, which could be due to high observed CV%. The CL/F of

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ALKS 6610 was similar (range of 65174 mL/h to 97253 mL/h) across the tested dose range. RDC-059525 was eliminated with a mean $t_{½}$ ranging from 8.900 hours to 13.294 hours over 25 mg to 450 mg. At the 750 mg and 825 mg dose levels, mean $t_{½}$ of 18.748 hours and 15.232 hours, respectively, were observed, which could be due to high observed CV%. Consistent with this observation, the CL/F of RDC-059525 was similar across the tested dose range with high %CV. The ratio of exposures of RDC-059525 (metabolite) to ALKS 6610 (parent) ranged from 11.574% to 62.116% across all doses tested, suggesting non-saturation of metabolism pathways of ALKS 6610 following single oral administration.

Administration of powder-in-capsule formulation of ALKS 6610 with high fat food reduced systemic exposure of ALKS 6610 by 40%, suggesting significant decrease in absorption of ALKS 6610. The observed decrease in the exposure of RDC-059525 (45%) was probably due to decreased availability of ALKS 6610 for metabolite formation. Consistent with preclinical observations, renal clearance suggested that renal excretion could play a prominent role in the elimination of ALKS 6610 and its metabolites.

Dose-related and post-dose time-dependent changes in pupillometry parameters were observed at doses up to 450 mg. Doses higher than 450 mg did not produce additional changes in pupillometry parameters.

Taken together, these results indicate that ALKS 6610 was generally tolerated at all dose levels up to 750 mg and further investigation is needed to assess once daily administration for pain management.

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