CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209830Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology Review

NDA #	209830
Related Past NDA's	207533
Brand Name:	ARISTADA INITIO
Generic Name:	Aripiprazole Lauroxil
Dosage Form:	Extended Release Nano-suspension formulation (AL-NCD)
Route of Administration:	Intra-muscular injection (gluteal or deltoid muscle)
Dosage Strength:	675 mg - single (b) (4) pre-filled syringe
Indications:	Treatment of Schizophrenia in adults
Applicant:	Alkermes
Submission Type:	Standard
Submission Date:	8/31/2017
PDUFA Date:	6/30/2018
OCP Review Team:	Praveen Balimane, Gopichand Gottipati, Kevin Krudys, Hao Zhu

Table of Contents

1 EXECUTIVE SUMMARY

Alkermes, Inc. has submitted an original New Drug Application (NDA) for ARISTADA INITIO (aripiprazole lauroxil) extended-release injectable nano-suspension (AL-NCD). ARISTADA INITIO will be provided in a single dose strength of 675 mg for administration as a starting dose to initiate ARISTADA treatment for schizophrenia or to re-initiate ARISTADA treatment following a missed dose of ARISTADA.

ARISTADA (aripiprazole lauroxil) is an injectable extended-release atypical antipsychotic developed by Alkermes for the treatment of schizophrenia and was approved by FDA on 10/5/2015. ARISTADA INITIO (NDA 209830) is a new formulation of aripiprazole lauroxil, a nano-suspension (AL-NCD), given as an intra-muscular injection. ARISTADA INITIO and ARISTADA predominantly differ in the particle size of aripiprazole lauroxil, the former in the nanometer range and the latter in the micrometer range. The reduced particle size of ARISTADA INITIO results in faster absorption and an earlier appearance of circulating aripiprazole compared to ARISTADA. Thus, ARISTADA INITIO may obviate the need for supplemental oral dosing of aripiprazole for 21 days.

Both oral aripiprazole and ARISTADA serve as the Listed Drugs (LD) for this NDA. The NDA submission is supported by 3 clinical pharmacology studies listed below. No additional clinical efficacy safety studies were conducted.

- ALK9072-B101: Single ascending dose safety, tolerability, PK study with different formulations of aripiprazole lauroxil nano-suspension (AL-NCD)
- ALK9072-B102: PK bridging study to demonstrate the adequacy of ARISTADA INITIO in obviating the need for supplemental oral dosing for aripiprazole for 21 days
- ALK9072-B103: Single dose safety, tolerability, PK study of ARISTADA INITIO in gluteal vs. deltoid muscle

Study ALK9072-B102 provides the pivotal PK bridging data to demonstrate the adequacy of ARISTADA INITIO in obviating the need for supplemental oral dosing of aripiprazole for 21 days per the current approved dosing regimen with ARISTADA. It was a randomized, double blind, PK study which compared the aripiprazole exposure when ARISTADA was initiated with ARISTADA INITIO and a single 30 mg dose of oral aripiprazole vs. the currently approved regimen of ARISTADA with 21 days of oral aripiprazole.

Our findings are summarized below:

- At the population level, the proposed dosing regimen of initiating ARISTADA with 675 mg of ARISTADA INITIO and a single oral dose of 30 mg of aripiprazole is anticipated to produce clinical response (i.e., effectiveness) similar to that obtained from the currently

approved regimen of ARISTADA with 21 days of oral aripiprazole. Aripiprazole exposures (i.e,, both Cmax and AUC0-28 days) were comparable between the proposed initiation regimen with ARISTADA INITIO and the currently approved initiation regimen.

- The proposed dosage initiation with ARISTADA INTIO is adequate for substituting for all approved dose levels of ARISTADA.

- The use of ARISTADA INITIO is acceptable for missed ARISTADA doses.

- Adequate PK bridging was established between ARISTADA INITIO and the listed drugs (i.e., oral aripiprazole and ARISTADA)

- ARISTADA INITIO is not recommended for use in patients who are known CYP2D6 poor metabolizers or are taking CYP modulators (strong inhibitors of CYP3A4 or CYP2D6 or inducer of CYP3A4).

- ARISTADA INITIO can be dosed to either gluteal or deltoid muscle.

- When initiating therapy, the 1st ARISTADA injection may be administered on the same day as ARISTADA INITIO or up to 10 days thereafter.

- ARISTADA INITIO and ARISTADA have unique and differing pharmacokinetic profiles and thus should not be used interchangeably.

- No evidence of dose dumping was observed in pharmacokinetic data collected from around 100 individual subjects across 3 different clinical trials.

1.1 Recommendation

The Office of Clinical Pharmacology has determined that there is sufficient clinical pharmacology information provided in the NDA package to support a recommendation of approval of ARISTADA INITIO. The acceptability of specific drug information is provided below.

Decision	Acceptable to OCP	Comment
Overall	Yes	Pending labeling agreement with the applicant
Evidence of	Yes	Based on PK-bridging

effectiveness and safety		
Proposed dose for adult patients	Yes	Based on PK-bridging
Labeling	Changes suggested	Pending satisfactory agreement with the applicant

1.2 Labeling Recommendations

The final labeling language is subject to change pending satisfactory agreement with the applicant.

1.3 Phase IV (PMR/PMC) Requirements/Commitments

No Phase IV studies are recommended.

Clarification:

The product is interchangeably referenced in different parts of the review as- ARISTADA INITIO, INITIO, extended-release injectable nano-suspension, NCD, and AL-NCD.

In earlier submission, the sponsor indicated ARISTADA INITIO as (b) (4) *However, they later revised it to a final strength of 675 mg. The agency agrees. Therefore, ARISTADA INITIO is* (b) (4) *675 mg throughout the review.*

2 QUESTION BASED REVIEW

2.1 Is the proposed dosage initiation with a single intramuscular dose of 675 mg of ARISTADA INITIO and a single dose of 30 mg oral aripiprazole and ARISTADA likely to be similar in efficacy and safety to the approved dosage initiation with ARISTADA and 21 days of oral aripiprazole? Is a single strength of 675 mg of ARISTADA INITIO adequate for all dose levels of ARISTADA and oral aripiprazole?

Yes. The proposed dosage initiation of ARISTADA with a single intramuscular dose of 675 mg of ARISTADA INTIO and a single dose of 30 mg oral aripiprazole is likely to produce similar efficacy and safety profiles to the approved dosage initiation with ARISTADA and 21 days of oral aripiprazole. Aripiprazole concentrations with ARISTADA INITIO regimen were generally similar with the exposures obtained following the approved dosage initiation (ARISTADA plus 21 days of oral aripiprazole) for the entire duration of the first month.

Study ALK9072-B102 provided the pivotal PK bridging data to demonstrate the adequacy of ARISTADA INITIO in obviating the need for supplemental oral dosing of aripiprazole for 21 days with ARISTADA (shown in Figure 1 below). It was a randomized, double blind, PK study which compared the aripiprazole exposure following initiation of ARISTADA with a single intramuscular injection of ARISTADA INITIO and a single dose of 30 mg oral aripiprazole vs. the currently approved regimen of ARISTADA with 21 days of oral aripiprazole. The following dosing regimens were used in the PK bridging study:

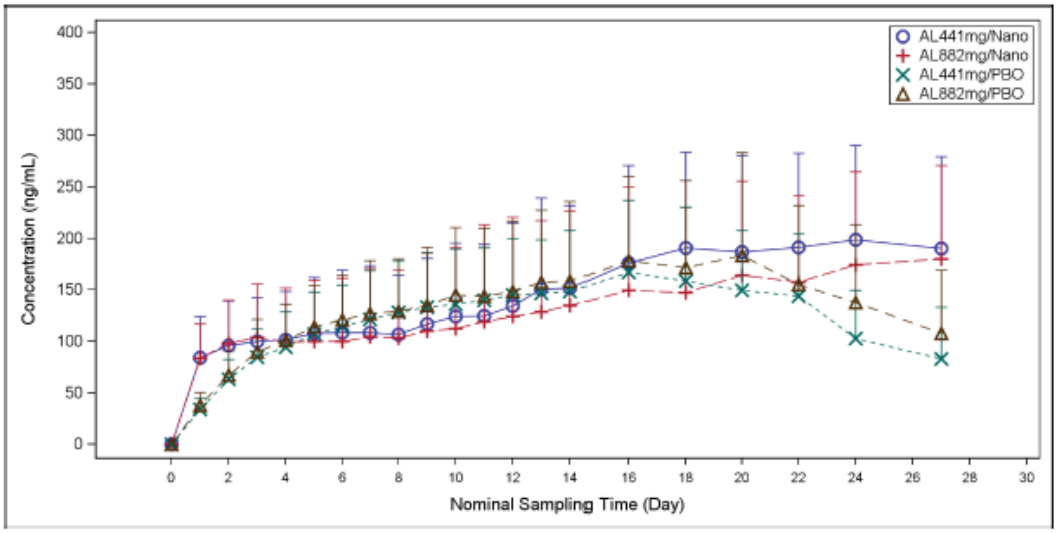
- ARISTADA INITIO arms ARISTADA INTIO at 675 mg, single oral aripiprazole dose of 30 mg and either 441 mg or 882 mg of ARISTADA.
- Approved dosage arms 21 days of oral aripiprazole at 15 mg/day and either 441 mg or 882 mg of ARISTADA.

The study demonstrated that initiation regimen with ARISTADA INITIO resulted in achievement of aripiprazole concentrations that (a) were similar to the concentrations achieved with the approved regimen of ARISTADA plus 21 days of oral regimen and (b) were within the range of aripiprazole concentrations (102 – 435 ng/ml) that were considered tolerable and effective, obtained from the approved oral aripiprazole dose range of 10 mg/day up to 30 mg/day (OCP review/NDA 207533/10-1-2015). The mean plasma aripiprazole concentrations over time overlapped across each of the initiation regimens through Day 21 (the last day of administration of oral aripiprazole in the oral initiation regimen). After Day 21, plasma aripiprazole concentrations persisted in each ARISTADA INITIO initiation regimen group, whereas plasma

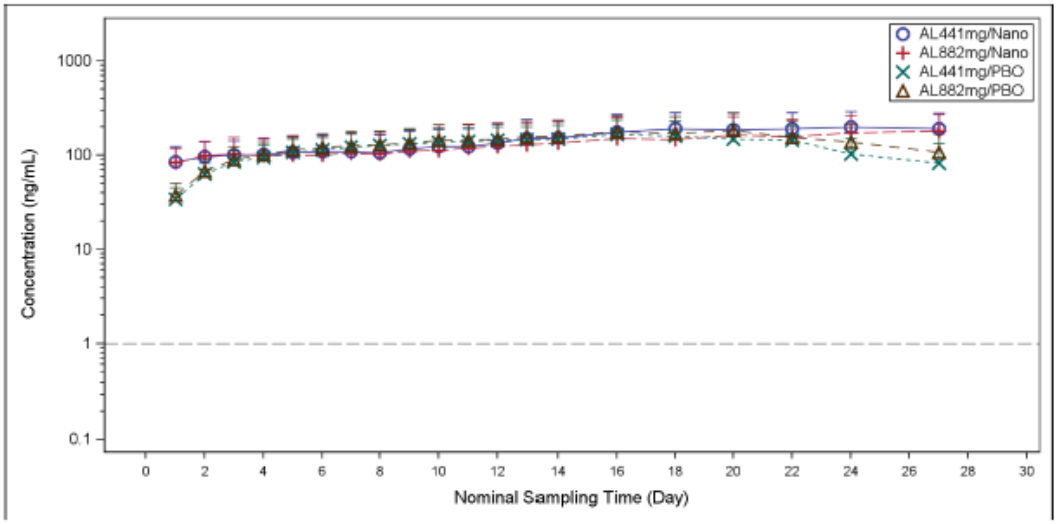
aripiprazole concentrations began to decline in each oral initiation regimen group. Mean aripiprazole concentrations in the initiation regimen with ARISTADA INITIO began to decline after Day 30, at an apparently less rapid rate as compared to the decline following the end of the oral initiation regimen (Figure 1). The ARISTADA INITIO initiation regimen could achieve aripiprazole concentrations that were tolerable and effective (i.e., >102 ng/mL; the mean steady state Cmin of aripiprazole following administration with the lowest approved 10 mg ABILIFY once/daily tablets—based on OCP review/NDA 207533/10-1-2015) within 4 days after treatment initiation. Additionally, it can also be noted that a larger proportion of subjects in each ARISTADA INITIO initiation regimen group had plasma concentrations >102 ng/mL as compared to each corresponding oral initiation regimen group by Day 4, as well as at the end on Day 28. This suggests that the initiation regimen with ARISTADA INITIO meets the intended exposure range similar to that of the approved initiation regimen with ARISTADA and 21 days of oral dosing.

Additionally, the initiation regimen with ARISTADA INITIO was well tolerated with a safety profile consistent with the known safety profile of the dosage initiation with ARISTADA plus 21 days of oral aripiprazole.

Figure 1: Mean (Standard Deviation) Plot of Aripiprazole Concentrations Over Time for the different Treatment Groups (ARISTADA INITIO regimen vs. approved ARISTADA regimen)



Semi-log Scale



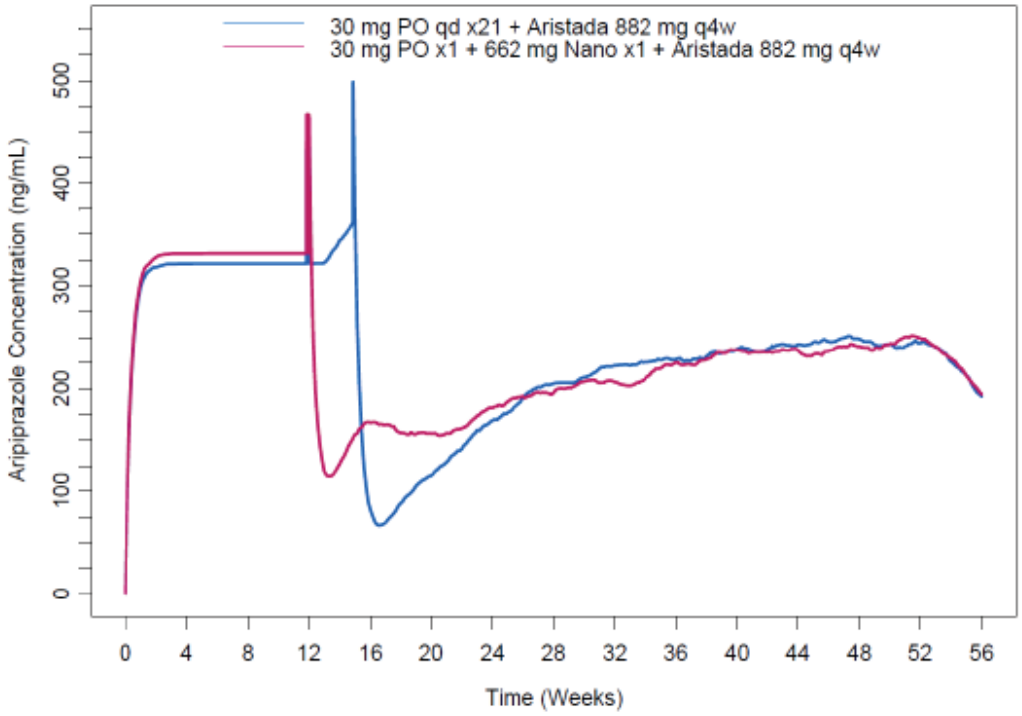
Legend: AL 441/Nano=30 mg oral aripiprazole on Day 1 followed by oral placebo for 20 days + AL-NCD 662 mg (gluteal) + 441 mg AL (deltoid) on Day 1.
AL 882/Nano=30 mg oral aripiprazole on Day 1 followed by oral placebo for 20 days + AL-NCD 662 mg (gluteal) + 882 mg AL (gluteal) on Day 1.
AL 441/PBO=15 mg oral aripiprazole for 21 days (Days 1-21) + placebo NCD IM injection (gluteal) + 441 mg AL (deltoid) on Day 1.
AL 882/PBO=15 mg oral aripiprazole for 21 days (Days 1-21) + placebo NCD IM injection (gluteal) + 882 mg AL (gluteal) on Day 1.

Source: Clinical study report ALK9072-B102 – Figure 3 on Page 55

In addition to the observed clinical data from Study ALK9072-B102, additional simulations were performed to demonstrate the adequacy of the proposed dosage initiation with 675 mg ARISTADA INTIO for patients transitioning from lowest approved oral ABILIFY dose of 10 mg/day all the way up to the highest approved oral ABILIFY dose of 30 mg/day (see detailed plots for all the relevant dose levels in the Appendix- section 3.2). Based on the similar aripiprazole exposures between the different arms (i.e., ARISTADA INITIO at 675 mg vs. 21 days of oral aripiprazole at 15 mg/day), Study ALK9072-B102 clearly demonstrates that the ARISTADA INITIO regimen is adequate for the lower dose levels of ABILIFY- 15 mg/day. The adequacy of the 675 mg ARISTADA INTIO for the higher oral daily doses of 30 mg/day was also assessed. Figure 2 below shows the comparison of aripiprazole concentrations achieved via ARISTADA INITIO regimen vs. approved ARISTADA regimen for patients switching from the highest approved oral ABILIFY dose of 30 mg/day.

The simulation was for patients on stable doses of 30 mg/day of oral aripiprazole who undergo the two switching strategies (a) patient gets IM ARISTADA 882 mg + continues to get 30 mg/day of oral aripiprazole for 21 days [already approved regimen] or (b) patient gets IM ARISTADA 882 mg + 30 mg oral aripiprazole + 675 mg *ARISTADA INITIO* [proposed dosing recommendation]. Steady state dosing was simulated with 30 mg/day oral aripiprazole for 12 weeks before simulating the 2 switching strategies. These regimens are shown in Figure 2 below. As expected, since the ARISTADA regimen continues with 21 days of oral dose of 30 mg/day, its exposure is higher than the exposures with ARISTADA INITIO regimen for the 3 weeks immediately after the switch (week 12-15 below). However, beyond the 3rd week (week 15 onwards), the exposures fall rapidly for the ARISTADA regimen (since oral dose is cleared rapidly and the exposure rise due to ARISTADA is slow), whereas the rapid rise in concentrations due to the nano-suspension formulation of ARISTADA INITIO leads to a sustained higher concentration from week 15 to week 24. Beyond week 24, the exposures are similar for both dosage initiation strategies. Though the exposures initially drop (week 12 to week 15) once the patients transition from oral to ARISTADA INITIO, the exposures are still higher than 102 ng/mL (established earlier as the lower limit of tolerable and effective aripiprazole concentration), and therefore better than the approved regimen of ARISTADA. Additionally, in short-term studies with acute schizophrenia patients, a lack of dose response has been noted with oral aripiprazole (ABILIFY label, flat dose-, or exposure-response from 10-to 30 mg; PK is dose-proportional). The lack of any dose (or exposure) based response in the past oral aripiprazole efficacy studies, suggests that exposure levels within the lowest and highest approvable dose levels of oral aripiprazole (i.e., 102 ng/mL for 10 mg/day to 435 ng/mL for 30 mg/day: OCP review/NDA 207533/10-1-2015) are likely to lead to similar efficacy and safety profile.

Figure 2: Median aripiprazole concentrations for subjects on a stable dose of 30 mg/day of oral aripiprazole that switch to ARISTADA 882 mg + continues to get 30 mg/day of oral aripiprazole for 21 days (blue line) or that switch to ARISTADA 882 mg + 30 mg oral aripiprazole + 675 mg *ARISTADA INITIO* (red line)



Note: Nano x1 refers to a single dose of AL-NCD

Source: Applicant's Response (dated 11/14/2017) to IR (dated 10/24/2017) Figure 4 on Page 7

Therefore, since exposure of aripiprazole with ARISTADA INTIO plus 30 mg oral aripiprazole and ARISTADA is likely to be similar to the approved dosage initiation with ARISTADA plus 21 days of oral aripiprazole, the applicant's proposed dosage regimen with ARISTADA INTIO is likely to yield efficacy and safety profiles similar to the already approved regimens of ARISTADA. The detailed plots demonstrating the adequacy of ARISTADA INTIO for initiating therapy with ARISTADA for all the relevant dose levels is presented in the Appendix (section 3.2)

2.2 Is ARISTADA INITIO suitable for use in patients who are known CYP2D6 poor metabolizers or taking CYP modulators (inhibitors of CYP3A4 or CYP2D6 or inducer of CYP3A4)?

No.

Since ARISTADA INTIO is available only in a single strength (i.e., fixed strength of 675 mg), it is not recommended for use in patients who are known CYP2D6 poor metabolizers or taking CYP modulators (inhibitors of CYP3A4 or CYP2D6 or inducer of CYP3A4). The aripiprazole exposures are anticipated to be very different when ARISTADA INITIO is administered to CYP2D6 poor metabolizers or in patients with concomitant use of a CYP2D6 inhibitor, a CYP3A4 inhibitor or a CYP3A4 inducer. For these patients, ARISTADA should be given with supplemental oral aripiprazole (and not ARISTADA INITIO).

Predicted plasma concentrations of aripiprazole in this patient sub-population (i.e., poor metabolizers of CYP2D6 or taking CYP modulators (inhibitors of CYP3A4 or CYP2D6 or inducer of CYP3A4) are shown below. The exposures for these patients are significantly different from the mean exposures in normal patients. As shown in Figure 3 - Figure 6, the simulations illustrate that CYP2D6 poor metabolizer (PM) status results in an approximately 2-fold increase in aripiprazole concentrations relative to non-PM subjects. As expected, simulations show that when co-administration with a strong CYP2D6 inhibitor, quinidine, CYP2D6 EM subjects demonstrated a similar extent of increase in aripiprazole concentrations. In addition to CYP2D6, CYP3A4 also contributes significantly to the metabolism of aripiprazole. Simulations illustrating co-administration with a strong CYP3A4 inhibitor resulted in an approximately 1.5-fold increase in mean concentrations of aripiprazole. In contrast, co-administration with rifampin, a strong CYP3A4 inducer, resulted in significantly lower aripiprazole concentrations that were below the levels for which the PK bridge to oral aripiprazole was established. Combinations of both CYP2D6 and CYP3A4 inhibitors or co-administration of a CYP3A4 inhibitor in the CYP2D6 PM subjects are expected to result in even higher plasma exposures of aripiprazole.

Figure 3 Predicted mean plasma concentrations of aripiprazole in CYP2D6 PM subjects (dotted lines) and non-CYP2D6 PM subjects (solid lines) administered the *ARISTADA INITIO* initiation regimen and once monthly ARISTADA doses of 441 mg (red lines), 662 mg (green lines) or 882 mg (blue lines).

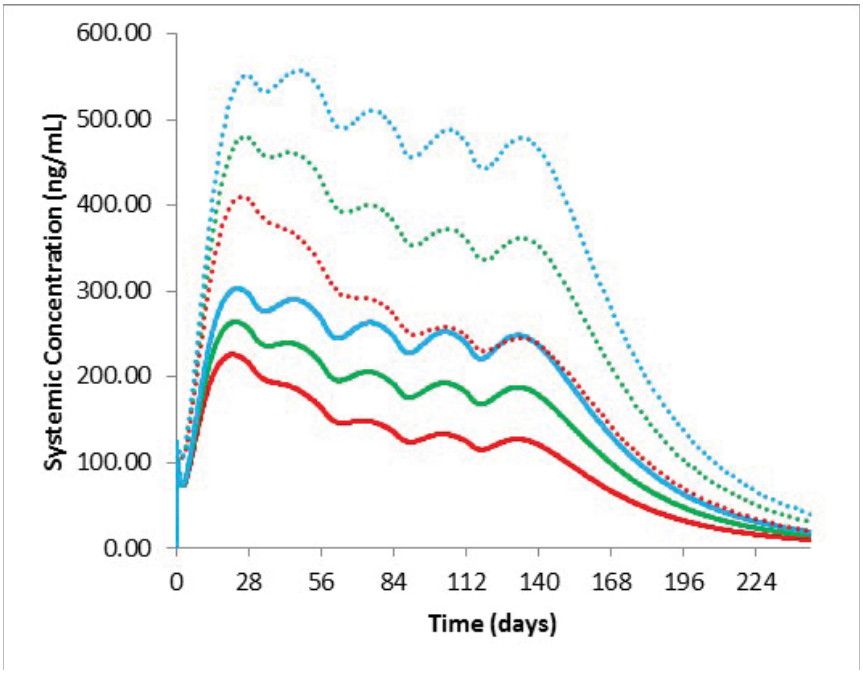


Figure 4 Predicted mean plasma concentrations of aripiprazole in CYP2D6 EM subjects administered the *ARISTADA INITIO* initiation regimen and once monthly ARISTADA doses of 441 mg (red lines), 662 mg (blue lines) or 882 mg (green lines) with (dotted lines) or without (solid lines) 200 mg BID dose of ketoconazole (strong CYP3A4 inhibitor)

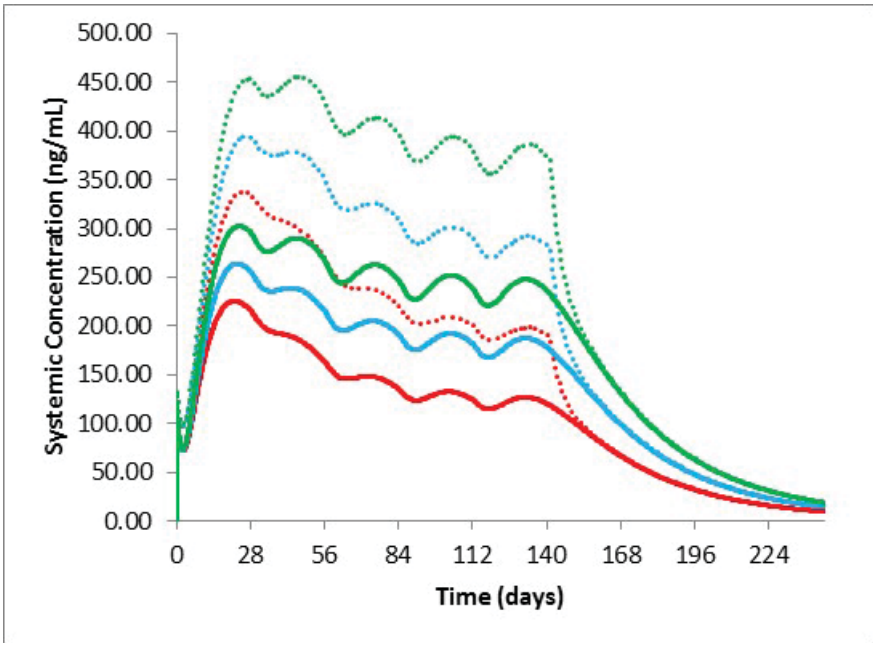


Figure 5 Predicted mean plasma concentrations of aripiprazole in CYP2D6 EM subjects administered the *ARISTADA INITIO* initiation regimen and once monthly ARISTADA doses of 441 mg (red lines), 662 mg (blue lines) or 882 mg (green lines) with (dotted lines) or without (solid lines) 200 mg QD dose of quinidine (strong CYP2D6 inhibitor)

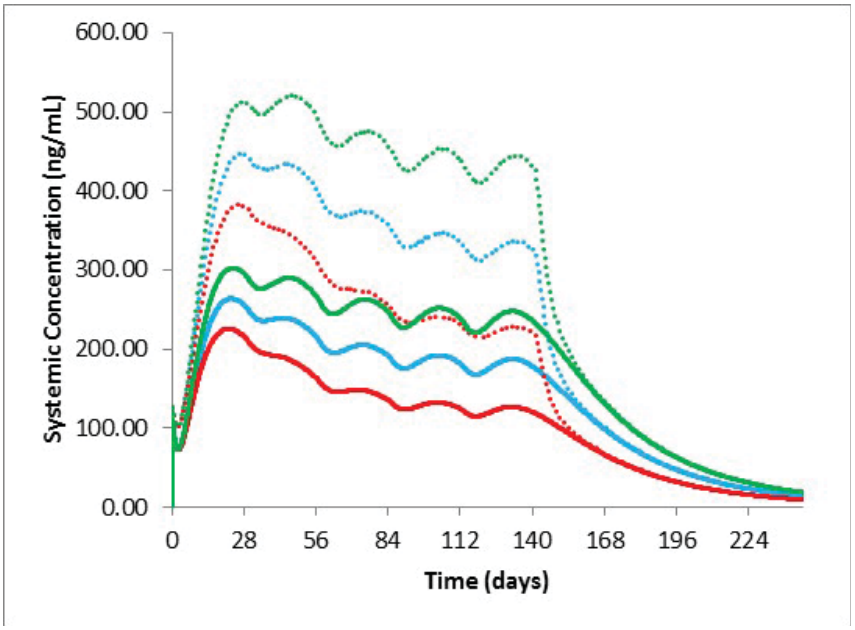
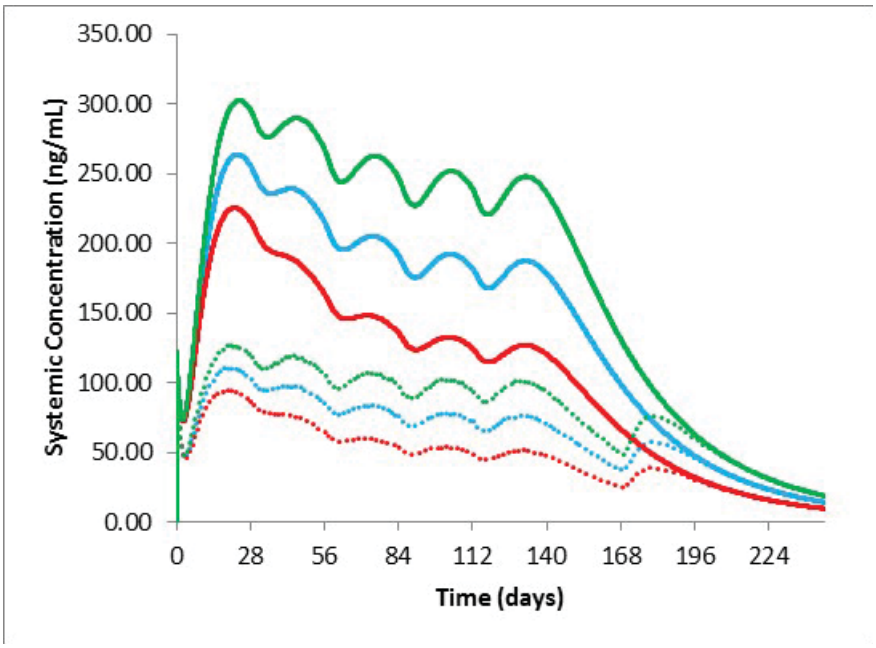


Figure 6 Predicted mean plasma concentrations of aripiprazole in CYP2D6 EM subjects administered the *ARISTADA INITIO* initiation regimen and once monthly ARISTADA doses of 441 mg (red lines), 662 mg (blue lines) or 882 mg (green lines) with (dotted lines) or without (solid lines) 600 mg QD dose of rifampin (strong CYP3A4 inducer)

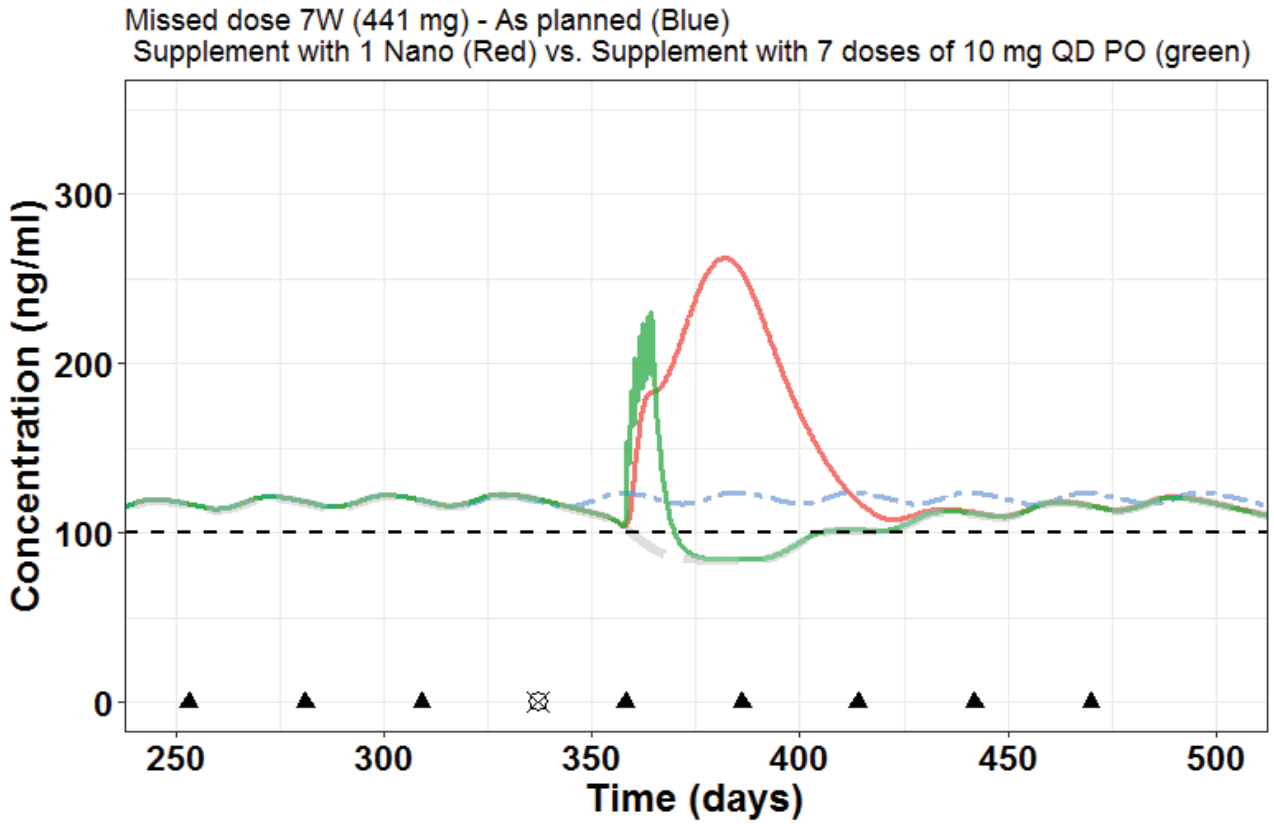


Since only a single strength for ARISTADA INITIO is available to the prescribing physicians, there is no opportunity for dose adjustments in patients who are either CYP2D6 PMs or those who require concomitant administration of drugs that are modulators of CYP2D6 or CYP3A4. Therefore, we agree with the proposed labeling language to use ARISTADA in conjunction with 21 days of oral aripiprazole as initiation rather than ARISTADA INTIO for these patients.

2.3 Is the applicant's proposed recommendation acceptable for use of *ARISTADA INITIO* when ARISTADA dose is missed?

Yes. The applicant performed simulations to support the recommendations under various scenarios of missed dosing (depending on the length of the time since last dose) and the review team agrees with these recommendations. It is worth noting that simulations show that supplementing with either single dose of ARISTADA INITIO or single dose each of ARISTADA INITIO and oral aripiprazole show more favorable aripiprazole profiles than supplementing with either 7 or 21 days of oral aripiprazole therapy respectively. For example, the expected aripiprazole profiles for the scenario when 441 mg ARISTADA dose was missed and the time since last dose is ≤7 weeks, the supplementation of ARISTADA with (a) single dose of ARISTADA INITIO or (b) 7 days of 10 mg of oral aripiprazole are shown in Figure 7. As described earlier, the aripiprazole concentrations following supplementation with ARISTADA INITIO remain higher compared to supplementation with 7 days of oral aripiprazole. This is a representative example of one of the scenarios, please refer appendix 3.3 (Figure 30 - Figure 33 representing reviewer's simulations for low and high monthly dosing scenarios) for more details

Figure 7 Scenario of missing 441 mg aristada lauroxil dose with 7 weeks or less since the last injection



Note: Dased blue line represents the scenario without missed dose (as reference);
solid green line represents the scenario of supplementation with 7 days of oral aripiprazole,
solid orange line represents the scenario of supplementation with single dose of ARISTADA INITIO ;
dashed grey line represents the scenario of no supplementation (i.e., administering aristada lauroxil alone)

At the bottom: Closed triangles at the bottom represent the doses of aristada lauroxil, while the circle with 'x' mark represents the missed dose

2.4 Was there any dose-dumping observed with ARISTADA INITIO in the clinical trials?

No.

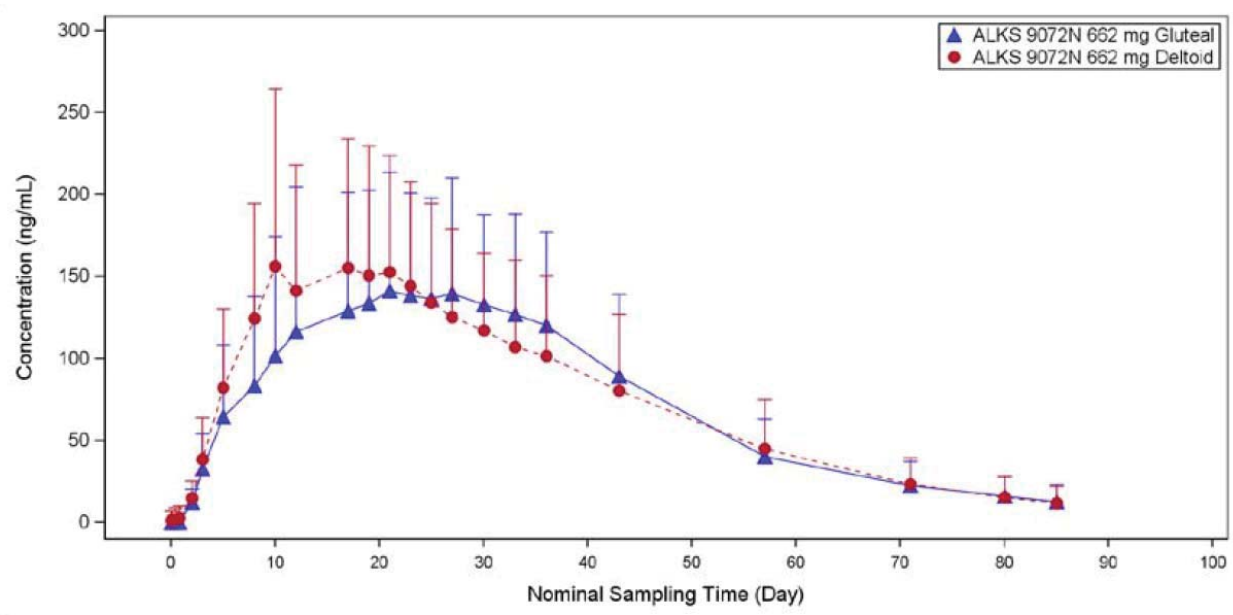
There was no evidence of dose-dumping in the clinical trials conducted with ARISTADA INITIO. A detailed assessment of the individual subject data for all subjects (N around 100) administered ARISTADA INITIO in all three trials (B101, B102 and B103) demonstrated that

none of the subjects in the PK trial showed any rapid or unexplainable rise in exposure of aripiprazole after the IM injection. The lack of any abrupt spikes in exposure of aripiprazole suggest that there was no dose-dumping or leakage after the ARISTADA INITIO injection. The overall lack of any new or unexpected safety findings with ARISTADA INITIO IM injection compared to the oral aripiprazole also suggests there were no dose-dumping. Additionally, the physiochemical properties of aripiprazole lauroxil (very limited solubility in aqueous solutions) also make it very unlikely that dose dumping into the systemic circulation is likely to occur in the clinic.

2.5 Can ARISTADA INITIO be dosed to either the gluteal or deltoid muscle?

Yes. Study ALK9072-B103 assessed the PK of ARISTADA INITIO after a single dose administration to deltoid or gluteal muscle in adults with Schizophrenia or Schizoaffective Disorder. The mean PK profiles of aripiprazole following the single IM injection to the deltoid or gluteal muscle, were similar as shown in Figure 8 below. The overall safety profiles are also similar when ARISTADA INITIO was administered in the deltoid or gluteal muscle, thus supporting the recommendation that ARISTADA INITIO can be dosed to either of the two injection sites.

Figure 8 Mean (SD) Aripiprazole Concentrations Over Time Following Deltoid or Gluteal Administration of ALKS 9072N 675 mg



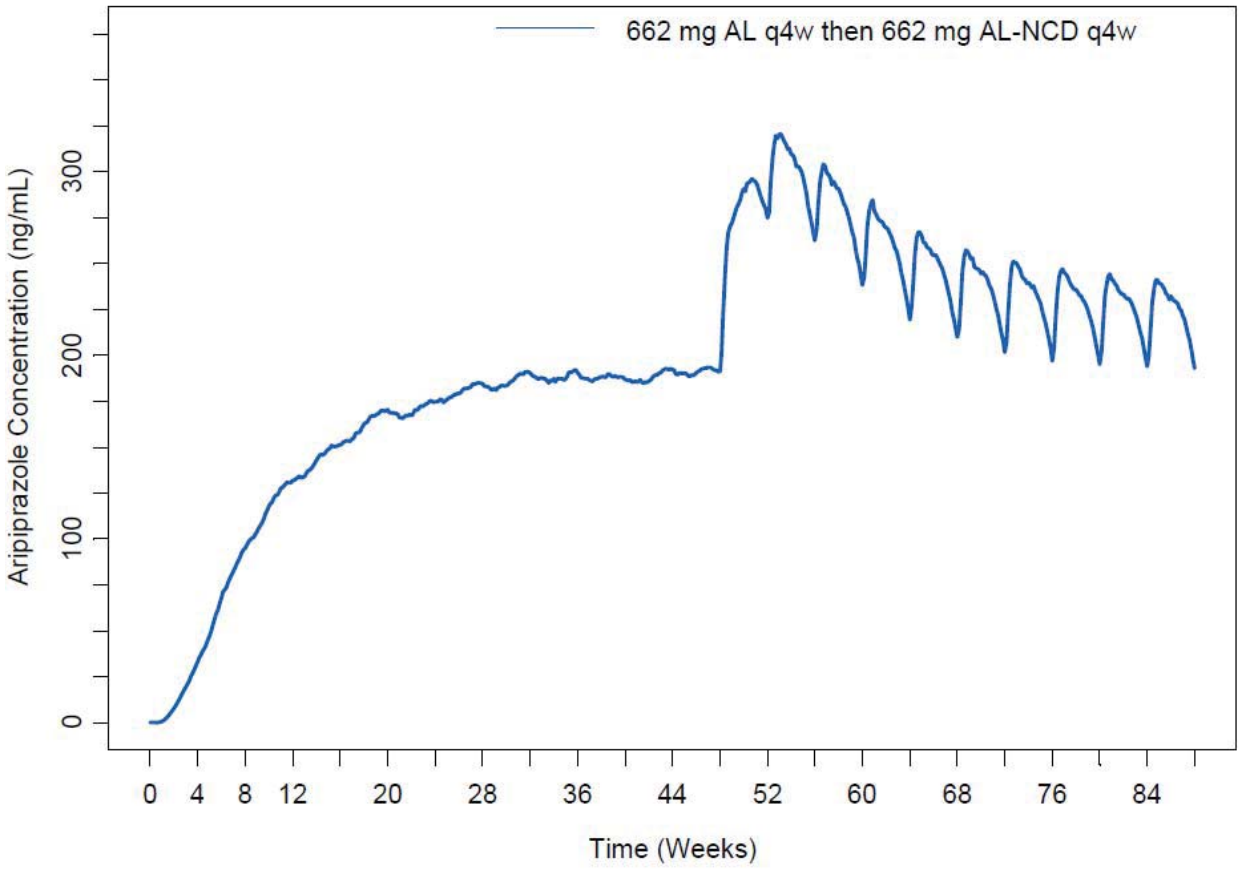
Source: Clinical study report ALK9072-B103 – Figure 2 on Page 42

2.6 What are some of the "clinically feasible scenarios" of erroneous dosing with ARISTADA INITIO and what are the corresponding aripiprazole exposures in such scenarios?

There are several clinical scenarios of potential erroneous dosing with ARISTADA INITIO. Each erroneous dosing scenario can lead to increased safety/tolerability concerns. Therefore, labeling language should be clear to avoid dosing errors. Some likely scenarios are listed below:

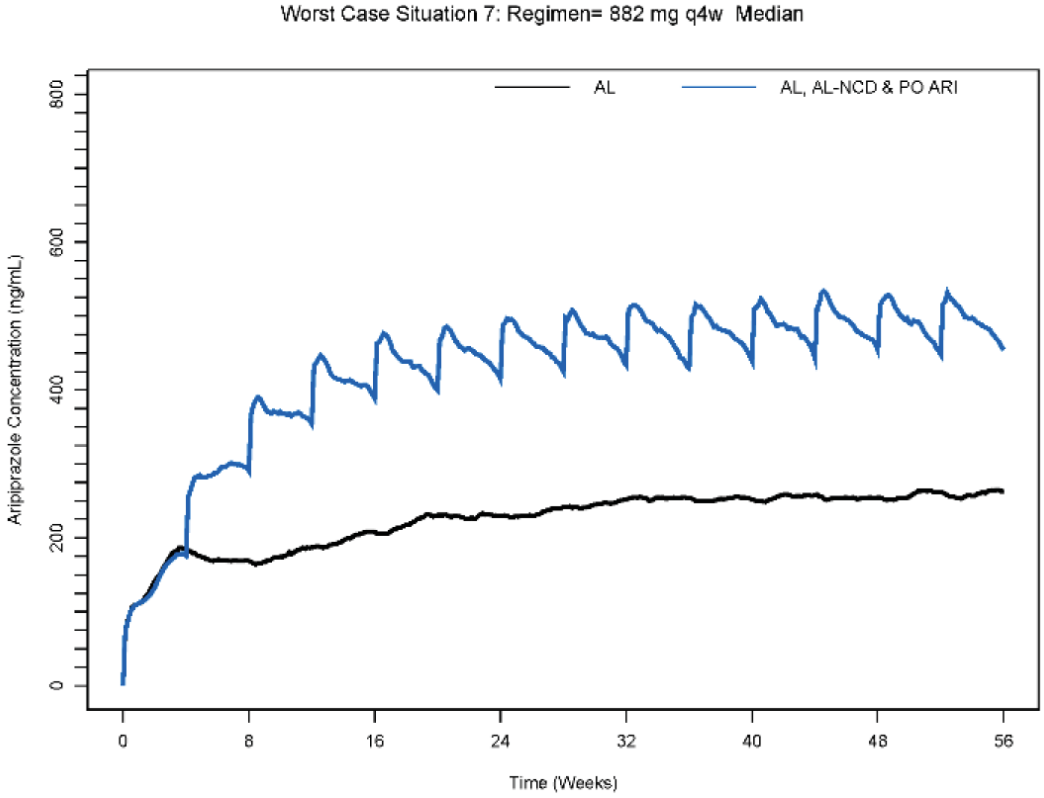
Scenario#1: Patients are on stable dose of 662 mg ARISTADA. They received 675 mg ARISTADA INITIO (instead of the correct 662 mg ARISTADA) on their monthly visits and erroneously continue getting the ARISTADA INITIO (675 mg/month) instead of ARISTADA (662 mg/month). Simulated aripiprazole concentrations illustrating a switch from monthly AL 662 mg to monthly ARISTADA INITIO 675 mg are provided in Figure 9 below. As expected, due to the more rapid release of aripiprazole from ARISTADA INITIO, concentrations of aripiprazole increase with ARISTADA INITIO administration as compared to the same dose of AL. The concentrations increase with monthly ARISTADA INITIO administration, though they do not exceed the upper end of the therapeutic range for oral aripiprazole, (435 ng/mL) based upon the mean Cmax at steady-state for a 30 mg oral dose (OCP review/NDA 207533/10-1-2015). Additionally, once a new steady-state is achieved for ARISTADA INITIO (675 mg/month), aripiprazole concentrations are higher than the steady state exposures with 662 mg ARISTADA and also demonstrate a higher peak-to-trough ratio which can lead to an increased safety/tolerability issue in patients.

Figure 9 Median aripiprazole concentrations for subjects on a stable dose of 662 mg ARISTADA monthly who subsequently receive monthly doses of ARISTADA INITIO 675 mg



Scenario#2: Simulations were conducted to evaluate the impact of administering the ARISTADA INITIO initiation regimen with every AL injection following treatment initiation (see **Figure 10** below). Thus, in this scenario, INITIO was administered every month in addition to ARISTADA instead of the recommended single dose of INITIO. As expected, administration of the ARISTADA INITIO initiation regimen alongside each AL dose resulted in increased aripiprazole concentrations compared to AL alone following treatment initiation. Additionally, the fluctuation in concentrations within a dosing interval was wider with INITIO treatments being administered rather than just AL alone. The predicted exposure levels when both INITIO and ARISTADA are administered every month are significantly higher than the exposures with ARISTADA only and can lead to significant safety/tolerability issues in the patients.

Figure 10 Median Simulated Aripiprazole Concentrations after Co-administration of AL and the ARISTADA INITIO Initiation Regimen at Every AL Dosing Occasion for 882 mg q4w.

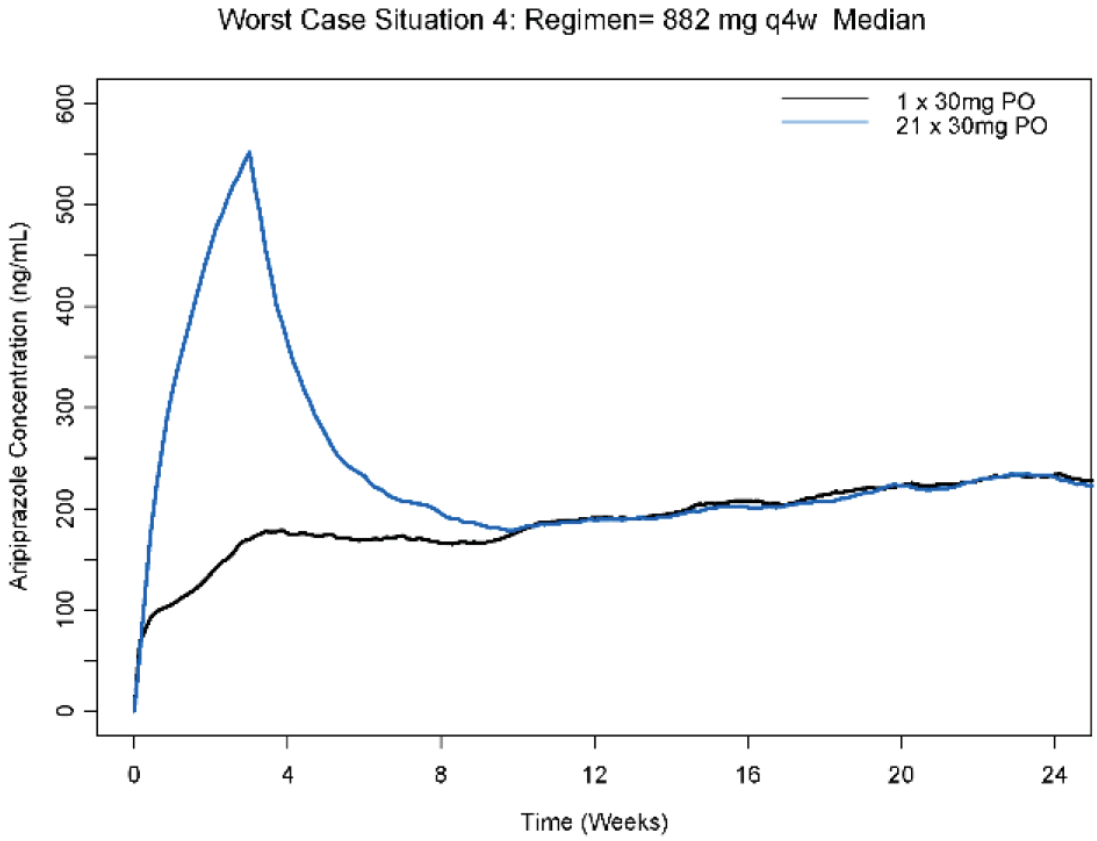


Source: Summary of clinical pharmacology: Table 19 on Page 77

Scenario#3: Simulations were performed to evaluate the impact of continued administration of 21-days oral aripiprazole when ARISTADA INITIO is administered in lieu of the recommended single oral aripiprazole dose (see **Figure 11** below). In this situation, an initiation regimen of 30 mg of oral aripiprazole was co-administered with ARISTADA INITIO for 21 days, rather than for 1 day. Median aripiprazole concentrations after co-administering ARISTADA INITIO with 21 days of 30 mg oral aripiprazole were substantially higher than the initiation regimen with 1 day of oral aripiprazole, and returned to nominal levels after 12 to 16 weeks of treatment. The predicted exposure levels can lead to significant safety/tolerability issues in the patients.

Figure 11 Median Simulated Aripiprazole Concentrations after Co-Administration of Oral Aripiprazole 30 mg for 1 and 21 Days with ARISTADA INITIO 675 mg for AL

882 mg q4w



Source: Summary of clinical pharmacology: Figure 31 on Page 74

2.7 Was adequate PK bridging established between ARISTADA INITIO and the listed drugs (i.e., oral aripiprazole and ARISTADA) and was the final to-be-marketed formulation of ARISTADA INITIO used in the key clinical studies?

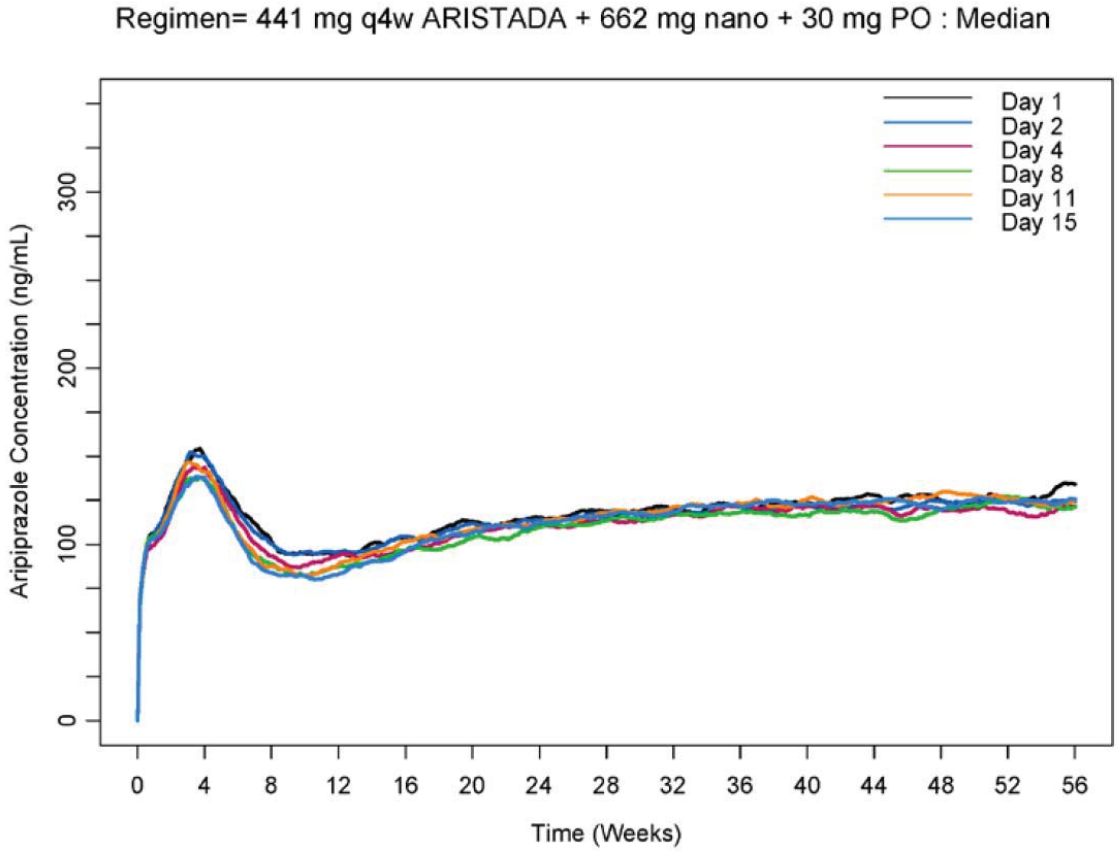
Yes. Study ALK9072-B102 provides the pivotal PK bridging data between ARISTADA INITIO and the two listed drugs. It was a randomized, double blind, PK study which compared the aripiprazole exposure when ARISTADA was initiated with ARISTADA INITIO and a single 30 mg dose of oral aripiprazole vs. the currently approved regimen of ARISTADA with 21 days of oral aripiprazole.

The final-to-be-marketed formulation of ARISTADA INITIO was used in all the clinical studies conducted. All 3 clinical studies (Study #101, 102 and 103) used the planned commercial formulation and the same Lot# 467-0002AA and 467-0013AA.

2.8 The proposed label suggests that "the first ARISTADA injection may be administered on the same day as INITIO or up to 10 days thereafter". Is the timing of injections acceptable?

Yes, if administration of the first ARISTADA injection is delayed by approximately 10 days the effectiveness of the regimen is unlikely to be affected. The applicant provided simulations of aripiprazole concentrations under various dosing regimen scenarios. For example, a representative plot of the median simulated aripiprazole concentrations for staggered treatment initiation with 675 mg ARISTADA + 30 mg oral aripiprazole and delaying the first ARISTADA dose by 0, 1, 3, 7, 10, 14 days (i.e. starting ARISTADA on Days 2, 4, 8, 11, and 15) is shown in Figure 12 below. It can be noted that a delay in the initiation of the first dose of ARISTADA is unlikely to impact the effectiveness of the regimen. Since these scenarios were not actively studied in the ARISTADA INITIO program, and based on the simulation scenarios (please refer Appendix 3.2, Figure 21 - Figure 25 for further details) it is difficult to derive a 'cut-off' for a delay that can be considered acceptable. We do not recommend including this in the highlights section of the label, as the preferred strategy is still to administer both injection at the same time.

Figure 12 Median simulated aripiprazole concentrations for staggered treatment initiation



Source: Population PK report (alk 9072-054) – Figure 36 on Page 136

3 PHARMACOMETRICS ASSESSMENT: POPULATION PK ANALYSES

3.1 Summary of the Applicant's Population PK analyses:

The key objectives of the applicant's population PK (popPK) analyses were to (1) describe the pharmacokinetics of aripiprazole following intramuscular injection of aripiprazole lauroxil (AL), aripiprazole lauroxil – ARISTADA INITIO [NanoCrystal® Dispersion] (ARISTADA INITIO) and oral (PO) aripiprazole (PO ARI) and (2) to evaluate the effects of intrinsic and extrinsic factors on the PK of aripiprazole. Additionally, the applicant used the final popPK model to perform simulations to evaluate the simultaneous initiation of treatment of ARISTADA INITIO and AL; the likely impact of staggered initiation of treatment with ARISTADA INITIO and AL dosing and the likely impact of missed dosing scenarios.

The applicant used a previously developed popPK model as the starting point for the base model development with the data from study B101, to characterize the IM absorption of ARISTADA INITIO and conversion to ARI. Next, the data from study B103 were included and the model parameters were re-estimated. Subsequently, data from study B102 were included to characterize the input functions for both PO ARI and IM AL in addition to ARISTADA INITIO, and perform a full covariate analysis. Lastly, the data from study A105 were included and the model parameters were revised. A brief description of these studies is given in **Table 1**

Overall, a total of 8944 ARI plasma concentrations from 249 individuals (including N=279 [3%] PK samples which were below LLOQ) were included in the popPK analyses. It should be noted PK data of only formulation B from study B101 was used in the final popPK analyses.

Table 1 Summary of studies included in the popPK analyses

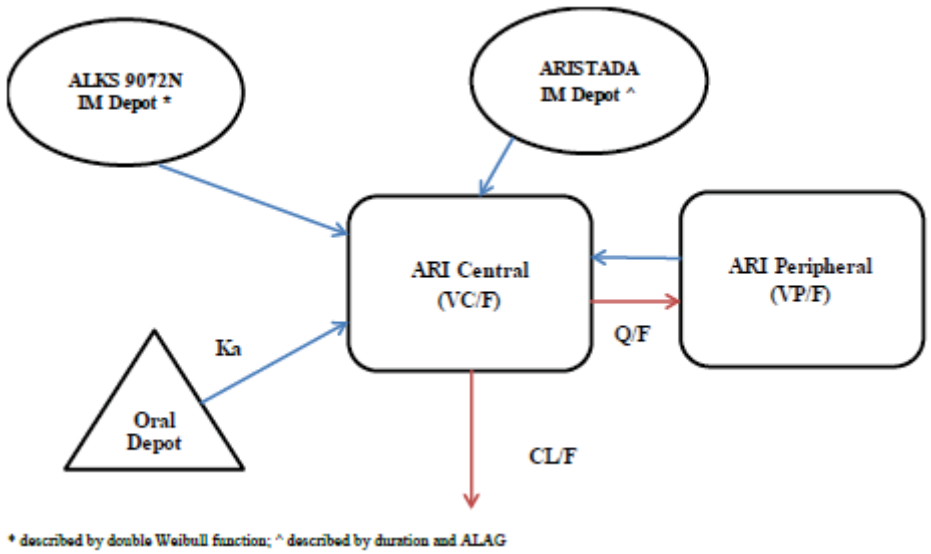
Study	Population and Planned No. Subjects	Dose/Treatment Duration	Planned PK Data
ALK9072-B101 (Phase 1)	Population: Adults with schizophrenia No. of planned subjects: 70	AL-NCD Formulation A: 221, and 441 mg AL-NCD Formulation B: 110, 221, 441, 662, and 882 mg AL-NCD Formulation C: 221, 441, and 622 mg	84-day PK profile
ALK9072-B102 (Phase 1)	Population: Adults with schizophrenia No. of planned subjects: 160	Treatment 1: 30 mg PO ARI + AL-NCD 662 mg (gluteal) + AL 441 mg (deltoid) on Day 1 Treatment 2: 30 mg PO ARI + AL-NCD 662 mg (gluteal) + AL 882 mg (gluteal) on Day 1 Treatment 3: 15 mg PO ARI + AL-NCD placebo IM injection (gluteal) + AL 441 mg (deltoid) on Day 1 and 15 mg PO ARI QD on Days 1 to 21 Treatment 4: 15 mg PO ARI + AL-NCD placebo IM injection (gluteal) + AL 882 mg (gluteal) on Day 1 and 15 mg PO ARI QD on Days 1 to 21	140-day PK profile
ALK9072-B103 (Phase 1)	Population: Adults with schizophrenia or schizoaffective disorder No. of planned subjects: 46	Treatment 1: AL-NCD 662 mg IM injection (deltoid) Treatment 2: AL-NCD 662 mg IM injection (gluteal)	84-day PK profile

Note: Formulation B from Study ALK9072-B101 was the only formulation used in ALK9072-B102 and ALK9072-B103.

Source: Population PK report (Alk9072-054) – Table – 1 on Page 28

The popPK data of aripiprazole was modeled using non-linear mixed effects in NONMEM. The structural model (shown in **Figure 13** below) developed by the applicant consists of multiple absorption components namely: (a) IM ARISTADA INITIO to ARI (following ARISTADA INITIO administration) described by a double Weibull function; (b) IM AL to ARI (following AL administration) described by a zero-order process with a parameter for duration (D) of conversion and first order process for ARI from the dosing depot defined as 1/D1, with a lag term for the delayed appearance of ARI in the central compartment and (c) PO ARI described by a first-order process. The rest of the disposition of ARI was described by a two-compartment model, namely, central and peripheral compartments and clearance from the central compartment.

Figure 13 Structure of ARI base popPK model for ARISTADA INITIO , AL and PO ARI input



Source: Population PK report (Alk9072-054) – Figure 2 on Page 78

Covariates that were evaluated include age and bodyweight at baseline, injection site (gluteal or deltoid), formulation, CYP2D6 genotype, ethnicity, gender and race. Bodyweight, formulation and CYP2D6 genotype were evaluated as part of the initial base model development with data from study B101. However, the full model with backwards deletion approach was utilized once all the data was included. Overall, bodyweight was retained on apparent volume of the central compartment (Vc/F) [with a fixed allometric coefficient of 1.0]. Lastly, a separate proportional error model for study A105 and ARISTADA INITIO studies (B101, 102 and 103) was used to characterize the residual variability.

The parameter estimates of the final PopPK model are shown in **Table 2**

The qualification of the final PopPK model was performed using the goodness of fit plots, shown in **Figure 14**. Furthermore, the simulation with the same design using the estimates of the population means and variability from the final popPK model were overlaid with the observed data and visualized using the prediction-corrected Visual Predictive Check (pc-VPC) shown in **Figure 15, Figure 16** and **Figure 17** for respective studies.

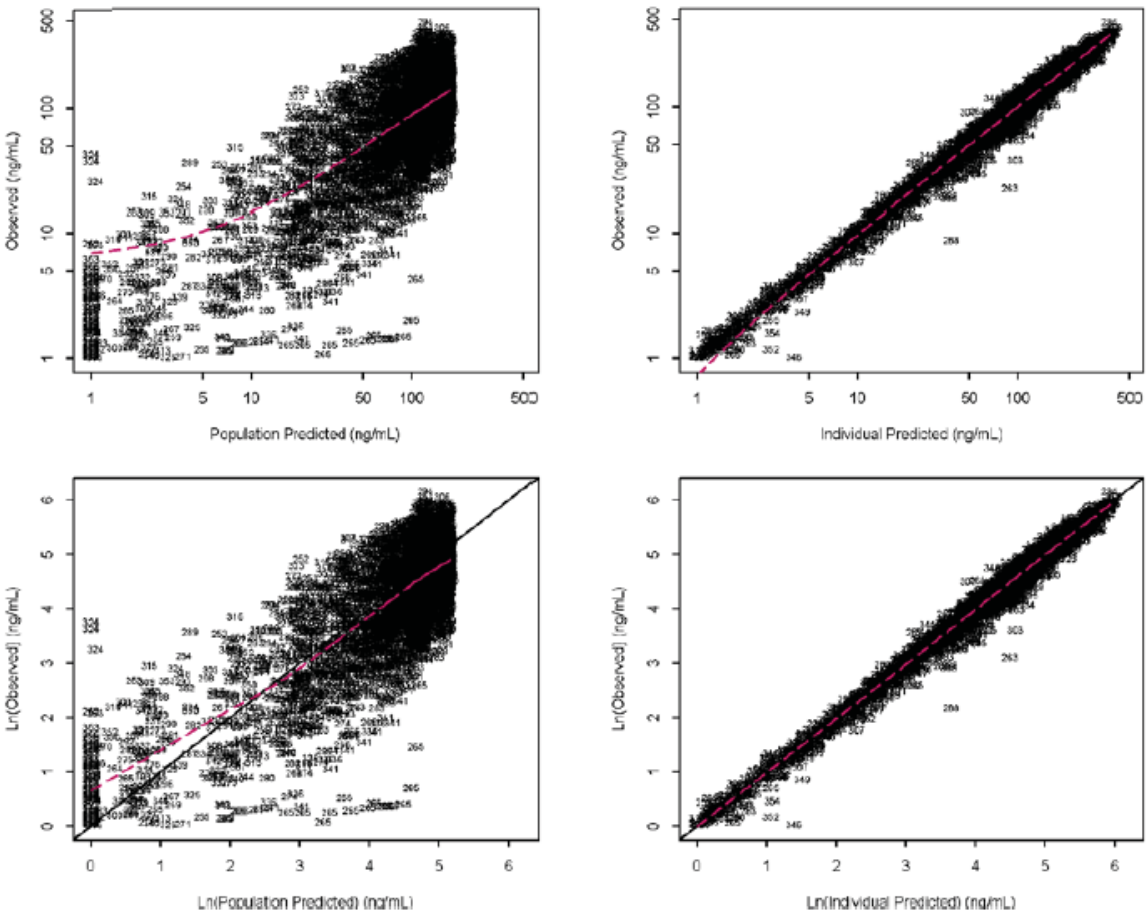
Table 2 Parameter estimates of final ARI popPK model

Parameter [Units]	NONMEM Estimates			
	Point Estimate	%RSE	95% CI	
CL/F (L/hr) ^	1.98	2.54	1.88, 2.07	
VC/F (L) ^	327	4.51	298, 356	
WT ON VC/F [1] [6]	1	-	-	
MDT1 (hr) ^	596	3.29	557, 634	
GAM1	2.20	2.85	2.08, 2.32	
MDT2 (hr) ^	76.7	4.47	70.0, 83.4	
GAM2	2.09	2.36	1.99, 2.19	
FRAC	2.02	3.88	1.87, 2.17	
VP/F (L) ^	1720	13.9	1251, 2188	
Q/F (L/hr) ^	0.102	10.9	0.080, 0.124	
Ka PO ARI (hr^{-1}) ^	0.47	14.2	0.339, 0.601	
D AL (hr) ^	934	3.86	864, 1005	
ALAG AL (hr) ^	106	7.85	89.4, 122	
FIM AL [2] ^	0.571	-	-	
FPO ARI [1] ^	1.00	-	-	
FIM AL-NCD [3] ^	1.12	3.56	1.04, 1.20	
FIM AL-NCD [4]	0.638	-	-	
ARI(0) (ng/mL) ^	0.378	14.8	0.269, 0.488	
Inter-individual variability				**CV%**
CL/F	0.539	10.8%	0.425, 0.653	84.5[5]
VC/F	0.239	16.8%	0.160, 0.318	52.0[5]
MDT1	0.197	13.0%	0.147, 0.247	46.7[5]
GAM1	0.461	20.8%	0.273, 0.649	76.5[5]
MDT2	0.274	15.1%	0.193, 0.355	56.1[5]
GAM2	0.129	24.0%	0.0684, 0.190	35.9
FRAC	0.978	17.9%	0.635, 1.32	129[5]
VP/F (L)	0.686	18.7%	0.435, 0.937	99.3[5]
Q/F (L/hr)	2.60	10.9%	2.05, 3.15	353[5]
Ka PO ARI (hr^{-1})	2.45	16.3%	1.67, 3.23	325[5]
D AL (hr)	0.147	21.7%	0.0845, 0.210	38.3
ALAG AL (hr)	0.895	15.1%	0.630, 1.16	120[5]
FIM AL	0.505	10.8%	0.399, 0.611	81.1[5]
Ari(0)	4.34	10.6%	3.44, 5.24	870[5]
Residual variability				**CV%**
σ^2 prop ARI Nano Studies	0.0359	3.93%	0.0331, 0.0387	18.9
σ^2 prop ARI Study A105	0.0207	2.70%	0.0196, 0.0218	14.4

Note: only diagonal elements of the full OMEGA block presented. ^ Indicates parameter was estimated on log-scale and subsequently, estimates exponentiated and CIs calculated using SE of exponentiated parameter estimate ($SE \times e^{P}$) [1] Fixed at 1.00; [2] Fixed at 57.1% from previous analysis[6]; [3] AL-NCD F estimated relative to AL; [4] AL-NCD F relative to PO ARI (calculated as 1.24*0.571 (note more decimal places used in calculation than presented)); [5] CV calculated as $CV_{TV_P} = \sqrt{e^{\omega_P^2} - 1}$ *100 rather than square root of ω_P^2*100. [6] power effect = VC/F*(WT/70)$^{1.0}$ Abbreviations: AL IM duration of absorption (D AL); AL IM lag-time (ALAG); oral rate of absorption (Ka); central apparent volume of distribution for aripiprazole (VC/F); peripheral apparent volume of distribution for aripiprazole (VP/F); apparent clearance of aripiprazole (CL/F); inter-compartmental CL for aripiprazole (Q/F); MDT1 & MDT2 mean dissolution time for each Weibull, GAM1 and GAM2 Weibull slope factors; FRAC Weibull fraction of dose; AL-NCD IM bioavailability (FIM AL-NCD); AL IM bioavailability (FIM AL); oral bioavailability (F PO); initial amounts of aripiprazole (Ari(0)); relative standard error (RSE); confidence interval (CI); coefficient of variation (CV).

Source: Population PK report (Alk9072-054) – Table 26 on Page 99

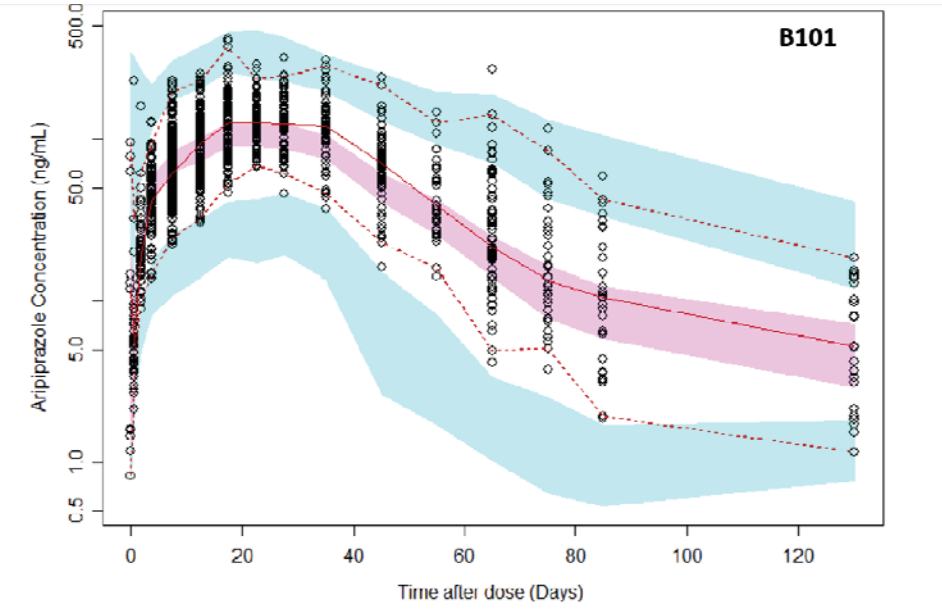
Figure 14 Goodness of fit plots for ARI from the final popPK model



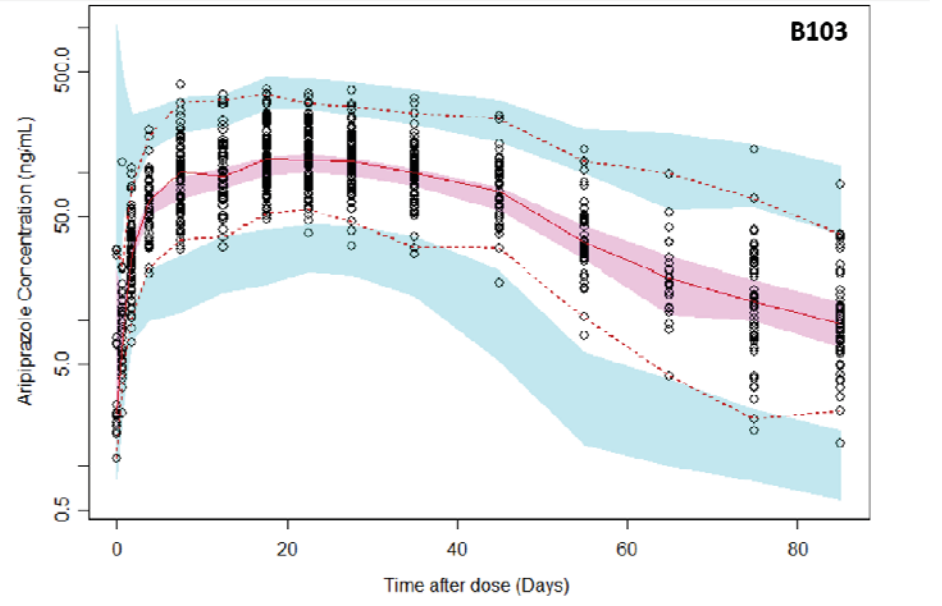
Red line represents Loess regression; LLOQ=1.0 ng/mL.
Source: F0004.tab

Source: Population PK report (Alk9072-054) – Figure 15 on Page 104

Figure 15 Prediction corrected visual predictive check for final popPK model for studies B101 and B103



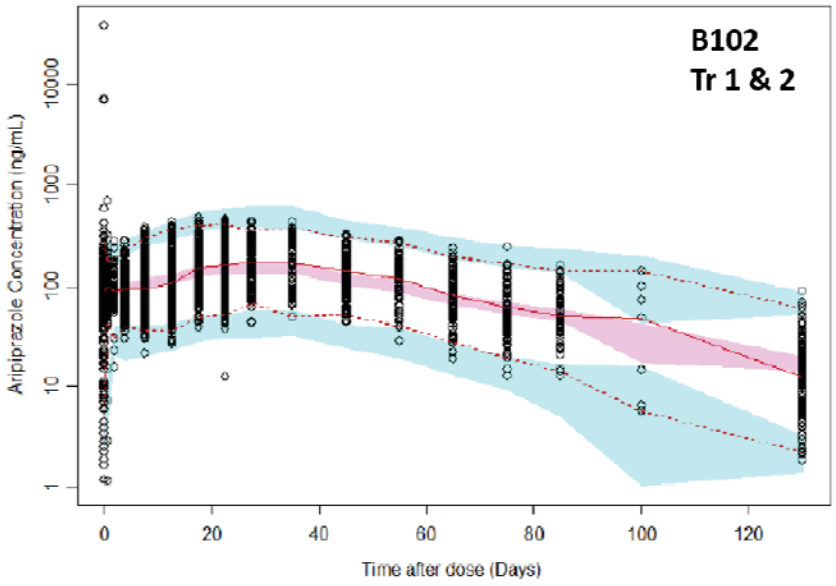
Open Circle: Observed Concentrations; Solid Line: Median of Observed Concentrations; Dashed Lines: 5th and 95th percentile of observed concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 5th and 95th percentiles of Predicted Concentrations.



Open Circle: Observed Concentrations; Solid Line: Median of Observed Concentrations; Dashed Lines: 5th and 95th percentile of observed concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 5th and 95th percentiles of Predicted Concentrations.

Source: Population PK report (Alk9072-054) – Figure 17 on Page 106 & Figure 20 on Page 109

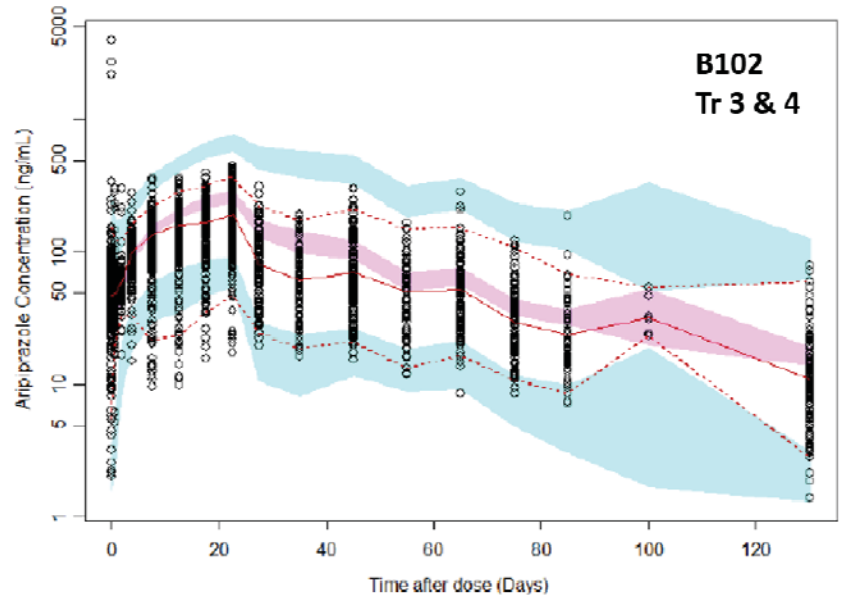
Figure 16 Prediction corrected visual predictive check for final popPK model for studies B102



Open Circle: Observed Concentrations; Solid Line: Median of Observed Concentrations; Dashed Lines: 5th and 95th percentile of observed concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 5th and 95th percentiles of Predicted Concentrations.

Treatment 1: 30 mg PO ARI + AL-NCD 662 mg (gluteal) + AL 441 mg (deltoid) on Day 1

Treatment 2: 30 mg PO ARI + AL-NCD 662 mg (gluteal) + AL 882 mg (gluteal) on Day 1



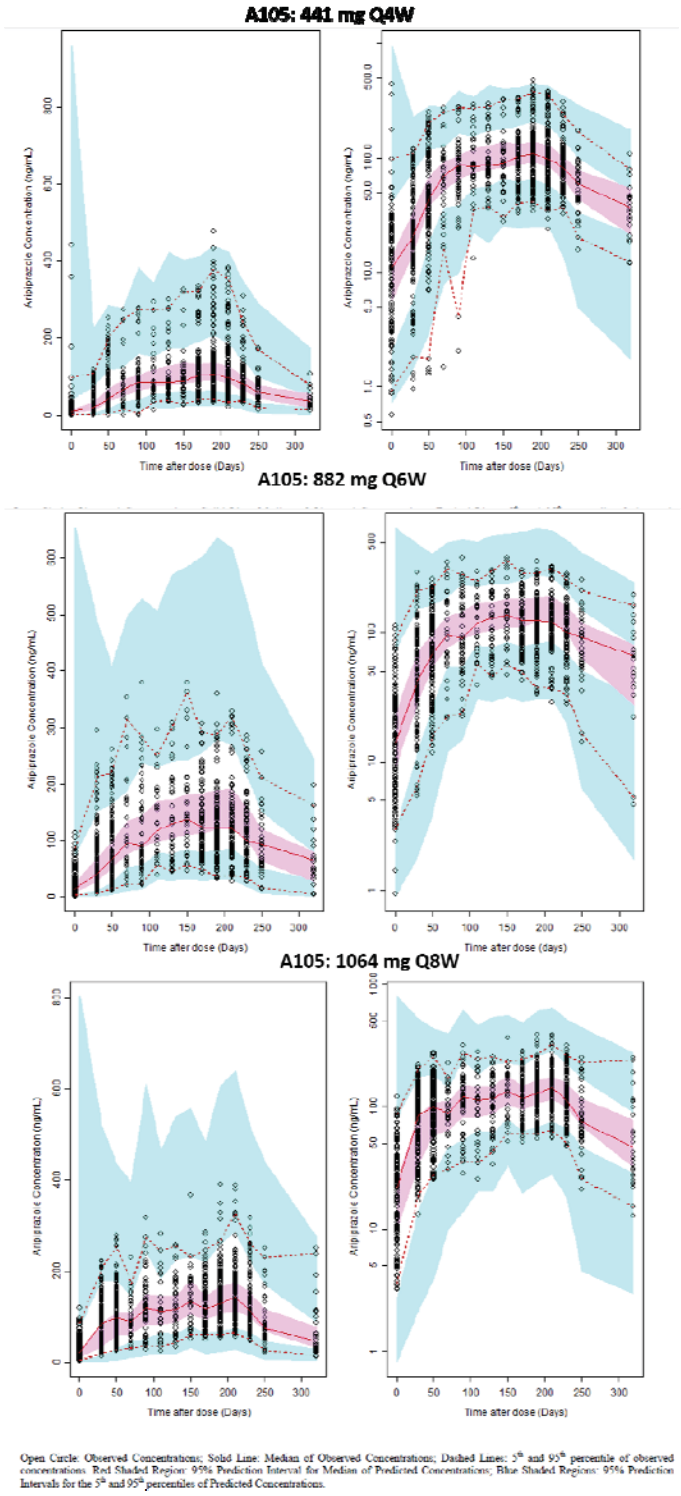
Open Circle: Observed Concentrations; Solid Line: Median of Observed Concentrations; Dashed Lines: 5th and 95th percentile of observed concentrations. Red Shaded Region: 95% Prediction Interval for Median of Predicted Concentrations; Blue Shaded Regions: 95% Prediction Intervals for the 5th and 95th percentiles of Predicted Concentrations.

Treatment 3: 15 mg PO ARI + AL-NCD placebo IM injection (gluteal) + AL 441 mg (deltoid) on Day 1 and 15 mg PO ARI QD on Days 1 to 21

Treatment 4: 15 mg PO ARI + AL-NCD placebo IM injection (gluteal) + AL 882 mg (gluteal) on Day 1 and 15 mg PO ARI QD on Days 1 to 21

Source: Population PK report (Alk9072-054) – Figures 18, 19 on Page 107 and 108

Figure 17 Prediction corrected visual predictive check for final popPK model for studies A105



Source: Population PK report (Alk9072-054) – Figures 21-23 on Page 110-112

Reviewer's Comments

*The applicant modeled the PK data of aripiprazole from studies listed in **Table 1**, which includes sparse sampling designs in adult patients with schizophrenia or schizoaffective disorder. They used a previously developed popPK model as a base model and included PK data from one of the studies and then refined it further by including PK data from other studies. Lastly, the applicant also included data from study A105 which did not involve administration of the ARISTADA INITIO formulation, but rather informed the estimation of other disposition parameters. Overall, the estimates in the final popPK model and associated uncertainty reported in **Table 2** seem reasonable for most parameters. In general, the predictive performance characteristics of the final model seem reasonable for studies B101 and 103 with the observed quartiles overlapping with the prediction intervals of the simulated quartiles (5^{th} quartile shows slight deviation). The simultaneous initiation regimen with AL, ARISTADA INITIO and PO ARI [treatment regimens 1 & 2] in study B102 was well described by the model. However, the final model seems to consistently over predict for the initiation regimens with AL and PO ARI (21 days) [treatment regimens 3 & 4].*

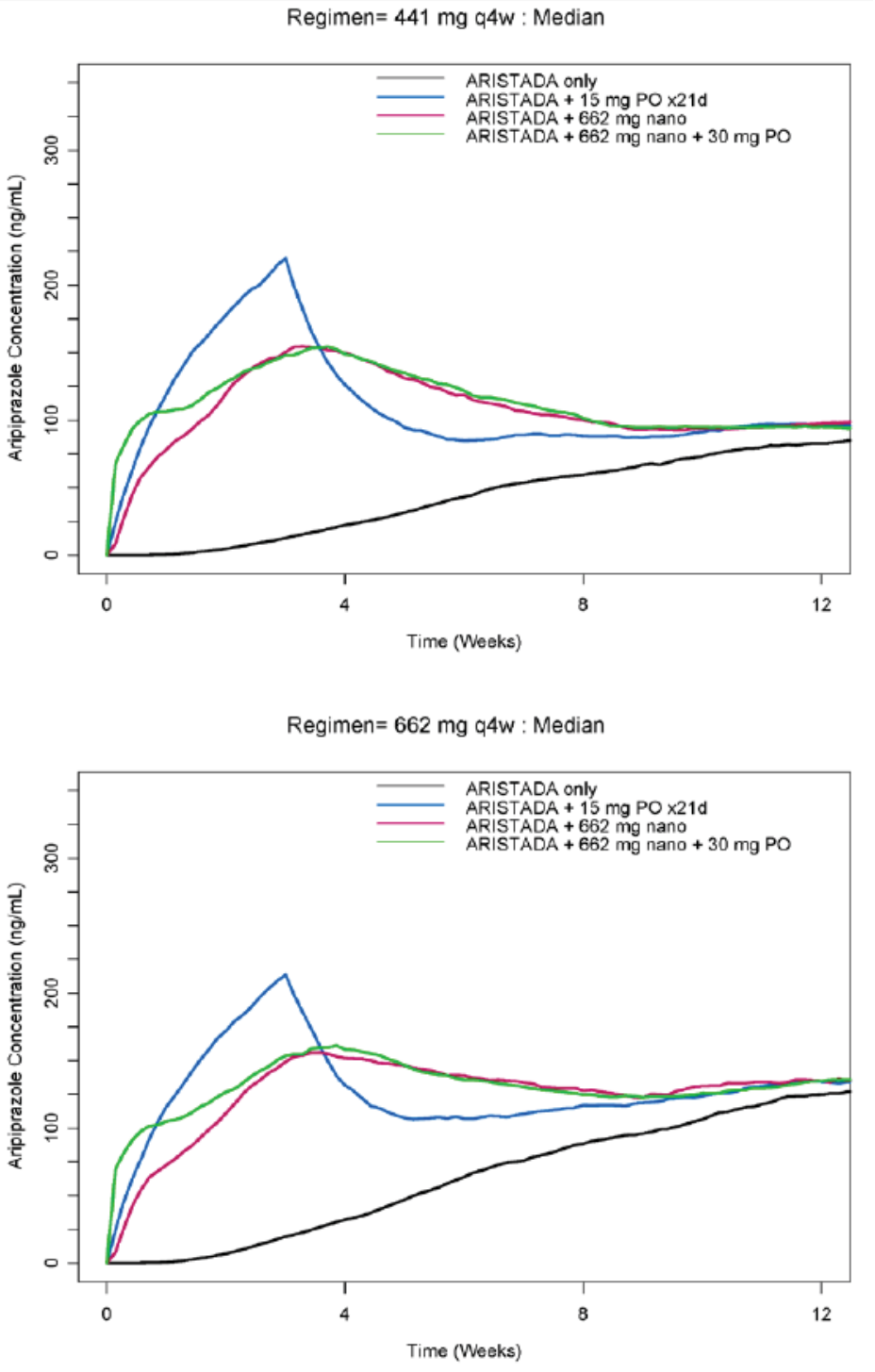
3.2 Simulations to Support Dosing Recommendations

As described above, the applicant's final popPK model seems reasonable in general, both in terms of the model parameter estimates and associated uncertainties, and the predictive performance characteristics. The applicant used this final popPK model to perform simulations to support the dosing recommendations under various scenarios such as for (simultaneous) initiation regimens, staggered initiation regimens and missed dosing of AL. Additionally, the applicant was also asked to provide simulations under various dosing scenarios when switching from (stable) oral aripiprazole therapy to either ARISTADA lauroxil IM (monthly, QM) + PO aripiprazole (daily, QD, for 21 days) regimen or ARISTADA lauroxil IM (QM) + PO aripiprazole (single dose of 30 mg) + ARISTADA INITIO IM (single dose of 675 mg) regimen as part of an information request (dated 24 October, 2017). In response (dated 14th November, 2017) to this IR, the applicant provided the simulations files in Trial Simulator (TS)®

Simultaneous Initiation Regimens

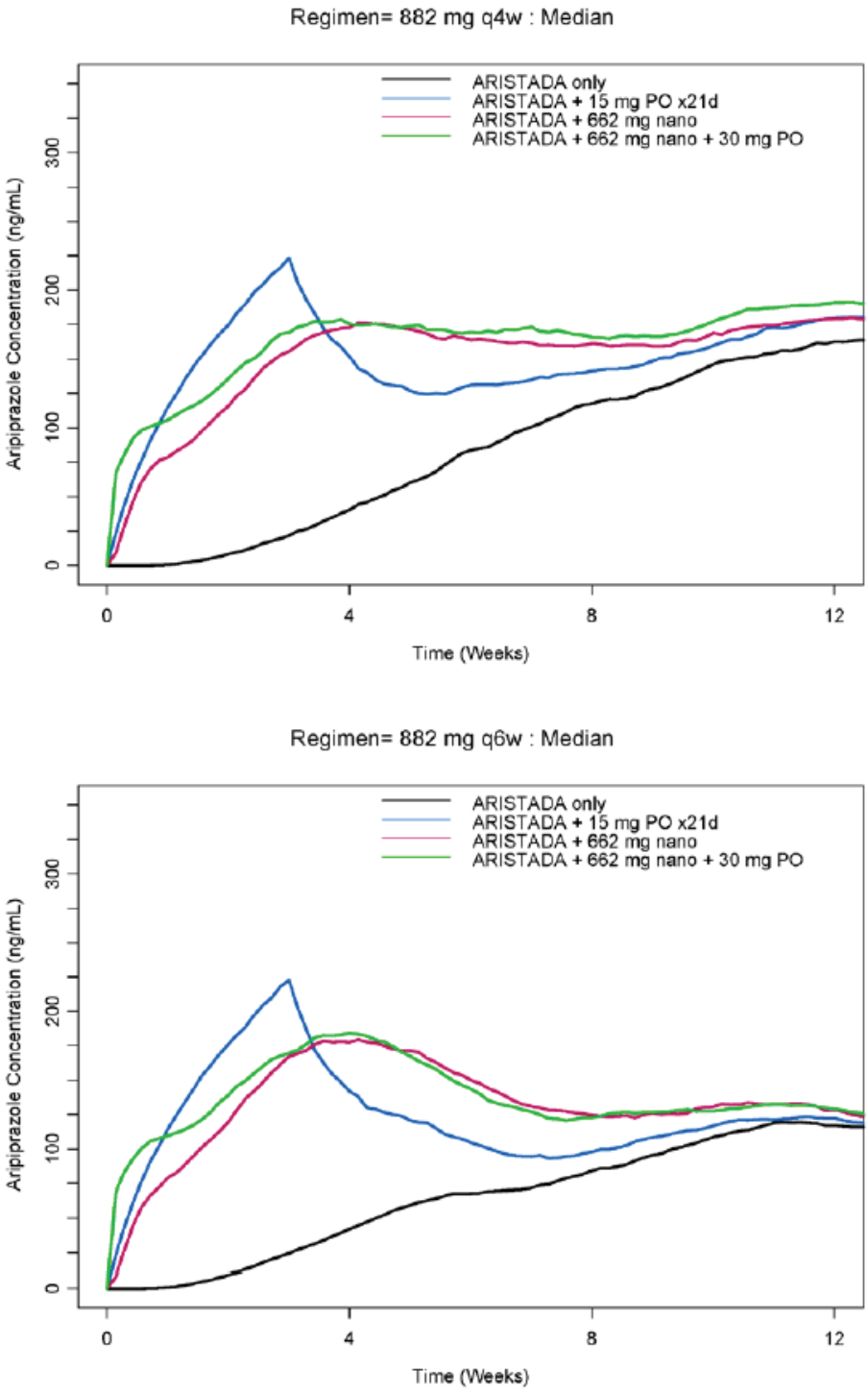
The applicant provided simulations for five ARISTADA lauroxil regimens (441 mg, 662 mg, 882 mg QM each, 882 mg Q6W, 1064 Q8W) (a) alone, (b) with 15 mg oral aripiprazole (only) for 21 consecutive days, (c) with single dose of ARISTADA INITIO and (d) with single dose of ARISTADA INITIO and single dose of 30 mg of oral aripiprazole. The 15 mg dose was chosen because in the original pivotal trial for ARISTADA, 21 days of 15 mg PO aripiprazole was used and was demonstrated to be effective. The median of the simulated aripiprazole concentrations during the first 12 weeks in Figure 18 - Figure 20 below

Figure 18 Median simulated aripiprazole concentrations for simultaneous treatment initiation



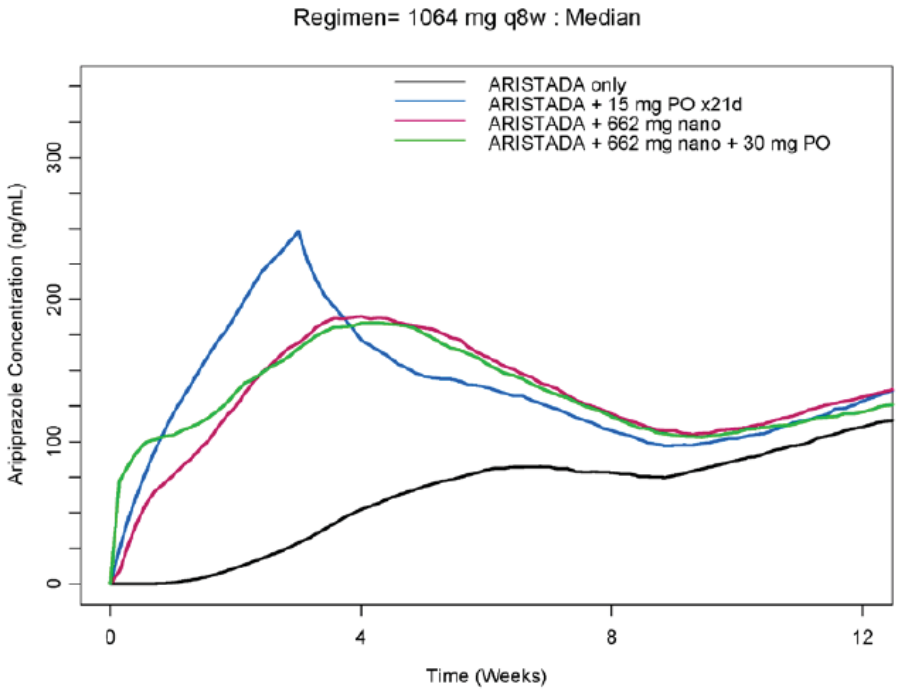
Source: Population PK report (alk 9072-054) – Figure 33 on Page 123

Figure 19 Median simulated aripiprazole concentrations for simultaneous treatment initiation



Source: Population PK report (alk 9072-054) – Figure 34 on Page 124

Figure 20 Median simulated aripiprazole concentrations for simultaneous treatment initiation

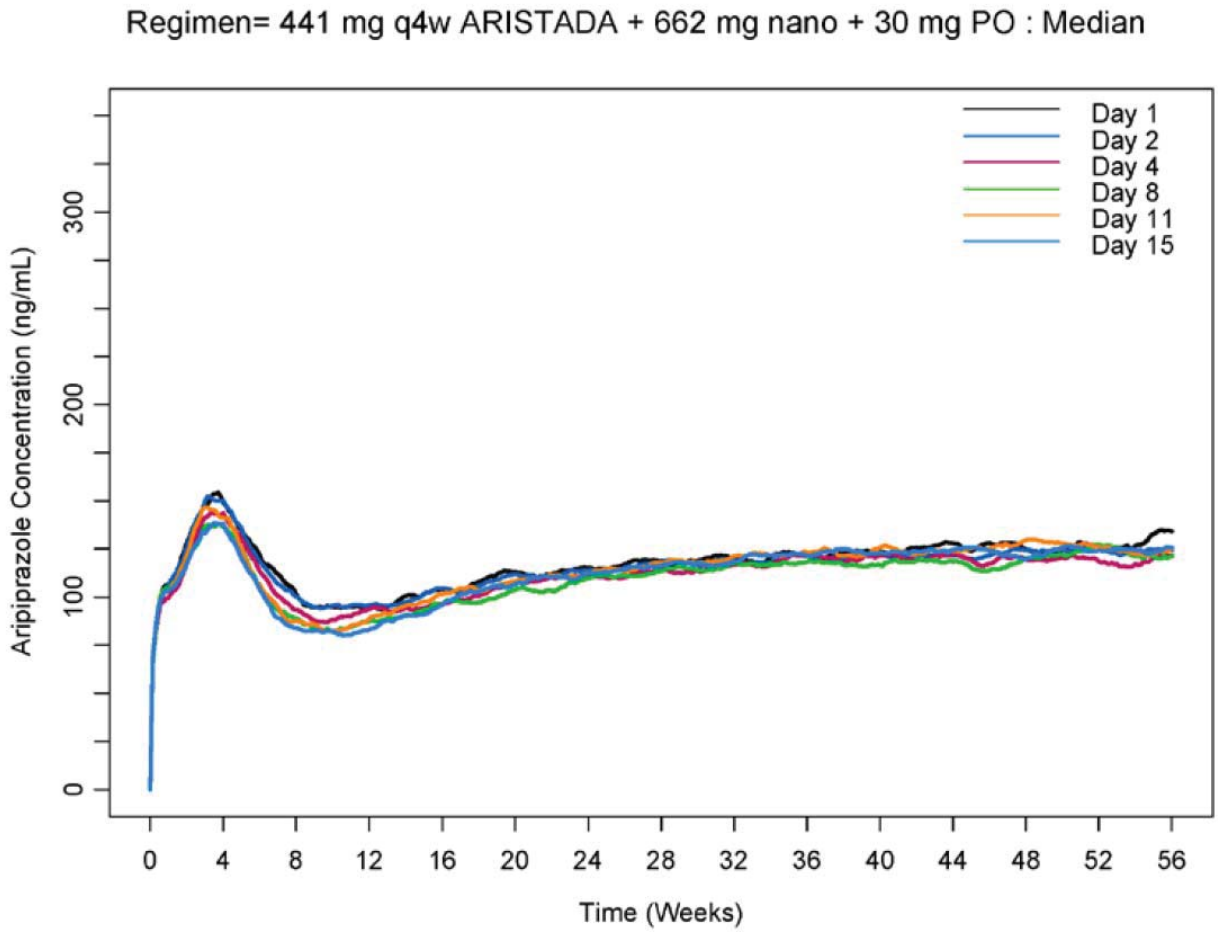


Source: Population PK report (alk 9072-054) – Figure 35 on Page 125

Staggered Treatment Initiation

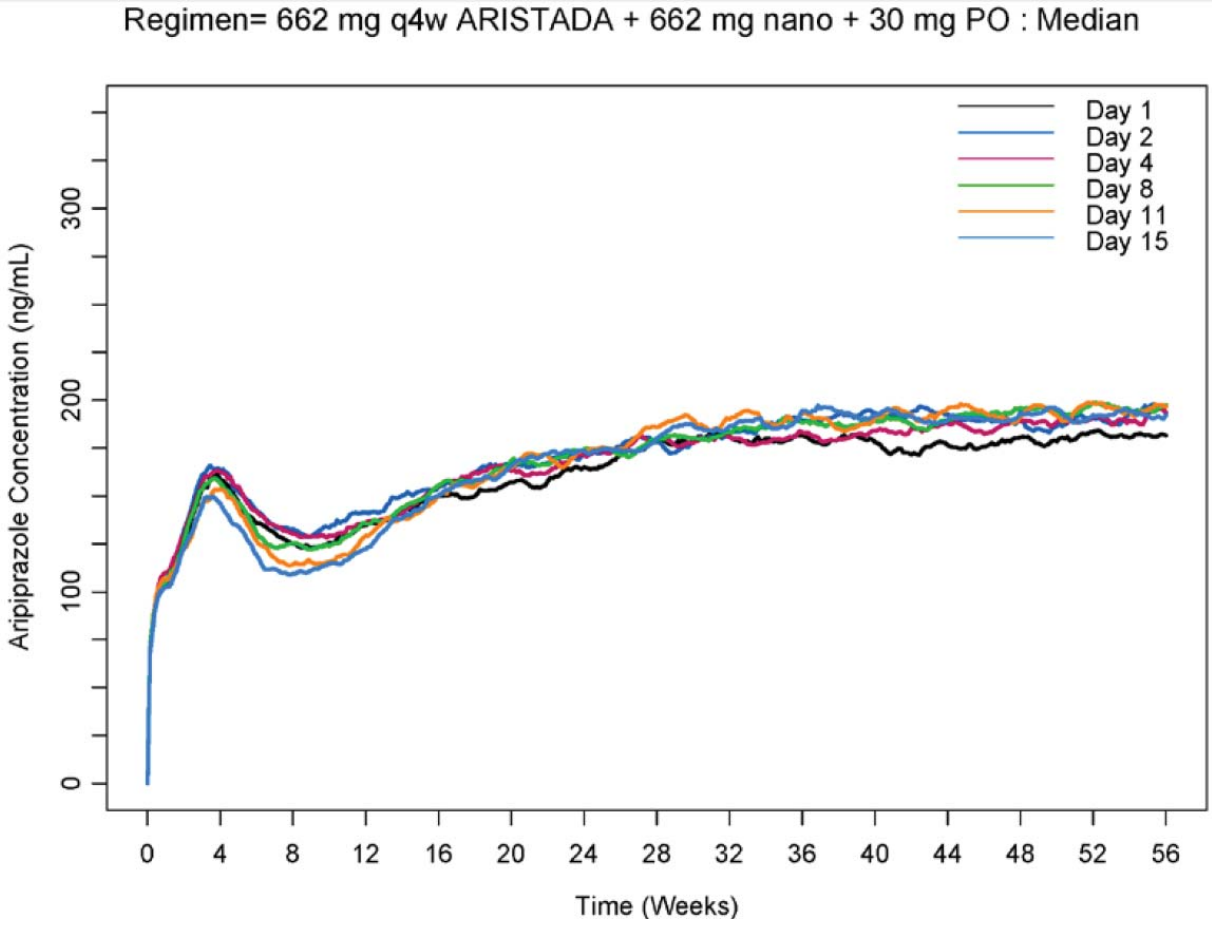
The applicant provided simulations for five ARISTADA lauroxil regimens (441 mg, 662 mg, 882 mg QM each, 882 mg Q6W, 1064 Q8W) with single dose of ARISTADA INITIO + single oral dose of 30 mg aripiprazole. The dosing of ARISTADA lauroxil was staggered by 0, 1, 3, 7, 10, 14 days following the initiation regimens (i.e. starting AL on Days 2, 4, 8, 11, and 15) and continued at the prescribed dosing interval from that point through at least 48 weeks. The median of the simulated aripiprazole concentrations over 56 weeks for the five regimens are presented in Figure 21 - Figure 25 below. Since these scenarios were not actively studied in the ARISTADA INITIO program, and based on the simulation scenarios, it is difficult to derive a 'cut-off' for a delay that can be considered acceptable. We do not recommend including this in the highlights section of the label, as the preferred strategy is still to administer both injection at the same time.

Figure 21 Median simulated aripiprazole concentrations for staggered treatment initiation



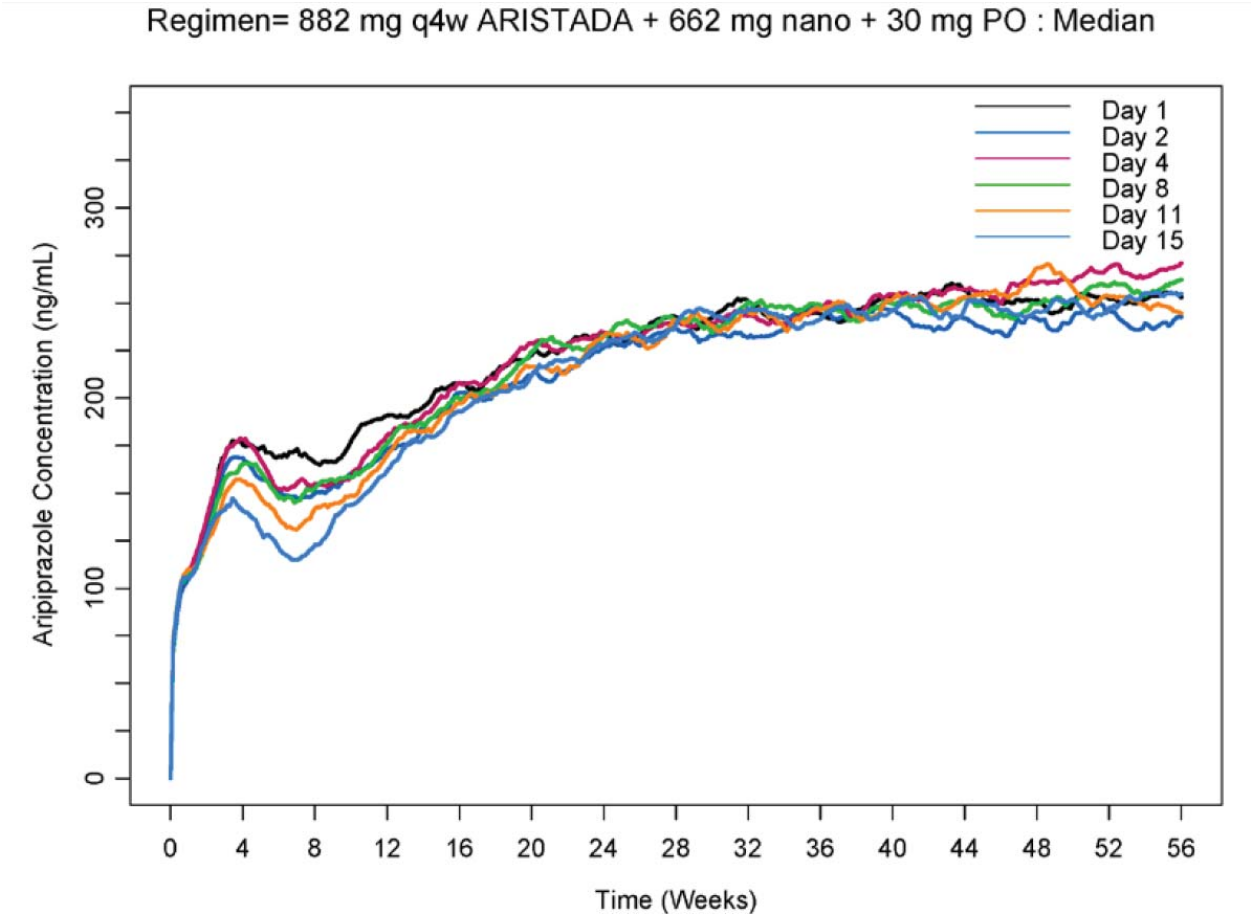
Source: Population PK report (alk 9072-054) – Figure 36 on Page 136

Figure 22 Median simulated aripiprazole concentrations for staggered treatment initiation



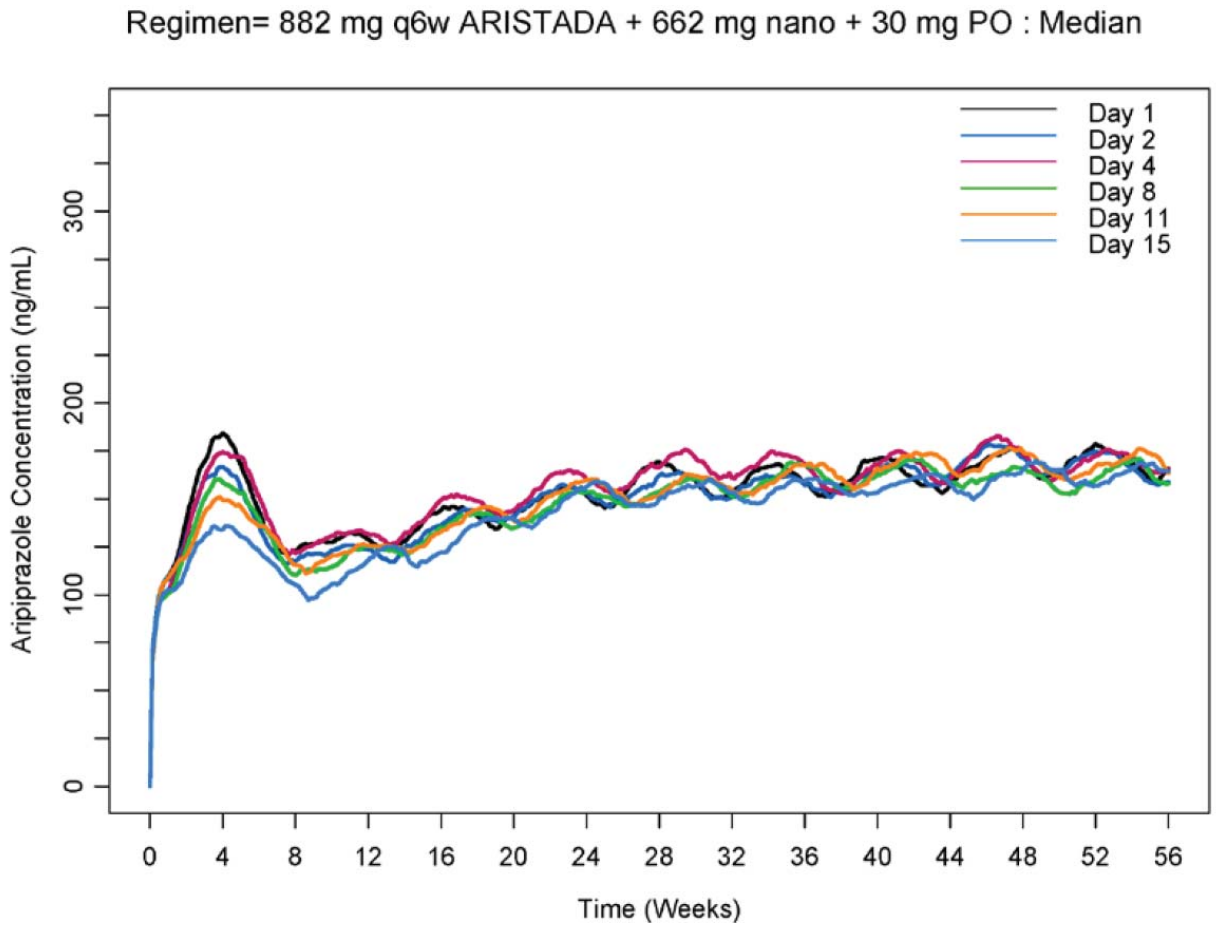
Source: Population PK report (alk 9072-054) – Figure on Page 137

Figure 23 Median simulated aripiprazole concentrations for staggered treatment initiation



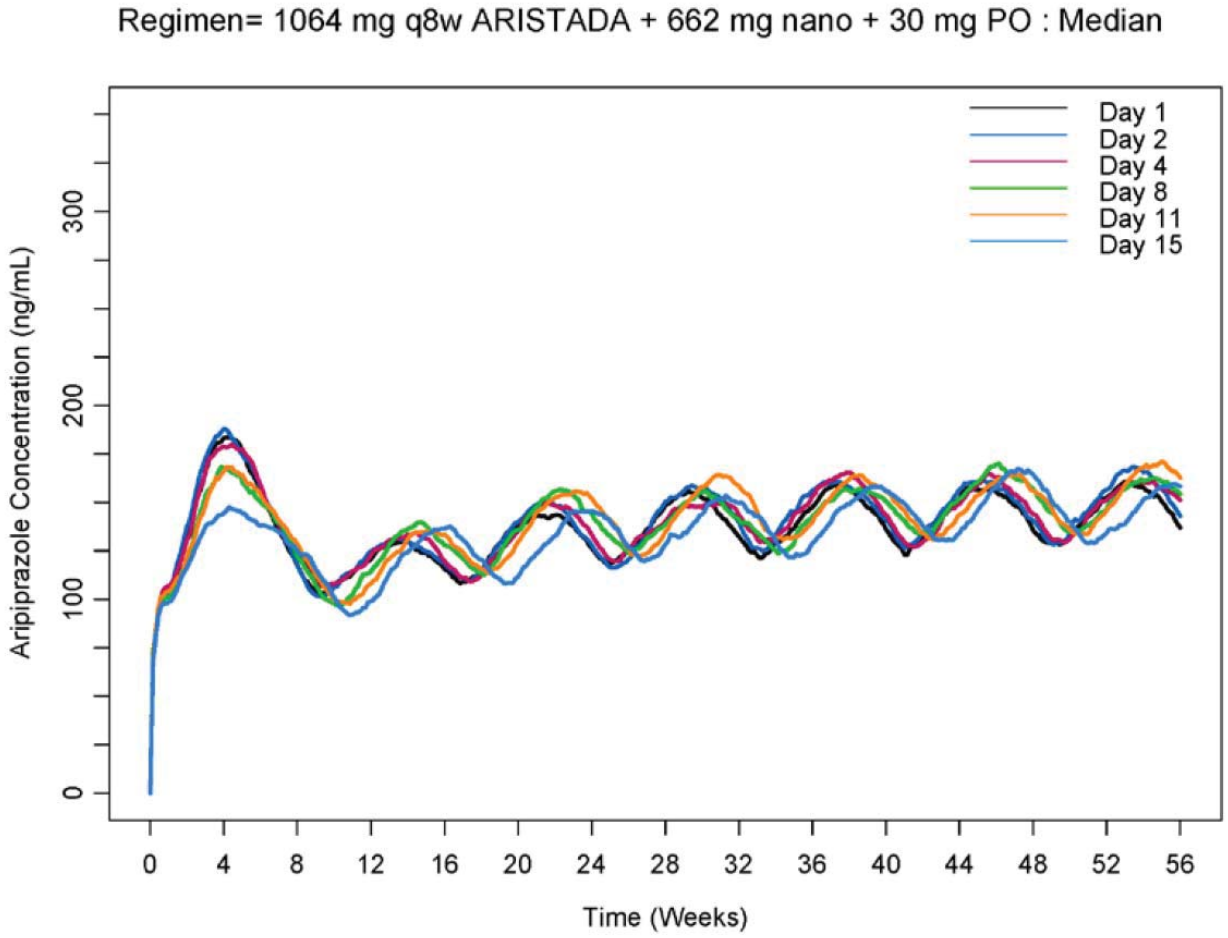
Source: Population PK report (alk 9072-054) – Figure on Page 138

Figure 24 Median simulated aripiprazole concentrations for staggered treatment initiation



Source: Population PK report (alk 9072-054) – Figure on Page 139

Figure 25 Median simulated aripiprazole concentrations for staggered treatment initiation

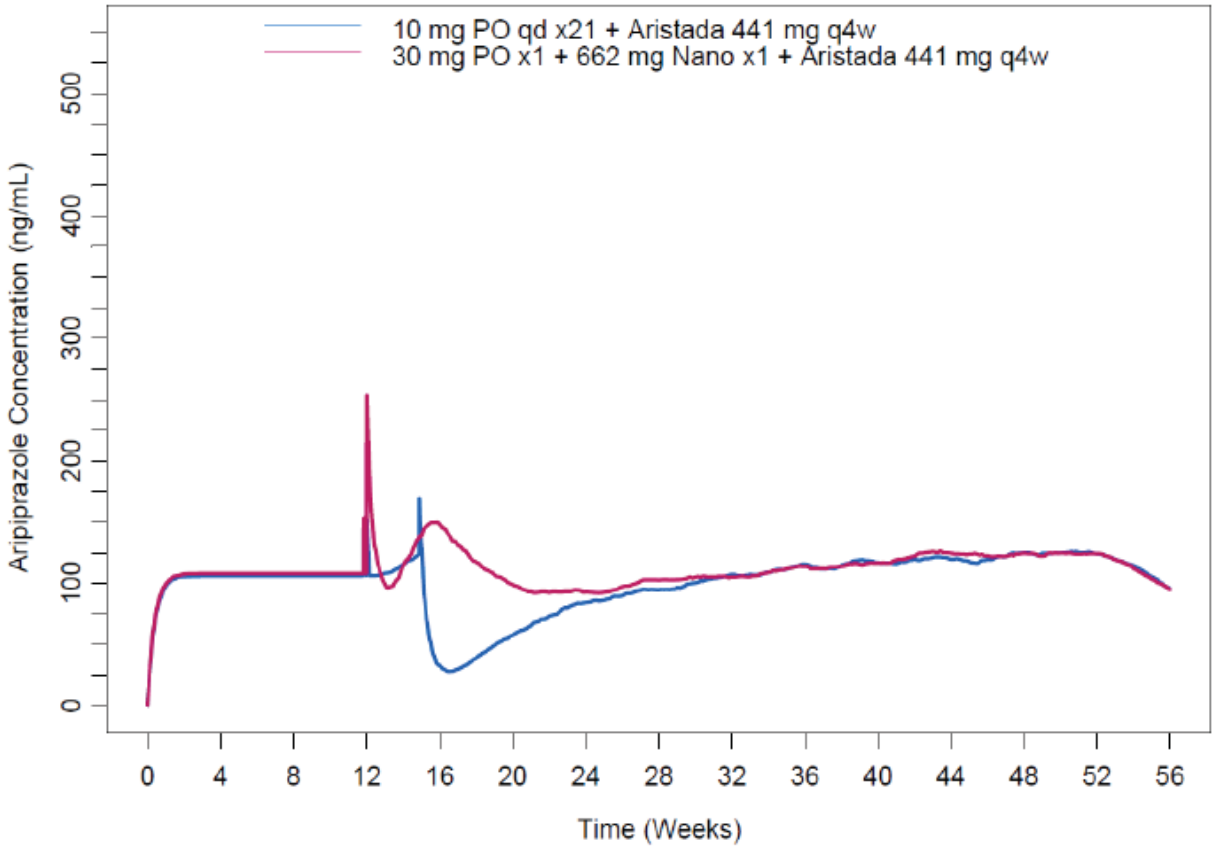


Source: Population PK report (alk 9072-054) – Figure on Page 140

Switching from (Stable) Oral Aripiprazole Therapy to Regimens with ARISTADA INITIO

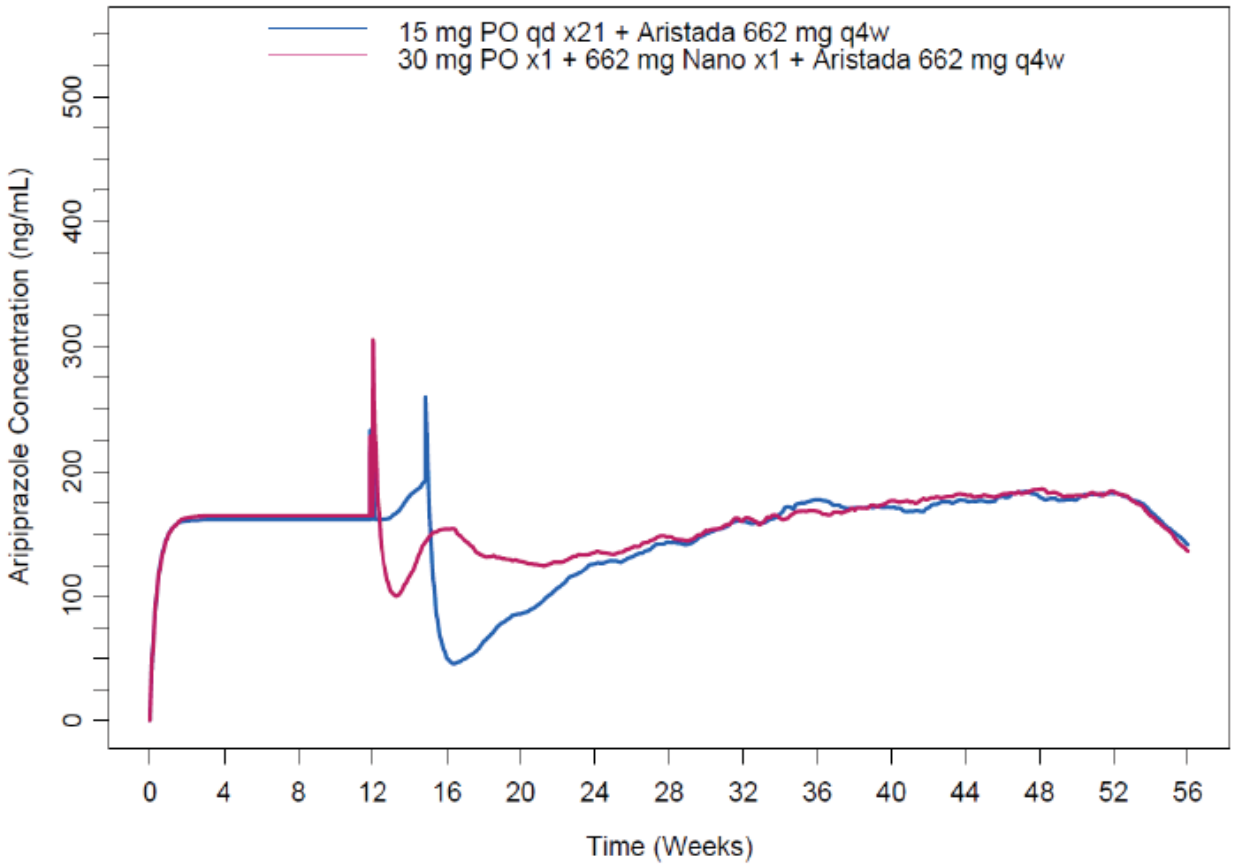
In response to the IR, the applicant provided simulations for switching from (stable) oral aripiprazole therapy to either the approved regimen of ARISTADA lauroxil and 21 days of oral aripiprazole or regimen with single dose of ARISTADA INITIO and single oral dose of 30 mg oral aripiprazole with ARISTADA lauroxil. The median of the simulated aripiprazole plasma concentrations under various scenarios are shown in Figure 26 - Figure 29 below

Figure 26 Median aripiprazole concentrations for subjects on a stable dose of 10 mg/day of oral aripiprazole that switch to ARISTADA 441 mg + continues to get 10 mg/day of oral aripiprazole for 21 days (blue line) or that switch to ARISTADA 441 mg + 30 mg oral aripiprazole + 675 mg ARISTADA INITIO (red line)



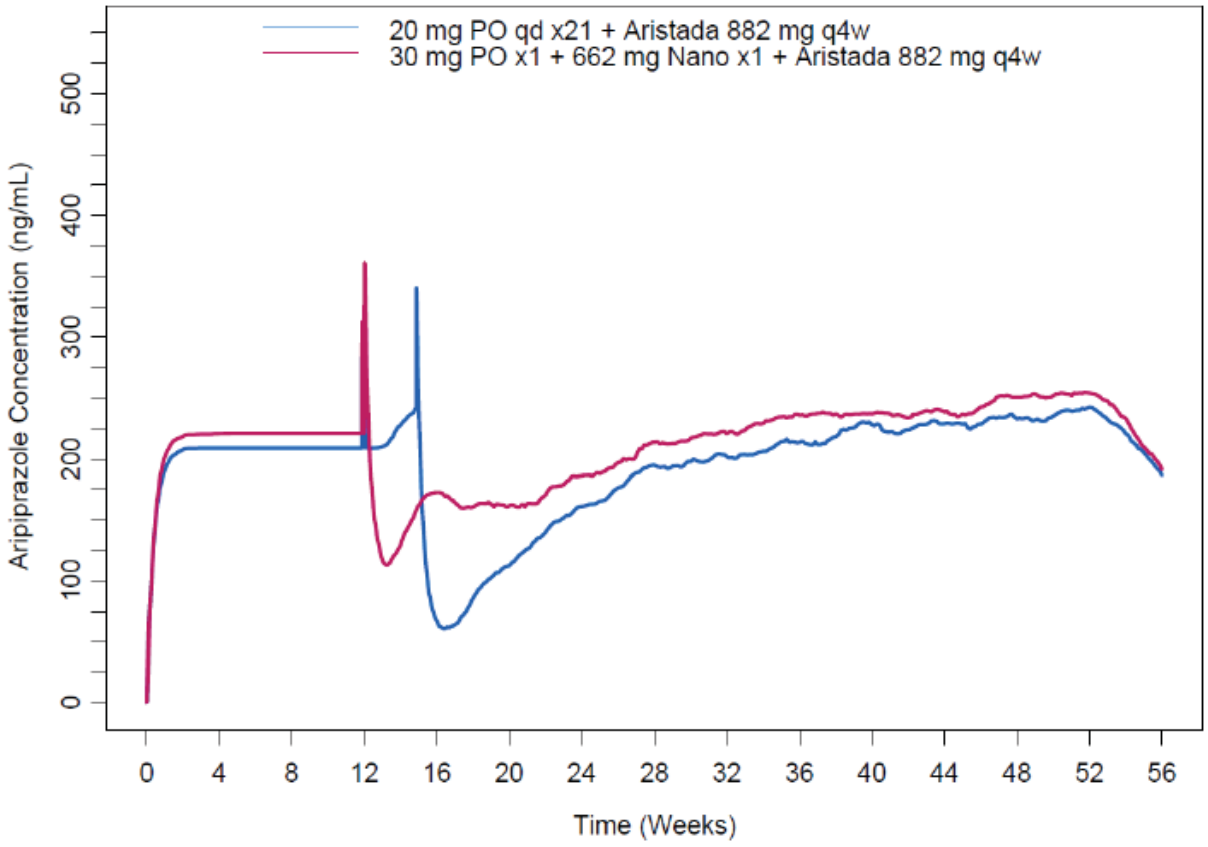
Source: Applicant's Response (dated 11/14/2017) to IR (dated 10/24/2017) Figure 1 on Page 4

Figure 27 Median aripiprazole concentrations for subjects on a stable dose of 15 mg/day of oral aripiprazole that switch to ARISTADA 662 mg + continues to get 15 mg/day of oral aripiprazole for 21 days (blue line) or that switch to ARISTADA 662 mg + 30 mg oral aripiprazole + 662 mg ARISTADA INITIO (red line)



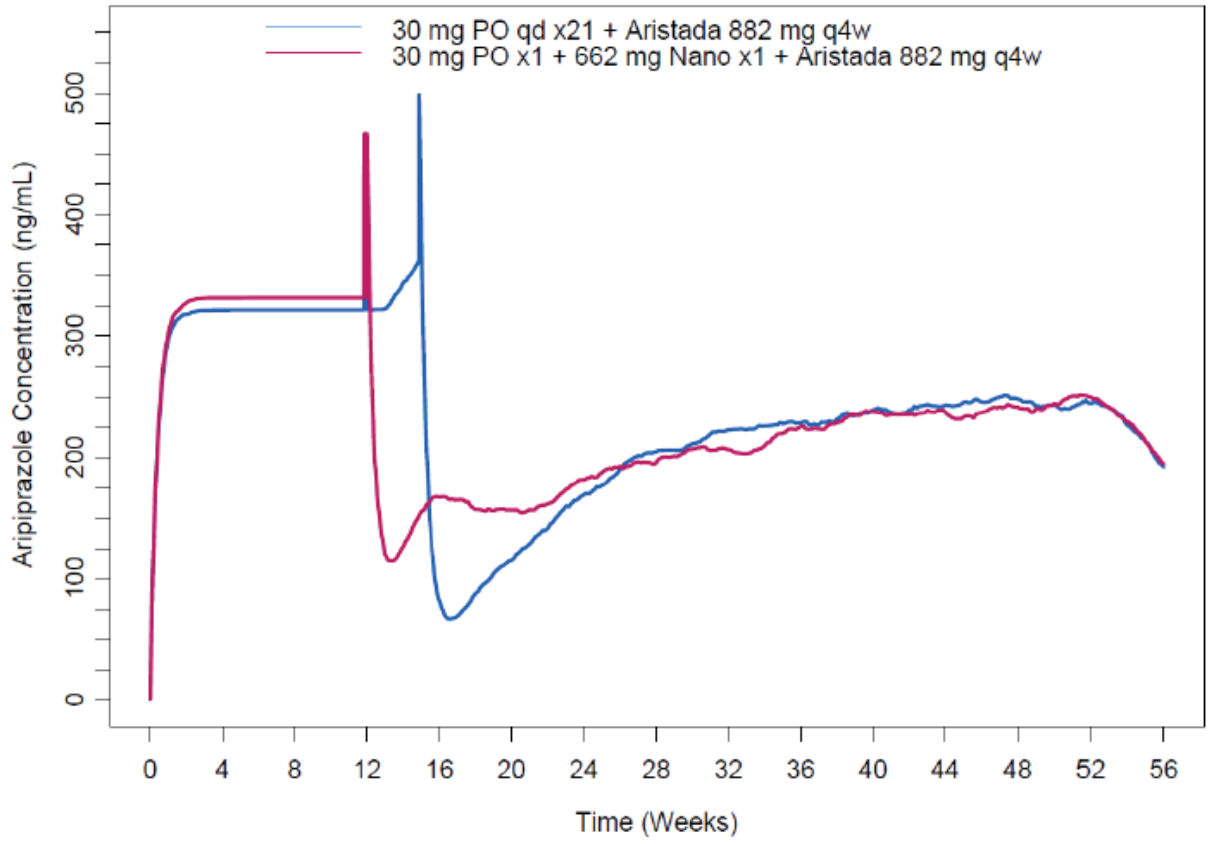
Source: Applicant's Response (dated 11/14/2017) to IR (dated 10/24/2017) Figure 2 on Page 5

Figure 28 Median aripiprazole concentrations for subjects on a stable dose of 20 mg/day of oral aripiprazole that switch to ARISTADA 882 mg + continues to get 20 mg/day of oral aripiprazole for 21 days (blue line) or that switch to ARISTADA 882 mg + 30 mg oral aripiprazole + 662 mg ARISTADA INITIO (red line)



Source: Applicant's Response (dated 11/14/2017) to IR (dated 10/24/2017) Figure 3 on Page 6

Figure 29 Median aripiprazole concentrations for subjects on a stable dose of 30 mg/day of oral aripiprazole that switch to ARISTADA 882 mg + continues to get 30 mg/day of oral aripiprazole for 21 days (blue line) or that switch to ARISTADA 882 mg + 30 mg oral aripiprazole + 662 mg ARISTADA INITIO (red line)



Source: Applicant's Response (dated 11/14/2017) to IR (dated 10/24/2017) Figure 4 on Page 7

Reviewer's comments:

The applicant reported the use of Trial Simulator (TS) ® and NONMEM® software tools to perform the simulations for various scenarios of (simultaneous) treatment initiation, staggered dosing and missed dosing of ARISTADA lauroxil, but did not include any of the datasets/files used for the simulations. Additionally, the response to the IR for simulation of switching from (stable) oral aripiprazole therapy to either approved regimen with ARISTADA lauroxil and 21 days of oral aripiprazole or regimen with single dose each of *ARISTADA INITIO and 30 mg oral aripiprazole included a poor description of the methodology underlying the simulations. When the PM reviewer performed the simulations using some of the files submitted by the applicant to evaluate the switching scenarios, it was found that the steady state-exposures following multiple oral aripiprazole dosing were ~2-fold higher (at a population level) compared to the applicant's simulations. Furthermore, there were issues with the absorption of aripiprazole* from *ARISTADA INITIO administration when the final popPK model parameters were used. Therefore, the reviewer conducted an independent simulation analysis to confirm the simulation results submitted by the applicant. Overall, the applicant's simulations under (simultaneous) initiation regimens, staggered treatment and switching from (stable) oral aripiprazole therapy to regimens with ARISTADA INITIO scenarios are reasonable and therefore their dosing recommendations under the respective scenarios are acceptable. The methodology used by the reviewer for performing the simulations and the considerations for the appropriateness of these regimens are discussed in detail in section 3.3 below.*

3.3 Reviewer's Simulations

In order to address these issues, the reviewer performed an independent analysis of each formulation separately, and used the principle of superimposition of the individual components, i.e., ARISTADA lauroxil IM, PO aripiprazole and ARISTADA INITIO IM to generate the profiles for the switching scenarios as described above. More specifically, the scenarios considered for simulations were: (a) switching (stable) oral aripiprazole therapy of 10 mg to either 441 mg ARISTADA lauroxil (QM) + 10 mg PO aripiprazole (QD, 21 days) regimen or 441 mg ARISTADA lauroxil (QM) + single dose of 30 mg of PO aripiprazole + single dose of 662 mg of ARISTADA INITIO regimen and (b) switching (stable) oral aripiprazole therapy of 30 mg to either 882 mg ARISTADA lauroxil (QM) + 30 mg PO aripiprazole (QD, 21 days) regimen or 882 mg ARISTADA lauroxil (QM) + single dose of 30 mg of PO aripiprazole + single dose of 662 mg of ARISTADA INITIO regimen. These scenarios were considered for simulations by the PM reviewer as they bracket the dosing regimen range. The following steps were considered for this:

1. The structural model following PO aripiprazole in the TS file used for simulations by the applicant (included in response to the IR dated 24th October, 2017) was similar to that of the final popPK model, but the parameter estimates were different. Additionally, it was also found that a previously developed aripiprazole PKPD model following oral aripiprazole administration by the same applicant, which was previously reviewed (NDA 021436, PKPD report 31-13-299, page 31) had the same structural model and relatively more comparable parameter estimates to those reported in the TS file. Please see Table 3 for these values. The PM reviewer used the estimates from the previously reviewed oral aripiprazole PK model to perform simulations for the PO aripiprazole dosing component.

Table 3 Parameter estimates

Parameter	Final popPK model	TS – PO model code used for simulation of switching scenarios	NDA 021436 PKPD Report (31-13-299)
CL or CL/F (L/hr)	1.98	3.15	3.44
V or Vc/F (L)	327	193	255
Ka (h^{-1})	0.47	1.06	1.67

2.&The parameter estimates from the final popPK model were used as is for simulations following ARISTADA lauroxil IM dosing and ARISTADA INITIO dosing, but were done separately to obtain their respective disposition profile components.

3.&Next, the profiles of the individual components were superimposed as follows:

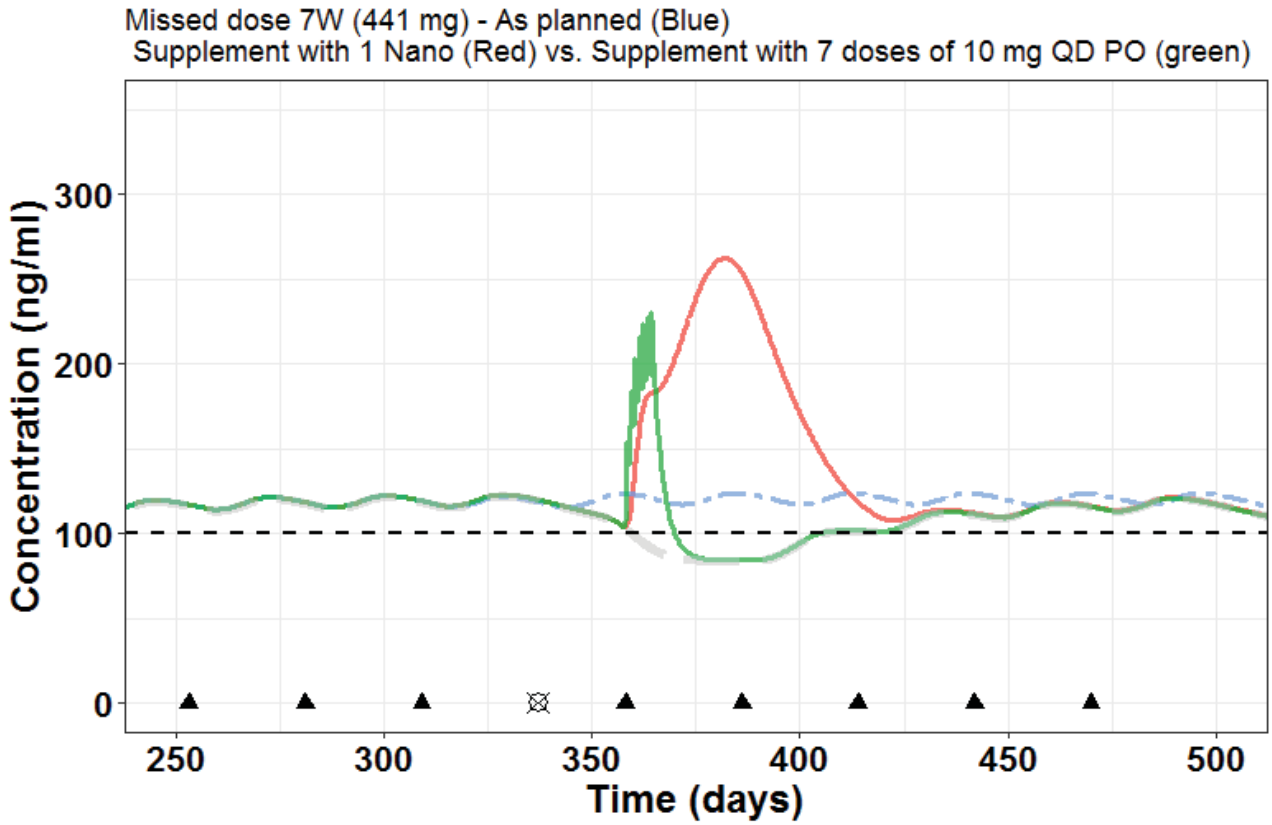
a.& Stable oral aripiprazole dosing was administered for 12 weeks [up to day 84]

b.&Switching [on day 85] to PO aripiprazole dosing for (additional) 3 weeks [up to day 105] + ARISTADA lauroxil IM QM regimen or to single dose of PO aripiprazole 30 mg + single dose of ARISTADA INITIO 662 mg + ARISTADA lauroxil IM QM regimen.

The reviewer performed 500 simulations under the scenarios discussed above and noted that the results were comparable to that reported by the applicant for switching stable oral aripiprazole therapy to regimen with or without ARISTADA INITIO, suggesting that the applicant's simulations were acceptable. The reviewer also performed independent analysis (by superimposition) in a similar way as described above for simulations under (simultaneous) initiation regimens, staggered initiation regimens and missed dosing scenarios and consider the applicant's results acceptable.

The dosing recommendations proposed by the applicant following missed doses of ARISTADA lauroxil include the following three scenarios based on the length of time since last injection: (a) when no supplementation is required, (b) supplement with single dose of ARISTADA INITIO and (c) supplement with single dose of ARISTADA INITIO and single dose of 30 mg PO aripiprazole. Additionally, the applicant suggests supplementing with 7 days of oral aripiprazole as an alternative to supplementing with single dose of ARISTADA INITIO (scenario b) and supplementing with 21 days of oral aripiprazole as an alternative to supplementing with single dose of ARISTADA INITIO and single dose of 30 mg PO aripiprazole (scenario c). Based on the reviewer's simulations, it was noted that the recommendations of supplementing with ARISTADA INITIO or ARISTADA INITIO + single dose of 30 mg oral aripiprazole were as good as, and even preferable to the currently approved options of supplementing with either 7 or 21 days of oral aripiprazole. This conclusion is based on the following considerations: (i) the aripiprazole plasma concentrations were consistently higher than the 102 ng/ml lower margin of the tolerable and effective concentration range and (ii) there is less peak to trough fluctuation and (iii) the aripiprazole plasma concentrations overshooting when administering 7 or 21 days of 30 mg oral aripiprazole relative to the scenario of not missing a dose. This is illustrated in the Figure 30 - Figure 33 shown below under scenarios when supplementation is required for missing either 441 mg or 882 mg of ARISTADA lauroxil.

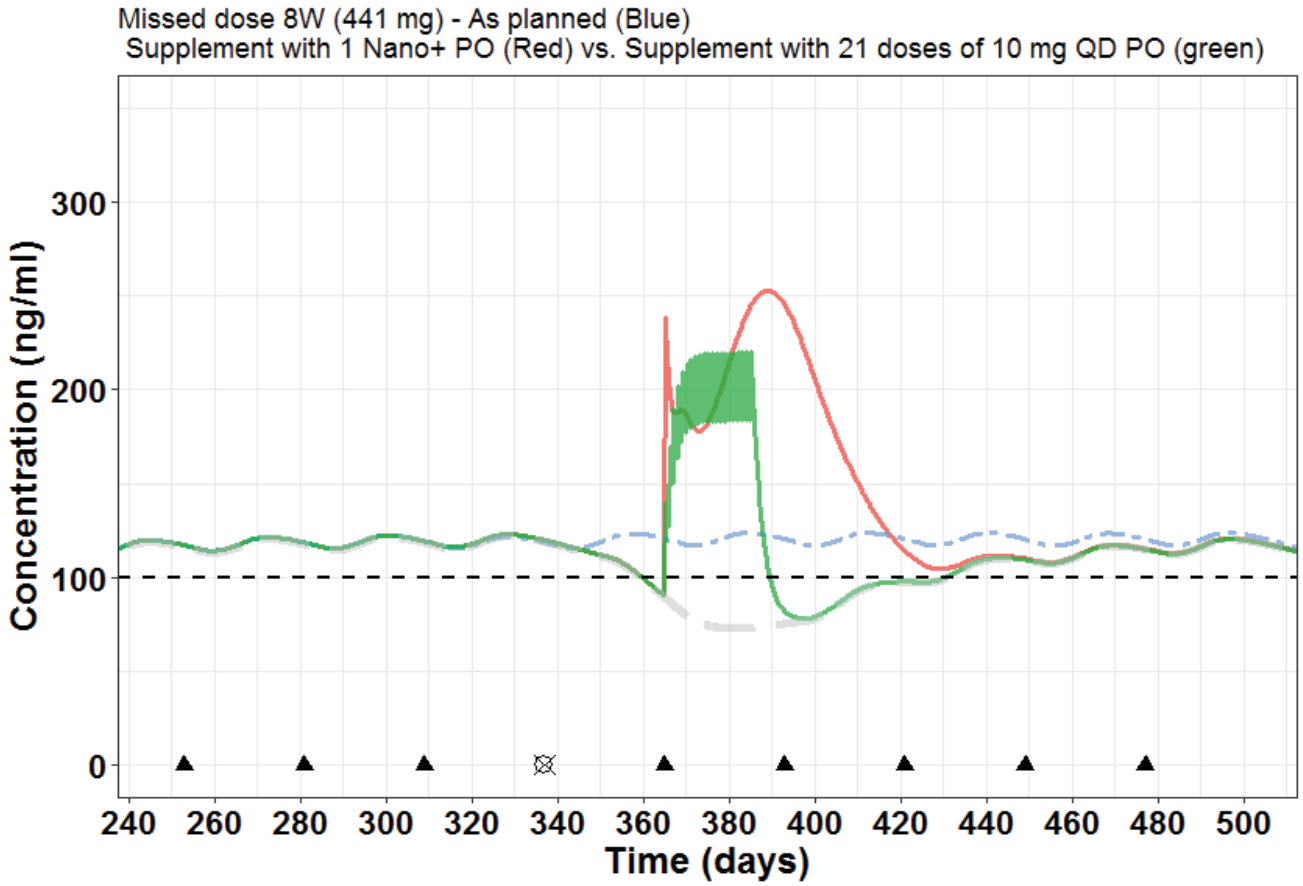
Figure 30 Scenario of missing 441 mg aristada lauroxil dose with 7 weeks or less since the last injection



Note: Dotted blue line represents the scenario without missed dose (as reference);
solid green line represents the scenario of supplementation with 7 days of oral aripiprazole,
solid orange line represents the scenario of supplementation with single dose of ARISTADA INITIO ;
dashed grey line represents the scenario of no supplementation (i.e., administering aristada lauroxil alone)

At the bottom: Closed triangles at the bottom represent the doses of aristada lauroxil, while the circle with 'x' mark represents the missed dose

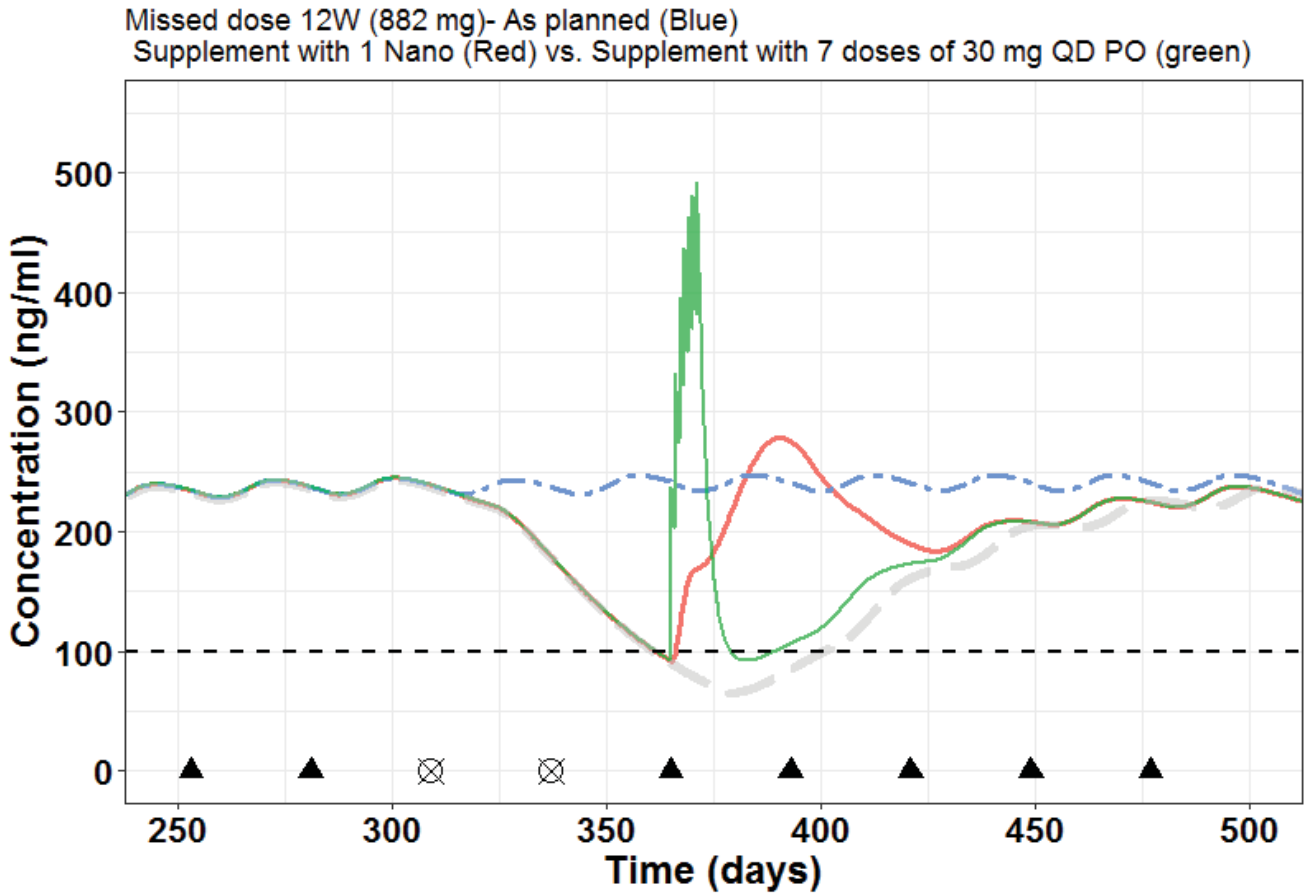
Figure 31 Scenario of missing 441 mg aristada lauroxil dose with 8 weeks or less since the last injection



Note: Dotted blue line represents the scenario without missed dose (as reference);
solid green line represents the scenario of supplementation with 21 days of oral aripiprazole,
solid orange line represents the scenario of supplementation with single dose of ARISTADA INITIO and a single dose of 30 mg oral aripiprazole;
dashed grey line represents the scenario of no supplementation (i.e., administering aristada lauroxil alone)

At the bottom: Closed triangles at the bottom represent the doses of aristada lauroxil, while the circle with 'x' mark represents the missed dose

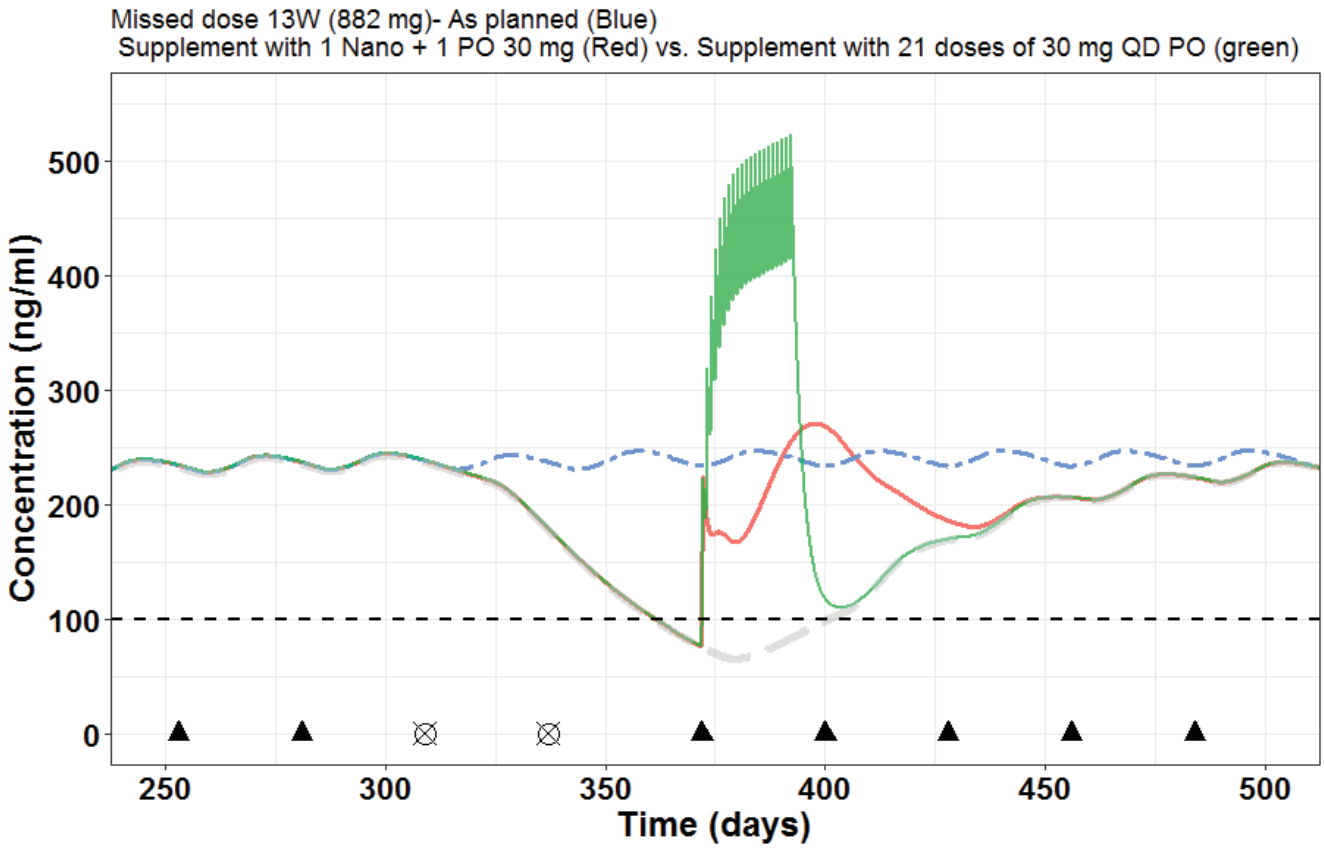
Figure 32 Scenario of missing 882 mg aristada lauroxil dose with 12 weeks or less since the last injection



Note: Dotted blue line represents the scenario without missed dose (as reference);
solid green line represents the scenario of supplementation with 7 days of oral aripiprazole,
solid orange line represents the scenario of supplementation with single dose of ARISTADA INITIO ; ;
dashed grey line represents the scenario of no supplementation (i.e., administering aristada lauroxil alone)

At the bottom: Closed triangles at the bottom represent the doses of aristada lauroxil, while the circle with 'x' mark represents the missed dose

Figure 33 Scenario of missing 882 mg aristada lauroxil dose with 13 weeks or less since the last injection



Note: Dotted blue line represents the scenario without missed dose (as reference); solid green line represents the scenario of supplementation with 21 days of oral aripiprazole, solid orange line represents the scenario of supplementation with single dose of ARISTADA INITIO and a single dose of 30 mg oral aripiprazole; ; dashed grey line represents the scenario of no supplementation (i.e., administering aristada lauroxil alone)

At the bottom: Closed triangles at the bottom represent the doses of aristada lauroxil, while the circle with 'x' mark represents the missed dose

4 APPENDIX: INDIVIDUAL CLINICAL STUDY REVIEWS

- ALK9072-B101: Single ascending dose safety, tolerability, PK study with different formulations of aripiprazole lauroxil nano-suspension (AL-NCD)

- ALK9072-B102: PK bridging study to demonstrate the adequacy of ARISTADA INITIO in obviating the need for supplemental oral dosing for aripiprazole for 21 days

- ALK9072-B103: Single dose safety, tolerability, PK study of ARISTADA INITIO in gluteal vs. deltoid muscle

CLINICAL PHARMACOLOGY STUDY REVIEW

Pharmacokinetic Study

Study # ALK9072-B101 **Study Period:** 28-Nov-2014 to 02-Sep-2015

NDA 209830

Title	A Phase 1, Placebo-controlled, Single Ascending-dose Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of ALKS 9072N in Adults with Schizophrenia
Objectives:	To determine the safety, tolerability, and pharmacokinetics (PK) of 3 formulations of ALKS 9072N over a range of dose levels in adults with schizophrenia

Study Design:

This was a Phase 1, placebo-controlled, single ascending-dose study to evaluate 3 ALKS 9072N formulations (A, B, and C) of aripiprazole lauroxil at ascending doses administered to cohorts of subjects with schizophrenia. Planned ALKS 9072N doses for the study cohorts ranged from 110 to 882 mg, with the dose of each subsequent cohort determined based on review of available safety and PK data from the preceding completed cohort.

Prospective subjects were evaluated for eligibility at a screening visit up to 30 days prior to study drug administration on Day 1. Only subjects who exhibited tolerability to oral aripiprazole (either following test doses or by documented experience) were eligible to enroll in the study. Subjects who successfully completed screening assessments were admitted to an inpatient study facility on Day -1, the day prior to dosing. Eligibility criteria were reviewed to ensure continued eligibility, and baseline assessments were conducted.

A sentinel cohort of 2 subjects received ALKS 9072N Formulation B 110 mg. After a review of available safety and PK data at 2 weeks, additional subjects were randomized in a 3:1 ratio to receive a single injection of either ALKS 9072N or placebo (phosphate-buffered saline). In addition to the sentinel cohort, the design included a total of 15 cohorts across 4 ALKS 9072N dose groups, with up to 3 sub-cohorts (for the 3 formulations) per ALKS 9072N dose group. Each subject could participate in only 1 cohort. The following table provides escalation details and reflects the planned doses and formulations to be evaluated.

Cohorts[1]	ALKS 9072N Dose	Subjects per Cohort[2]
S1B	110 mg	2
1A, 1B, 1C	221 mg	4
2A, 2B, 2C	441 mg	8
3A, 3B, 3C	441 mg	8
4A, 4B, 4C	662 mg	16
5A, 5B, 5C	882 mg	16

[1] The A, B, and C designation refers to the respective formulation (A, B, or C) administered to a given cohort. Dose escalation could have been halted for 1 or more formulations at any time.
[2] With the exception of Cohort S1B, subjects were randomized 3:1 ALKS 9072N:placebo within a cohort.

Cohorts within a grouping (eg, 1A, 1B, and 1C) were enrolled and evaluated in parallel.

Following Day 15 postdose assessments scheduled at the end of the inpatient stay, a review of available safety and PK data was conducted for each grouping. Dosing for subsequent groupings, including escalation to subsequent dose levels (eg, 2A, 2B, and 2C), was contingent upon a safety and PK review for the cohorts in the prior grouping.

Subjects were discharged from the inpatient study facility upon completion of all scheduled Day 15 postdose assessments. Following discharge, subjects returned to the study site for 16 outpatient visits through Day 113. If a subject was prematurely discontinued from the study, an early termination visit was completed using the assessments scheduled for Day 85.

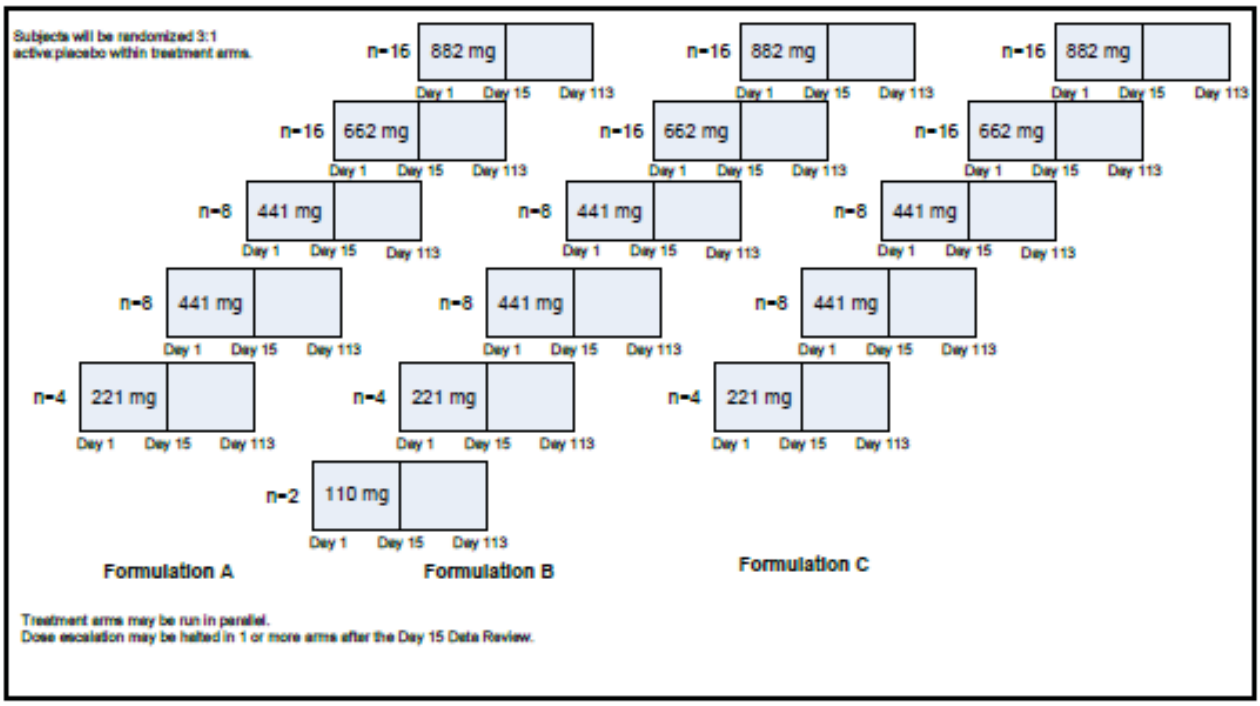
Study Treatment (including dose, mode of administration, and batch numbers):

Aripiprazole lauroxil, a micron-particle formulation of an extended-release injectable antipsychotic, is a covalent non-ester modification of aripiprazole to form *N*-lauroyloxymethyl aripiprazole. ALKS 9072N is an alternative formulation of aripiprazole lauroxil. The following cohorts and dose levels were planned for investigation:

- ALKS 9072N Formulation A: 221, 441, 662, and 882 mg (662- and 882-mg doses not used)
- ALKS 9072N Formulation B: 110, 221, 441, 662, and 882 mg
- ALKS 9072N Formulation C: 221, 441, 662, and 882 mg (882-mg dose not used)

Actual doses could be lowered based on safety review results. All formulas were administered as an intramuscular (IM) injection into the gluteal muscle. Each subject assigned to ALKS 9072N received a single injection.

Study Drug	Lot Number
ALKS 9072N Formulation A 221 and 441 mg	467-0005AB
ALKS 9072N Formulation B 110, 221, and 441 mg	467-0002AB
ALKS 9072N Formulation B 662 mg	467-0002AA
ALKS 9072N Formulation B 882 mg	467-0007AA
ALKS 9072N Formulation C 221 and 441 mg	467-0003AB
ALKS 9072N Formulation C 662 mg	467-0003AA



Route of Administration	Intra-muscular injection—Gluteal
PK Sampling Times and Parameters	**Pharmacokinetics:** • Maximum plasma concentration (C_{max}) • Time to C_{max} (t_{max}) • Area under the concentration-time curve (AUC) from time zero to the last quantifiable time interval (AUC_{last}) • AUC from time zero to infinity (AUC_{∞}) • Terminal elimination half-life ($t_{½}$) • Apparent total body clearance (CL/F) • Apparent volume of distribution during the terminal phase (Vz/F) • AUC calculated using the trapezoidal method normalized to the dose (AUC/D) • C_{max} normalized to the dose (C_{max}/D) On Day 17 through Day 21, a single sample was drawn within ±1 hour (±15 minutes) of Day 1 dosing or as close to this timeframe as possible. For Day 23 through Day 85, a single sample was collected within ±2 hours (±15 minutes) of the Day 1 dosing time or as close to this timeframe as possible. A single PK sample was drawn anytime during the day on Day 113.
Safety Parameters	

	Safety: The following assessments were collected to measure safety and tolerability throughout the study: adverse events (AEs), injection site assessment, vital signs (blood pressure, heart rate, respiratory rate, and internal body temperature), weight, clinical laboratory parameters (chemistry [including prolactin], hematology, and urinalysis), electrocardiogram (ECG) parameters, concomitant medications, Columbia Suicide Severity Rating Scale (C-SSRS) responses, Clinical Global Impressions – Severity (CGI-S) scale score, and movement disorder measures: Abnormal Involuntary Movement Scale (AIMS), Barnes Akathisia Rating Scale (BARS), and Simpson Angus Scale (SAS). In addition, safety and tolerability were assessed throughout the study on the basis of: • AEs • Injection site assessment • Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) and weight • Clinical laboratory parameters (biochemistry [including prolactin], hematology, and urinalysis) • ECG parameters • C-SSRS responses • Movement disorder measures − Abnormal Involuntary Movement Scale (AIMS) − Barnes Akathisia Rating Scale (BARS) − Simpson Angus Scale (SAS) • CGI-S responses
PK Moieties	Concentrations of Aripiprazole Lauroxil, *N*-hydroxymethyl aripiprazole, aripiprazole, and dehydro-aripiprazole (the primary metabolite of aripiprazole) were quantified in plasma samples
PD Endpoint(s)	NA
PD Parameters	NA
Statistical Methods	The enrolled population included all subjects who signed inform consent and were enrolled to a treatment cohort including the sentinel cohort, regardless of whether they received study drug or not. The safety population included all subjects who received study drug. The PK population included all subjects who received study drug and had at least 1 measurable concentration. **Pharmacokinetics:** Individual concentrations for each analyte were summarized over time for each dose and formulation using descriptive statistics. Pharmacokinetic parameters were calculated using noncompartmental techniques, and actual elapsed time from dosing was used to estimate individual plasma PK parameters, which were summarized using descriptive statistics. Dose proportionality of aripiprazole was assessed for AUC_{∞}, AUC_{last}, and C_{max} over the studied dose range using a power model for each formulation where at least 3 dose levels were administered. Safety: Treatment-emergent AEs (TEAEs) were defined as AEs that were newly occurring or worsening from the time of administration of IM study drug. The number and percentage of subjects with TEAEs were summarized by cohort, treatment group, and overall; by severity; and by relationship to study drug. Serious AEs and AEs resulting in treatment discontinuation were also summarized. Laboratory parameters (including prolactin results) vital signs findings, and ECG results were summarized as follows: • Change from baseline by visit and treatment group for each dose. • Number (%) of subjects with potentially clinically significant (PCS) values at any post-baseline visit by dose and pooled placebo for each formulation.

Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	Aripiprazole Lauroxil, *N*-hydroxymethyl aripiprazole Aripiprazole (Parent) Dehydro-aripiprazole (Primary metabolite)		

Validation	▪ Method validated prior to use	☑ Yes	☐ No
	▪ Method validation acceptable	☑ Yes	☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes	☐ No
	▪ Quality control samples range acceptable	☑ Yes	☐ No
	▪ Chromatograms provided	☑ Yes	☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes	☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes	☐ No
	▪ Overall performance acceptable	☑ Yes	☐ No

Study Population:

- 18-65 years patients with diagnosis of either chronic schizophrenia or schizoaffective disorder
- A total of 114 subjects were enrolled in this study and all received 1 dose of study drug. Two of these were sentinel subjects who received open-label ALKS 9072N. A total of 112 subjects were randomized to either placebo (29 subjects) or ALKS 9072N (83 subjects).

Main Criteria for Subject Inclusion:

Subjects with a diagnosis of either chronic schizophrenia or schizoaffective disorder, as defined by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria at Screening, and demonstration of clinical stability, as evidenced by a) no hospitalizations for acute psychiatric exacerbations within 3 months prior to Screening and upon admission; and b) a Clinical Global Impression-Severity Scale (CGI-S) score of ≤3 (mild) at Screening and upon admission were eligible for enrollment. Subjects were to have been receiving a stable oral antipsychotic medication regimen (excluding clozapine) for at least 2 months prior to Screening and have no antipsychotic medication regimen change between Screening and admission.

Table 1: Demography of subjects

Parameter/Statistic	221 mg		441 mg		662 mg		882 mg	
	Placebo N=3	ALKS 9072N N=10	Placebo N=13	ALKS 9072N N=37	Placebo N=9	ALKS 9072N N=24	Placebo N=4	ALKS 9072N N=12
Age (years)								
Mean (SD)	45.7 (11.37)	43.1 (6.72)	44.0 (12.29)	48.4 (9.11)	46.0 (5.34)	45.3 (12.16)	49.3 (4.11)	42.3 (9.64)
Median (Min, Max)	49.0 (33, 55)	41.5 (35, 55)	45.0 (25, 61)	52.0 (29, 61)	47.0 (36, 54)	48.5 (20, 63)	49.5 (44, 54)	44.5 (24, 57)
Gender, n (%)								
Male	3 (100.0)	7 (70.0)	11 (84.6)	26 (70.3)	6 (66.7)	22 (91.7)	2 (50.0)	9 (75.0)
Female	0	3 (30.0)	2 (15.4)	11 (29.7)	3 (33.3)	2 (8.3)	2 (50.0)	3 (25.0)
Race, n (%)								
Asian	0	0	0	1 (2.7)	0	0	0	0
Black or African American	3 (100.0)	8 (80.0)	10 (76.9)	30 (81.1)	8 (88.9)	18 (75.0)	4 (100.0)	10 (83.3)
White	0	2 (20.0)	3 (23.1)	6 (16.2)	1 (11.1)	6 (25.0)	0	2 (16.7)
Ethnicity, n (%)								
Hispanic or Latino	0	0	2 (15.4)	5 (13.5)	0	2 (8.3)	0	1 (8.3)
Not Hispanic or Latino	3 (100.0)	10 (100.0)	11 (84.6)	32 (86.5)	9 (100.0)	22 (91.7)	4 (100.0)	11 (91.7)
Body Mass Index (kg/m^2)								
Mean (SD)	31.57 (6.266)	28.88 (5.602)	30.16 (5.908)	30.68 (5.533)	30.71 (5.272)	28.44 (5.190)	26.85 (5.587)	28.05 (4.750)
Median (Min, Max)	28.10 (27.8, 38.8)	28.20 (19.9, 37.5)	29.20 (20.9, 38.1)	30.40 (18.5, 39.7)	30.80 (21.4, 37.1)	27.20 (18.4, 38.9)	26.65 (21.4, 32.7)	27.05 (21.5, 38.2)

Inclusion Crietria:

1. Willing and able to provide informed consent
2. 18–65 years of age, inclusive, at Screening
3. Met either of the following tolerability criteria upon admission to the inpatient study facility:
   - Demonstrated tolerability to test doses of oral aripiprazole during Screening
   - Had a history of tolerated use of aripiprazole
4. Diagnosis of either chronic schizophrenia or schizoaffective disorder, as defined by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (American Psychiatric Association 2013) criteria at Screening, and demonstration of clinical stability, as evidenced by the following criteria:
   a. No hospitalizations for acute psychiatric exacerbations within 3 months prior to Screening and upon admission
   b. Clinical Global Impression-Severity Scale (CGI-S) score of ≤3 (mild) at Screening and upon admission
5. Had been on a stable oral antipsychotic medication regimen (excluding clozapine) for at least 2 months prior to Screening and had no antipsychotic medication regimen change between Screening and admission. A medication or dose level change that occurred after Screening and before admission was allowed if tolerability improved before admission
6. Agreed to remain on current antipsychotic regimen (medication and dose level) for the duration of the study, unless a change was medically indicated

Exclusion Criteria:

1. Pregnant, planning to become pregnant, or currently breastfeeding at Screening or upon admission
2. Met any of the following exclusionary medication criteria:
   a. Had received oral aripiprazole within 28 days prior to randomization
   b. Had received AL or IM depot aripiprazole within 6 months prior to admission
   c. Had taken any other extended release (also known as long-acting) injectable antipsychotic within 3 months prior to admission
   d. Was currently being treated with clozapine
3. Had participated in a clinical trial involving any investigational product (ie, drug, device, biologic) within the past 3 months, or was currently participating in a clinical trial involving an investigational product
4. History of psychopathology, other than schizophrenia or schizoaffective disorder, as indicated by any of the following:
   - DSM-5 (American Psychiatric Association 2013) Axis I diagnosis other than chronic schizophrenia or schizoaffective disorder within the 12 months prior to Screening or upon admission
   - DSM-5 (American Psychiatric Association 2013) diagnosis of moderate or severe substance use disorder (except tobacco use disorder), within the 12 months prior to Screening or upon admission
5. In the opinion of the Investigator, the subject was deemed to be a danger to himself/herself or others at Screening or upon admission or met one of the following criteria for elevated suicidal ideation or behavior:
6. History or current evidence of a clinically significant condition or abnormality (including clinical laboratory test results or electrocardiogram [ECG] findings) that, in the opinion of the Investigator, could preclude safe participation in the study, or had any other disease or condition that could prevent, limit, or confound protocol specified assessments including, but not limited to:
   a. Uncontrolled diabetes (hemoglobin A1c [HbA1c] >7%), heart disease, or stroke
   b. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels ≥2 times the upper limit of the laboratory reference range
   c. Thyroid stimulating hormone (TSH) >10% above upper limit of laboratory reference range
   d. An absolute neutrophil count $\leq 1.5\times10^3/\mu L$
   e. A platelet count $\leq 100\times10^3/\mu L$
   f. History of or positive test result for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen, or antihepatitis C virus antibody
7. History or evidence of neuroleptic malignant syndrome or clinically significant tardive dyskinesia
8. Had a QT interval (corrected using the Fridericia formula; QTcF) >450 ms for men or >470 ms for women at Screening or upon admission
9. Had used potent cytochrome P450 (CYP) 3A4 inducers or inhibitors or CYP2D6 inhibitors (prescription medications, over-the-counter [OTC] medications, or dietary supplements) within 30 days prior to admission
10. Was a CYP2D6 "Poor Metabolizer" as determined by pharmacogenetic testing conducted at Screening
11. Had a positive urine drug test for amphetamines, barbiturates, cocaine, methadone, opiates, or phencyclidine at Screening or upon admission

Results

Based on the results of this study, the following PK conclusions can be made:

- Exposure to aripiprazole, dehydro-aripiprazole, and N-hydroxymethyl aripiprazole increased with increasing dose of IM ALKS 9072N over the 221 to 882 mg dose range tested for these 3 formulations. There were no meaningful differences among the 3 formulations for these analytes.
- Formulation B was selected for continued development on the basis of drug product stability, and process and manufacturing capabilities at the time of the study.
- Aripiprazole lauroxil was generally not measurable following IM administration of ALKS 9072N at doses up to 882 mg.
- Plasma aripiprazole concentrations following ALKS 9072N administration increased steadily (median tmax 16-31 days), then gradually declined through Day 115. There was no evidence of early release of aripiprazole following IM administration of ALKS 9072N.
- Aripiprazole exposure (C_{max}, AUC) was dose-proportional for Formulation B across the dose range of 441 mg to 882 mg.
- Dehydro-aripiprazole concentrations increased slowly following IM administration of ALKS 9072N (median tmax Day 21 to 35 days), and then declined through Day 115.
- The metabolite-to-parent ratios (dehydro-aripiprazole/ aripiprazole) were 35% to 49% over the 221- to 882-mg dose range for the 3 formulations combined.
- Total N-hydroxymethyl aripiprazole exposure (AUC_{last}) was, on average, approximately 5% to 10% of that for aripiprazole exposure across all dose levels and formulations.
- Overall variability in aripiprazole, *N*-hydroxymethyl aripiprazole, and dehydro-aripiprazole PK following IM ALKS 9072N administration was consistent, and generally not greater, as compared to previously reported variability for ARISTADA® (Alkermes Inc 2016).

Figure 1: Mean (SD) Aripiprazole Concentrations Over Time for the different formulations (A, B and C) **of ALKS 9072N at 441 mg**

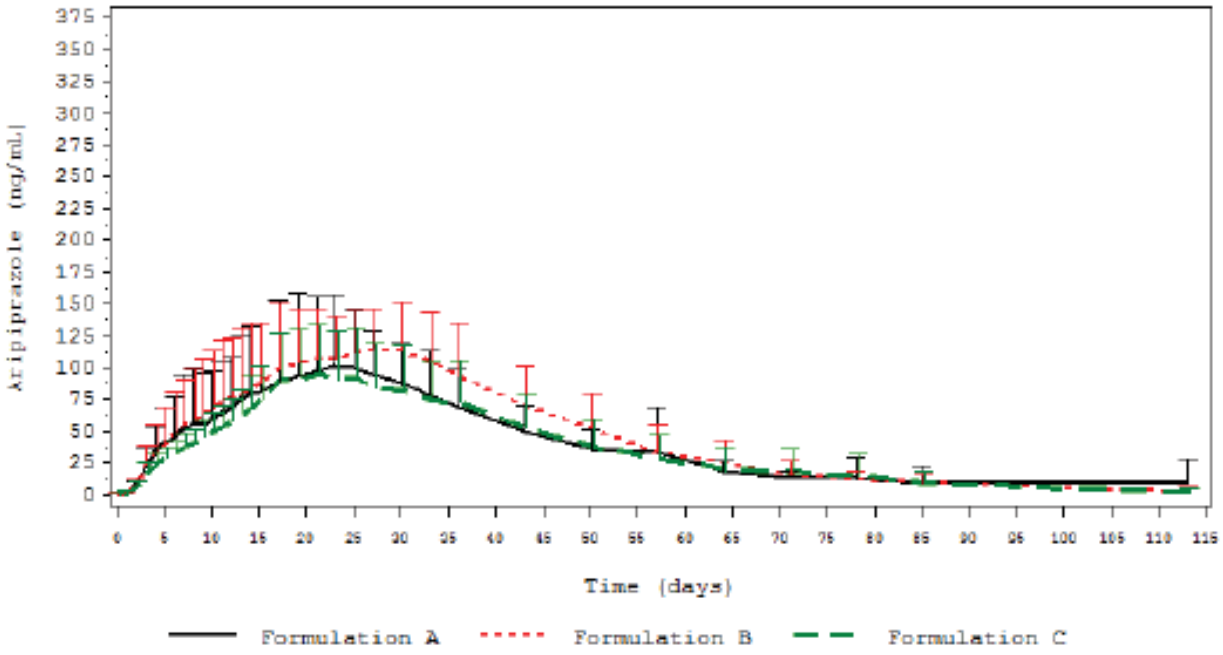


Figure 2: Mean (SD) Aripiprazole Concentrations Over Time for formulations B of ALKS 9072N at different dose levels

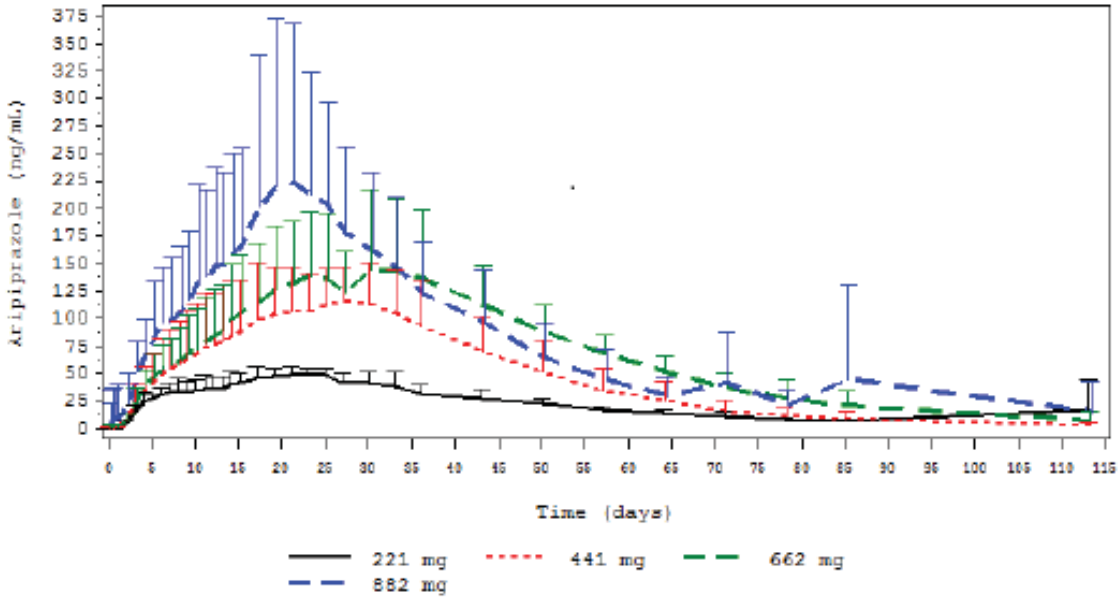


Table 1: **PK Parameters for Aripiprazole in Plasma Following a Single IM Administration of ALKS 9072N in Subjects With Schizophrenia**

Aripiprazole									
	Formulation A		Formulation B				Formulation C		
Parameter	221 mg	441 mg	221 mg	441 mg	662 mg	882 mg	221 mg	441 mg	662 mg
C_{max} (ng/mL)									
n	3	12	4	12	12	12	3	12	12
Mean (SD)	90.30 (26.848)	126.19 (60.340)	52.45 (6.638)	136.48 (45.835)	171.55 (73.670)	233.92 (136.213)	74.27 (33.851)	108.40 (37.529)	199.82 (80.399)
Geometric Mean	87.69	115.79	52.12	127.95	158.16	207.31	68.70	102.34	181.41
Median	86.10	105.50	53.95	140.50	163.00	196.00	74.50	110.50	196.50
Min, Max	65.8, 119.0	69.2, 280.0	43.3, 58.6	58.4, 191.0	84.1, 344.0	86.0, 605.0	40.3, 108.0	54.5, 177.0	60.2, 352.0
t_{max} (day)									
n	3	12	4	12	12	12	3	12	12
Median	31.0	24.0	22.0	24.0	26.5	19.0	22.1	20.0	16.0
Min, Max	18, 35	7, 29	16, 33	13, 35	16, 35	9, 32	22, 29	10, 35	12, 35
AUC_{last} (day*ng/mL)									
N	3	12	4	12	12	12	3	12	12
Mean (SD)	3782.84 (1394.763)	4182.58 (1487.521)	1922.07 (658.892)	4796.34 (1683.658)	6942.40 (2264.835)	7012.92 (4469.921)	2369.37 (121.295)	4015.26 (1564.597)	6545.19 (2398.914)
Geometric Mean	3619.41	4000.00	1818.88	4423.64	6565.10	5237.35	2367.27	3736.07	6079.17
Median	3430.49	3605.16	2045.24	4878.05	6570.82	6895.38	2400.94	3630.62	6838.94
Min, Max	2698.0, 5320.0	2922.4, 8291.7	1013.3, 2584.5	1260.4, 8135.0	2549.1, 11997.1	688.3, 15934.3	2235.4, 2471.8	2070.7, 6692.9	2206.5, 11388.3

Aripiprazole									
	Formulation A		Formulation B				Formulation C		
Parameter	221 mg	441 mg	221 mg	441 mg	662 mg	882 mg	221 mg	441 mg	662 mg
AUC_{∞} (day*ng/mL)									
n	3	10	3	11	12	8	3	12	10
Mean (SD)	3874.16 (1347.205)	4197.70 (1600.361)	2335.21 (245.380)	5221.96 (1307.818)	7382.45 (2068.137)	8092.24 (2772.045)	2411.21 (84.936)	4177.35 (1794.931)	7361.20 (1903.968)
Geometric Mean	3723.32	3999.93	2326.93	5077.43	7108.26	7682.08	2410.21	3848.06	7149.11
Median	3585.13	3592.28	2207.24	5050.21	7591.06	8241.22	2425.86	3667.50	7412.90
Min, Max	2694.9, 5342.4	2987.9, 8424.5	2180.3, 2618.1	2946.9, 8329.9	3606.4, 12098.9	4338.5, 13262.4	2319.9, 2487.9	2080.9, 7976.5	4816.6, 11436.8
$t_{½}$ (day)									
n	3	10	3	11	12	8	3	12	10
Mean (SD)	15.486 (5.1301)	14.162 (4.2779)	20.096 (8.1238)	15.693 (7.9238)	18.175 (12.4240)	17.340 (7.2481)	11.104 (2.7613)	14.519 (7.2847)	16.855 (5.5925)
Geometric Mean	14.830	13.600	19.114	14.193	15.233	15.876	10.890	13.034	15.946
Median	17.488	12.962	16.394	11.694	13.544	18.168	9.984	15.097	16.091
Min, Max	9.66, 19.31	9.96, 20.70	14.48, 29.41	7.50, 33.60	7.83, 44.50	7.71, 28.40	9.08, 14.25	6.34, 31.89	7.44, 26.46

AUC=Area under the concentration versus time curve calculated; C_{max}=Maximum observed concentration; IM=intramuscular; max=maximum; min=minimum; PK=pharmacokinetic; SD=standard deviation; $t_{½}$=terminal elimination half-life; t_{max}=time to maximum observed concentration

Table 2: **Dose-Proportionality Assessment of Aripiprazole Across the Dose Range of 221 to 882 mg ALKS 9072N for Formulation B**

Formulation/Parameter	n	Slope Estimate	Standard Error	95% Confidence Interval
Formulation B (221 mg-882 mg)				
AUC_{∞} (day·ng/mL)	34	0.8304	0.1269	(0.62, 1.05)
AUC_{last} (day·ng /mL)	40	0.7135	0.2453	(0.30, 1.13)
C_{max} (ng/mL)	40	0.9073	0.1598	(0.64, 1.18)

Safety Results

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Based on the results of this study, the following safety conclusions can be made:

- Treatment with IM ALKS 9072N in subjects with schizophrenia was generally safe and well tolerated.
- Adverse events were generally consistent with what is established and known of the safety of aripiprazole.
- No subjects died during the study.
- Serious TEAEs were reported for 1 subject each receiving placebo (schizoaffective disorder) or ALKS 9072N 221 mg (schizoaffective disorder) and for 2 subjects receiving ALKS 9072N 441 mg (schizophrenia and hypothyroidism, 1 subject each). None of these was assessed as related to study drug. Two of these subjects discontinued the study as a result of the SAEs (schizoaffective disorder [placebo] and hypothyroidism [ALKS 9072N 441 mg]). No formulation or dose-dependent patterns were observed.
- The frequency of TEAEs was 44.8% in subjects who received placebo, 60.0% in subjects who received ALKS 9072N 221 mg, 70.3% in subjects who received ALKS 9072N 441 mg, 62.5% in subjects who received ALKS 9072N 662 mg, and 50.0% in subjects who received ALKS 9072N 882 mg. Most TEAEs were of mild or moderate intensity.
- The TEAE with the highest frequency during the study was injection site pain, which was reported by subjects at ALKS 9072N doses of 441 mg and higher for all 3 formulations; no subjects who received placebo or ALKS 9072N 221 mg reported this AE.
- No clinically meaningful trends were observed for laboratory, vital sign, or ECG results. There were no systematic effects on hepatic function or notable cases of apparent hepatic injury (ie, no cases that met Hy's Law).
- A larger proportion of subjects in the highest ALKS 9072N dose groups gained ≥7% body weight compared with placebo, however, in the cases that were reported as TEAEs the investigator did not regard these as related to study drug.

Table 3: Summary of Adverse Events

Category	ALKS 9072N				
	Placebo N=29 n (%)	221 mg N=10 n (%)	441 mg N=37 n (%)	662 mg N=24 n (%)	882 mg N=12 n (%)
Any TEAE	13 (44.8)	6 (60.0)	26 (70.3)	15 (62.5)	6 (50.0)
Drug-Related TEAE	4 (13.8)	2 (20.0)	14 (37.8)	12 (50.0)	4 (33.3)
Severe TEAE	1 (3.4)	1 (10.0)	1 (2.7)	0	0
Serious AE	1 (3.4)	1 (10.0)	2 (5.4)	0	0
AE Leading to Discontinuation	1 (3.4)	0	1 (2.7)	0	0

TEAE=treatment-emergent adverse event
Severity was summarized using the maximum severity per subject.
Treatment-related AEs were defined as those events with a "Relationship to Study Treatment" recorded on the case report form as "Definitely Related," "Probably Related," or "Possibly Related"; other categories were not considered related.

Overall Sponsor Conslusions

In conclusion, this study of 3 formulations of ALKS 9072N at doses from 221 mg to 882 mg showed that there were no meaningful differences among the formulations and aripiprazole exposure was dose-proportional across the dose range. The PK properties of ALKS 9072N demonstrated more rapid uptake than ARISTADA, as intended. Analytes *N*-hydroxymethyl aripiprazole and dehydro-aripiprazole had exposures within the range that has previously been observed for ARISTADA. Under the conditions of this study, this drug product was safe and well tolerated.

Reviewer Comments

1. *Study Design: This was Phase 1, placebo-controlled, single ascending-dose study to evaluate 3 ALKS 9072N formulations (A, B, and C) of aripiprazole lauroxil at ascending doses administered to cohorts of subjects with schizophrenia.*
   - *The study was conducted with the 3 different formulations to select the final to-be-marketed formulation of ALKS9072N*
   - *The study was conducted at the acceptable dose range which was previously determined to be safe and tolerated in schizophrenia patients.*
   - *It was a single ascending-dose study with each dose-escalation only after a review of safety/PK assessment of preceding cohort.*
   - *Adequate numbers (N=114) of adult patients (male and females) between the age of 18-65 year were used.*
   - *PK analysis using a validated method was performed for aripiprazole and its metabolites and*

appropriate PK parameters (i.e., Cmax, AUC, Tmax etc.) were assessed.

- *The study excluded all strong inhibitors of CYP3A4 or CYP2D6 as well as patients who were poor metabolizers of CYP2D6, which minimized the potential for drug interactions and variability of PK due to pharmacogenomics effects.*
- *Therefore, the overall study design was acceptable.*

2. *Protocol deviation: No major or minor protocol deviations were reported.*

3. *Data Analysis (i.e., any outliers etc.): There were no outliers and the PK data from all subjects were included in the analysis.*

4. *Bioanalytical Method: A validated bio-analytical methodology was used which was acceptable.*

5. *Inclusion and Exclusion Criteria: Subjects were adult males and females between the ages of 18 and 65 years. They all had diagnosis of either chronic schizophrenia or schizoaffective disorder, as defined by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). Since Aripiprazole is known to be metabolized via the CYP3A4 and CYP2D6 pathway, the study excluded any subjects who had potent cytochrome P450 (CYP) 3A4 inducers or inhibitors or CYP2D6 inhibitors (prescription medications, over-the-counter [OTC] medications, or dietary supplements) within 30 days prior to admission as well as CYP2D6 "Poor Metabolizer" as determined by pharmacogenetic testing conducted at Screening*

6. *Pharmacokinetic findings: We agree with the sponsor's PK analysis and conclusions from the study.*

Overall Reviewer Conslusions:

We agree with the sponsor's overall conclusions. This was an investigative study to help them select an appropriate formulation that they could use in their subsequent clinical studies (i.e., PK-bridging study as well as injection site study). The sponsor selected formulation B which demonstrated slightly higher Cmax and AUC compared to the other 2 formulations. Subsequently, the PK-bridging study as well as the injection site study was done with formulation B.

CLINICAL PHARMACOLOGY STUDY REVIEW

Pharmacokinetic Study

Study # ALK9072-B102	**Study Period:** 27-Oct-2015 to 26-July-2016
NDA 209830	
Title	A Phase 1 Study of an ALKS 9072N Initiation Regimen in Adults with Schizophrenia
Objectives:	**Primary Objective** The primary objective of this study was to compare the pharmacokinetics (PK) of aripiprazole following administration of an NCD initiation regimen versus an oral aripiprazole initiation regimen. **Secondary Objectives** The secondary objective of this study was to determine the safety and tolerability of administration of an NCD initiation regimen versus an oral aripiprazole initiation regimen.

Study Design:

This was a Phase 1, double-blind, placebo-controlled study to assess the PK, safety, and tolerability of 2 initiation regimens administered prior to either a 441 or 882 mg IM dose of AL:

- NCD initiation regimen, consisting of a single 662 mg IM dose of AL-NCD coadministered with a single 30 mg oral dose of aripiprazole
- Oral initiation regimen, consisting of 21 days of 15 mg oral aripiprazole (with only the first oral aripiprazole dose given prior to the IM dose of AL)

Prospective subjects were evaluated during a 30-day screening period prior to enrollment in the study. For subjects who had never taken aripiprazole, 5 mg test doses of oral aripiprazole were administered on Day -30 and Day -29. Only subjects who exhibited tolerability to oral aripiprazole (either following test doses or from past reported experience) were eligible to enroll in the study. For eligible subjects who received oral aripiprazole during Screening, 28 days elapsed between the last dose of oral aripiprazole and the IM injection of study drug on Day 1. Subjects remained on their regular oral antipsychotic regimens, excluding oral aripiprazole, for the duration of the study.

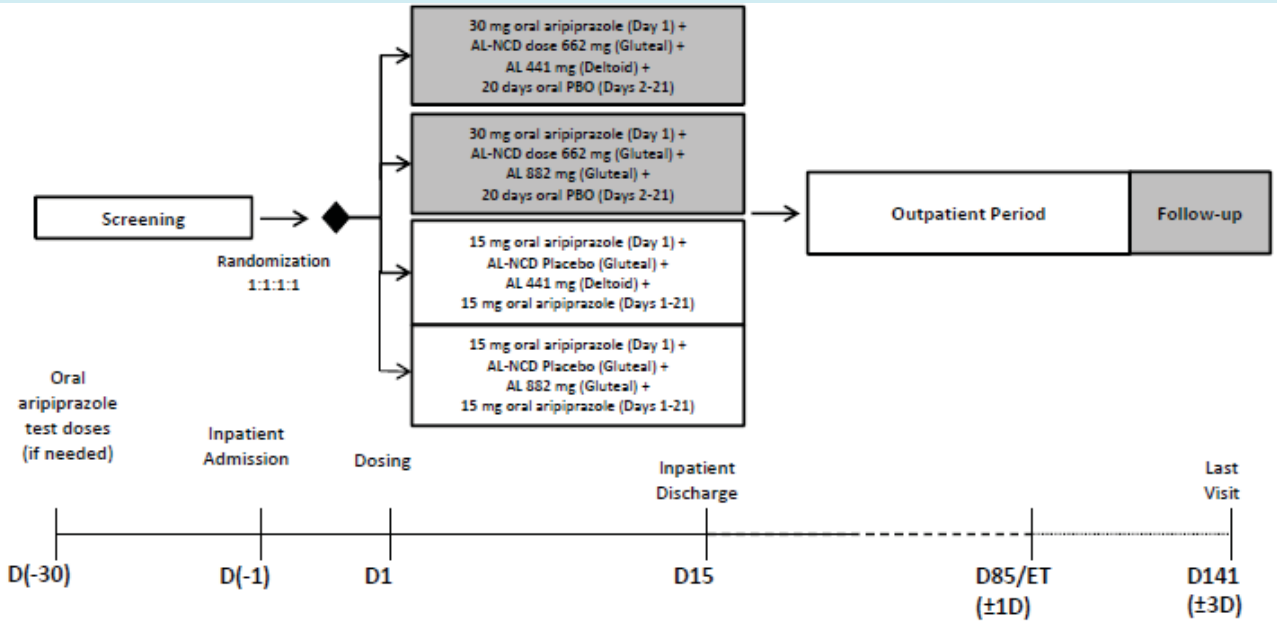
All subjects were admitted to an inpatient study facility the day prior to scheduled dosing (Day -1). Upon admission, subjects were re-evaluated for eligibility and safety assessments were conducted. A total of 160 subjects were planned to be enrolled and randomly assigned in a 1:1:1:1 fashion to 1 of 4 treatment groups, as follows:

- Group 1: **NCD initiation regimen/AL 441 mg**: NCD initiation regimen (30 mg oral aripiprazole on Day 1 followed by oral placebo for 20 days + AL-NCD 662 mg [gluteal]) + 441 mg AL (deltoid) on Day 1
- Group 2: **NCD initiation regimen/AL 882 mg**: NCD initiation regimen (30 mg oral aripiprazole on Day 1 followed by oral placebo for 20 days + AL-NCD 662 mg [gluteal]) + 882 mg AL (gluteal) on Day 1
- Group 3: **Oral initiation regimen/AL 441 mg**: oral initiation regimen (15 mg oral aripiprazole for 21 days [Days 1-21] + placebo NCD IM injection [gluteal]) + 441 mg AL (deltoid) on Day 1
- Group 4: **Oral initiation regimen/AL 882 mg**: oral initiation regimen (15 mg oral aripiprazole for 21 days [Days 1-21] + placebo NCD IM injection [gluteal]) + 882 mg AL (gluteal) on Day 1

In all study groups, the order of administration was fixed as follows:

1. Oral aripiprazole
2. Intramuscular injection of AL-NCD or placebo NCD (administered no more than 15 minutes after oral aripiprazole)

3. Intramuscular injection of AL (administered no more than 30 minutes after IM injection of AL-NCD or placebo NCD)



Abbreviations: AL=aripiprazole lauroxil; D=Day; ET=early termination; PBO=placebo

Route of Administration	Oral and Intra-muscular injection
PK Sampling Times and Parameters	**Pharmacokinetics:** Blood samples were collected within 1 hour predose and 1, 2, 3, 4, 5, 6, and 8 hours (±15 minutes) postdose on Day 1. On Days 2 to 15, a single sample was collected prior to oral aripiprazole (or oral placebo) administration and after the ECG assessment. On Days 16 to 21, a single sample was collected prior to oral aripiprazole (or oral placebo) administration. Following collection of the predose sample on Day 21, additional samples were collected at 1, 2, 3, 4, 5, 6, and 8 hours (±15 minutes) postdose. For Days 23 to 85, a single sample was collected within ±2 hours of the Day 1 oral dosing time or as close to that timeframe as possible. A single PK sample was collected on Day 113 and Day 141. Concentrations of AL, *N*-hydroxymethyl aripiprazole, aripiprazole, and dehydro-aripiprazole (the primary metabolite of aripiprazole) were quantified in these plasma samples for the computation of the following PK parameters: **Parameter** — **Description** C_{max} — Maximum observed concentration T_{max} — Time to the C_{max} AUC_{last} — Area under the concentration-vs-time curve from time 0 to the time of the last quantifiable concentration, using the linear trapezoidal rule AUC_{0-28} — Area under the concentration-vs-time curve from time 0 to 28 days postdose, using the linear trapezoidal rule T_{last} — Time of last measurable concentration
Safety Parameters	

	Safety and tolerability were assessed throughout the study on the basis of adverse events (AEs); injection site assessment; vital signs (blood pressure, heart rate, respiratory rate, and body temperature) and weight; clinical laboratory parameters (biochemistry [including prolactin], hematology, and urinalysis); electrocardiogram (ECG) parameters; Columbia-Suicide Severity Rating Scale (C-SSRS) responses; and Clinical Global Impression – Severity (CGI-S) responses. Subjects were assessed for movement disorders using the Abnormal Involuntary Movement Scale (AIMS); Barnes Akathisia Rating Scale (BARS); and Simpson Angus Scale (SAS). In addition, safety and tolerability were assessed throughout the study on the basis of: • AEs • Injection site assessment • Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) and weight • Clinical laboratory parameters (biochemistry [including prolactin], hematology, and urinalysis) • ECG parameters • C-SSRS responses • Movement disorder measures − Abnormal Involuntary Movement Scale (AIMS) − Barnes Akathisia Rating Scale (BARS) − Simpson Angus Scale (SAS) • CGI-S responses
PK Moieties	Concentrations of Aripiprazole Lauroxil, *N*-hydroxymethyl aripiprazole, aripiprazole, and dehydro-aripiprazole (the primary metabolite of aripiprazole) were quantified in plasma samples
PD Endpoint(s)	NA
PD Parameters	NA
Statistical Methods	

Statistical Methods:

In general, descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum for continuous variables, and number and percentage of subjects in each category for categorical variables) were summarized by treatment group for evaluated variables.

All analyses were based on observed data only, and no missing values were imputed. Source data for the summary tables and statistical analyses were presented as subject data listings.

Pharmacokinetics:

Concentration data were summarized according to nominal (protocol-specified) sampling times. Pharmacokinetic parameters were calculated for 4 analytes: AL, *N*-hydroxymethyl aripiprazole, aripiprazole, and dehydro-aripiprazole, using noncompartmental analysis. Actual elapsed time from dosing was used to estimate individual plasma PK parameters. Given the limited number of quantifiable samples for AL, no PK parameters were computed for this analyte. On days where intensive PK samples were collected following oral aripiprazole administration (Day 1 and Day 21), only the trough plasma concentrations were used in the PK parameter calculations.

Pharmacokinetic parameters for *N*-hydroxymethyl aripiprazole, aripiprazole, and dehydro-aripiprazole in plasma were listed separately and summarized by treatment group. Descriptive statistics of PK parameters consisted of number of subjects (n), arithmetic mean, geometric mean, SD, standard error, percent coefficient of variation, median, minimum, and maximum. A by-subject listing of individual PK parameters for each treatment group is provided.

Safety:

Adverse events were coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA, Version 18.0). Treatment-emergent AEs (TEAEs), including drug-related TEAEs, serious adverse events (SAEs), and TEAEs leading to discontinuation, were summarized by treatment group, by MedDRA SOC and PT. Injection site reactions reported as AEs, and any associated information (eg, injection site pain, redness, swelling), were summarized separately for aripiprazole lauroxil NCD and AL injections, by treatment group.

The absolute value and changes from baseline of laboratory test results, vital sign measurements, weight, and ECG findings were summarized by treatment group and timepoint. Subjects with potentially clinically significant values were summarized.

Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	Aripiprazole Lauroxil, *N*-hydroxymethyl aripiprazole Aripiprazole (Parent) Dehydro-aripiprazole (Primary metabolite)		

Validation	▪ Method validated prior to use	☑ Yes ☐ No
	▪ Method validation acceptable	☑ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No

Study Population: 18-65 years patients with diagnosis of either chronic schizophrenia or schizoaffective disorder

Planned: A total of 160 subjects were planned to be enrolled, with 40 subjects each included in each of 4 treatment groups.

Actual: A total of 161 subjects were enrolled, including 39 in Group 1 (NCD initiation regimen/AL 441 mg); 41 in Group 2 (NCD initiation regimen/AL 882 mg); 40 in Group 3 (Oral initiation regimen/AL 441 mg); and 41 in Group 4 (Oral initiation regimen/AL 882 mg). All 161 subjects were included in analyses of safety and PK data.

Main Criteria for Subject Inclusion:

Subjects with a diagnosis of either chronic schizophrenia or schizoaffective disorder, as defined by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria at Screening, and demonstration of clinical stability, as evidenced by a) no hospitalizations for acute psychiatric exacerbations within 3 months prior to Screening and upon admission; and b) a Clinical Global Impression-Severity Scale (CGI-S) score of ≤3 (mild) at Screening and upon admission were eligible for enrollment. Subjects were to have been receiving a stable oral antipsychotic medication regimen (excluding clozapine) for at least 2 months prior to Screening and have no antipsychotic medication regimen change between Screening and admission.

Table 1: Demography of subjects

Category	Treatment Group				All (N=161)
	NCD Initiation/ AL 441 mg (N=39)[a]	NCD Initiation/ AL 882 mg (N=41)[b]	Oral Initiation/ AL 441 mg (N=40)[c]	Oral Initiation/ AL 882 mg (N=41)[d]	
Age (years)					
Mean (SD)	44.4 (10.03)	42.3 (12.39)	44.2 (9.67)	45.0 (10.19)	44.0 (10.59)
Median	44.0	45.0	46.5	47.0	46.0
Min – Max	25 – 61	20 - 61	18 - 59	22 - 64	18 - 64
Sex, n (%)					
Male	30 (76.9)	29 (70.7)	27 (67.5)	32 (78.0)	118 (73.3)
Female	9 (23.1)	12 (29.3)	13 (32.5)	9 (22.0)	43 (26.7)
Ethnicity, n (%)					
Not Hispanic or Latino	39 (100.0)	38 (92.7)	38 (95.0)	40 (97.6)	155 (96.3)
Hispanic or Latino	0	3 (7.3)	2 (5.0)	1 (2.4)	6 (3.7)
Primary Race, n (%)					
Black or African American	31 (79.5)	33 (80.5)	26 (65.0)	35 (85.4)	125 (77.6)
White	8 (20.5)	8 (19.5)	14 (35.0)	5 (12.2)	35 (21.7)
Asian	0	0	0	1 (2.4)	1 (0.6)
Height (cm)					
Mean (SD)	176.18 (9.43)	175.06 (9.25)	171.67 (9.68)	172.97 (8.80)	173.95 (9.37)
Median	176.50	177.00	172.70	175.20	175.30
Min – Max	152.4 - 194.3	157.5 - 188.0	152.4 - 191.0	154.0 - 190.5	152.4 - 194.3
Weight (kg)					
Mean (SD)	87.06 (18.23)	91.87 (19.12)	89.26 (17.98)	89.25 (20.49)	89.39 (18.89)
Median	82.10	86.40	84.55	88.70	86.20
Min – Max	59.4 - 126.5	56.6 - 132.2	66.7 - 143.6	50.5 - 138.9	50.5 - 143.6
Body Mass Index (kg/m^2)					
Mean (SD)	28.06 (5.46)	29.79 (4.66)	30.30 (5.29)	29.71 (5.88)	29.48 (5.35)
Median	27.80	29.60	29.45	28.80	28.80
Min – Max	19.1 - 38.9	20.8 - 39.5	22.3 - 41.4	19.7 - 39.4	19.1 - 41.4
Metabolizer Status					
Extensive Metabolizer	26 (66.7)	29 (70.7)	25 (62.5)	26 (63.4)	106 (65.8)
Intermediate Metabolizer	13 (33.3)	10 (24.4)	13 (32.5)	15 (36.6)	51 (31.7)
Inconclusive	0	2 (4.9)	2 (5.0)	0	4 (2.5)

Abbreviations: AL=aripiprazole lauroxil; NCD=NanoCrystal® Dispersion ; SD=standard deviation

[a] 30 mg oral aripiprazole on Day 1 followed by oral placebo for 20 days + AL-NCD 662 mg (gluteal) + 441 mg AL (deltoid) on Day 1.

[b] 30 mg oral aripiprazole on Day 1 followed by oral placebo for 20 days + AL-NCD 662 mg (gluteal) + 882 mg AL (gluteal) on Day 1.

[c] 15 mg oral aripiprazole for 21 days (Days 1-21) + placebo NCD IM injection (gluteal) + 441 mg AL (deltoid) on Day 1.

[d] 15 mg oral aripiprazole for 21 days (Days 1-21) + placebo NCD IM injection (gluteal) + 882 mg AL (gluteal) on Day 1.

Inclusion Crietria:

1. Willing and able to provide informed consent
2. 18–65 years of age, inclusive, at Screening
3. Met either of the following tolerability criteria upon admission to the inpatient study facility:
   - Demonstrated tolerability to test doses of oral aripiprazole during Screening
   - Had a history of tolerated use of aripiprazole
4. Diagnosis of either chronic schizophrenia or schizoaffective disorder, as defined by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (American Psychiatric Association 2013) criteria at Screening, and demonstration of clinical stability, as evidenced by the following criteria:
   a. No hospitalizations for acute psychiatric exacerbations within 3 months prior to Screening and upon admission
   b. Clinical Global Impression-Severity Scale (CGI-S) score of ≤3 (mild) at Screening and upon admission
5. Had been on a stable oral antipsychotic medication regimen (excluding clozapine) for at least 2 months prior to Screening and had no antipsychotic medication regimen change between Screening and admission. A medication or dose level change that occurred after Screening and before admission was allowed if tolerability improved before admission
6. Agreed to remain on current antipsychotic regimen (medication and dose level) for the duration of the study, unless a change was medically indicated

Exclusion Criteria:

1. Pregnant, planning to become pregnant, or currently breastfeeding at Screening or upon admission
2. Met any of the following exclusionary medication criteria:
   a. Had received oral aripiprazole within 28 days prior to randomization
   b. Had received AL or IM depot aripiprazole within 6 months prior to admission
   c. Had taken any other extended release (also known as long-acting) injectable antipsychotic within 3 months prior to admission
   d. Was currently being treated with clozapine
3. Had participated in a clinical trial involving any investigational product (ie, drug, device, biologic) within the past 3 months, or was currently participating in a clinical trial involving an investigational product
4. History of psychopathology, other than schizophrenia or schizoaffective disorder, as indicated by any of the following:
   - DSM-5 (American Psychiatric Association 2013) Axis I diagnosis other than chronic schizophrenia or schizoaffective disorder within the 12 months prior to Screening or upon admission
   - DSM-5 (American Psychiatric Association 2013) diagnosis of moderate or severe substance use disorder (except tobacco use disorder), within the 12 months prior to Screening or upon admission
5. In the opinion of the Investigator, the subject was deemed to be a danger to himself/herself or others at Screening or upon admission or met one of the following criteria for elevated suicidal ideation or behavior:

6. History or current evidence of a clinically significant condition or abnormality (including clinical laboratory test results or electrocardiogram [ECG] findings) that, in the opinion of the Investigator, could preclude safe participation in the study, or had any other disease or condition that could prevent, limit, or confound protocol specified assessments including, but not limited to:
    a. Uncontrolled diabetes (hemoglobin A1c [HbA1c] >7%), heart disease, or stroke
    b. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels ≥2 times the upper limit of the laboratory reference range
    c. Thyroid stimulating hormone (TSH) >10% above upper limit of laboratory reference range
    d. An absolute neutrophil count $\leq 1.5 \times 10^3/\mu L$
    e. A platelet count $\leq 100 \times 10^3/\mu L$
    f. History of or positive test result for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen, or antihepatitis C virus antibody
7. History or evidence of neuroleptic malignant syndrome or clinically significant tardive dyskinesia
8. Had a QT interval (corrected using the Fridericia formula; QTcF) >450 ms for men or >470 ms for women at Screening or upon admission
9. Had used potent cytochrome P450 (CYP) 3A4 inducers or inhibitors or CYP2D6 inhibitors (prescription medications, over-the-counter [OTC] medications, or dietary supplements) within 30 days prior to admission
10. Was a CYP2D6 "Poor Metabolizer" as determined by pharmacogenetic testing conducted at Screening
11. Had a positive urine drug test for amphetamines, barbiturates, cocaine, methadone, opiates, or phencyclidine at Screening or upon admission

Results

Aripiprazole

A rapid increase in mean plasma aripiprazole concentrations was seen in each NCD initiation regimen group, which was comparable to each corresponding oral initiation regimen group.

As anticipated, higher aripiprazole concentrations were observed during the first 24 hours upon initiation with the NCD initiation regimen as compared to the oral initiation regimen. This is due to the administration of 30 mg oral aripiprazole on Day 1 in the NCD initiation regimen versus daily 15 mg oral aripiprazole in the oral initiation regimen.

Mean plasma aripiprazole concentrations over time overlapped across each of the initiation regimen through Day 21 (the last day of administration of oral aripiprazole in the oral initiation regimen).

After Day 21, plasma aripiprazole concentrations persisted in each NCD initiation regimen group, whereas plasma aripiprazole concentrations began to decline in each oral initiation regimen group. Mean aripiprazole concentrations in the NCD initiation regimen began to decline after Day 30, at an apparently less rapid rate as compared to the decline following the end of the oral initiation regimen.

The NCD initiation regimen was designed to achieve therapeutic aripiprazole concentrations (ie, >102 ng/mL) within 4 days after treatment initiation. A larger proportion of subjects in each NCD initiation regimen group had plasma concentrations >102 ng/mL as compared to each corresponding oral initiation regimen group by Day 4, indicating the NCD initiation regimen met the intended target exposure within a comparable timeframe to that of the oral initiation regimen. While the proportions of subjects with aripiprazole concentrations >102 ng/mL varied over time, at the end of a monthly dosing interval (Day 28), the proportion of subjects with therapeutic aripiprazole concentrations was greater in the NCD initiation regimens than the oral initiation regimens.

There were no meaningful differences among treatment regimens with respect to exposure to aripiprazole. Although T_{max} was longer in each NCD initiation regimen group compared to the corresponding oral initiation regimen group, mean AUC_{0-28} and AUC_{last} values were relatively similar between the NCD initiation regimen groups and the corresponding oral initiation regimen groups. Overall, the NCD initiation regimen resulted in total exposure of aripiprazole that was at or above the total exposure achieved with the 21-day oral aripiprazole initiation regimen.

Dehydro-aripiprazole

Overall, the NCD initiation regimen resulted in total dehydro-aripiprazole exposure similar to that achieved with the 21-day oral initiation regimen. The exposure to dehydro-aripiprazole following administration of aripiprazole lauroxil NCD was approximately 37% to 39% of the exposure to the parent aripiprazole, with exposures of 37% to 47% with the oral initiation regimen.

N-Hydroxymethyl Aripiprazole

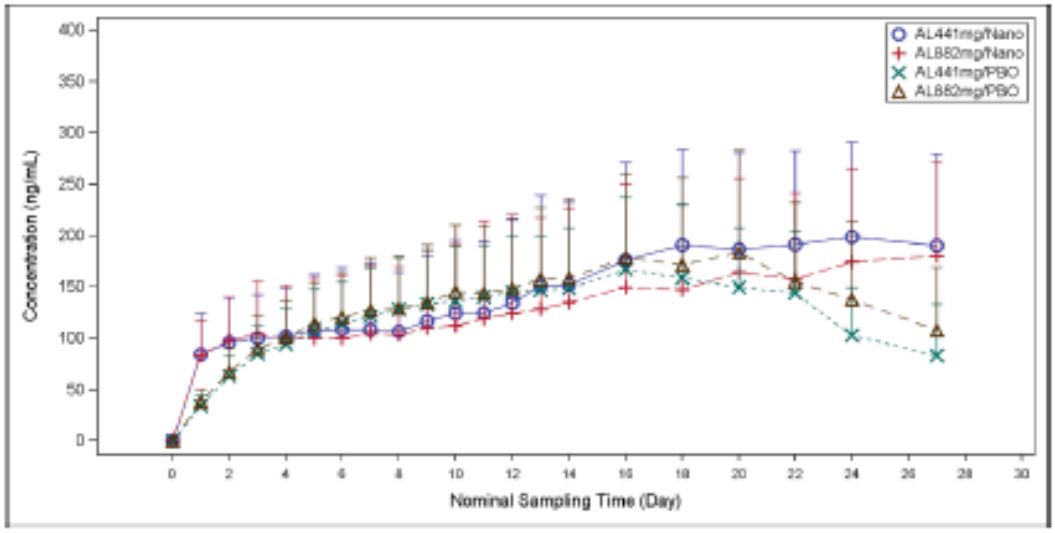
Exposure to *N*-hydroxymethyl aripiprazole relative to the parent aripiprazole was low (6% to 10%) regardless of treatment regimen.

Aripiprazole Lauroxil

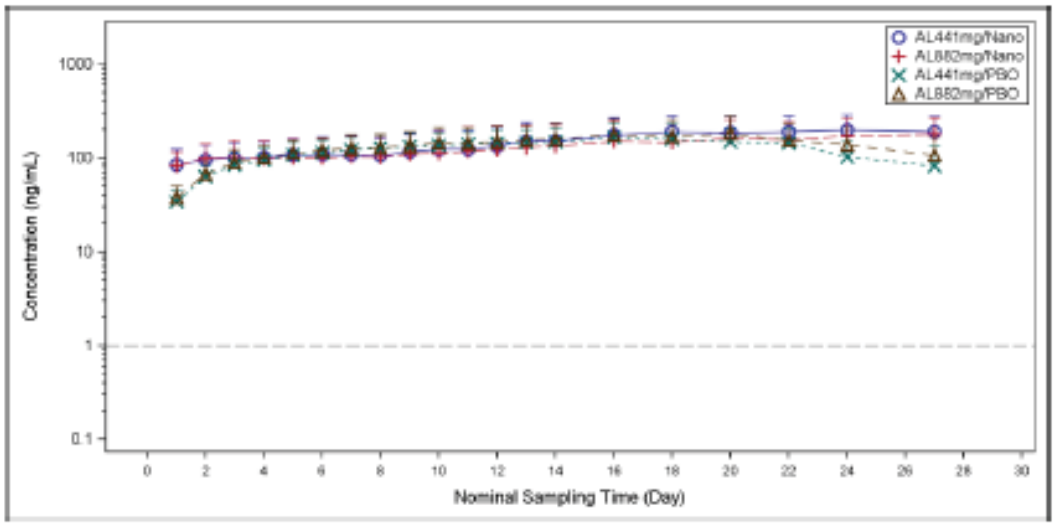
Aripiprazole lauroxil is generally not quantifiable in plasma, therefore PK parameters could not be computed for AL.

Figure 1: Mean (Standard Deviation) Plot of Aripiprazole Concentrations Over Time for the different Treatment Groups (ARISTADA INITIO regimen vs. approved ARISTADA regimen)

Linear Scale



Semi-log Scale



Legend: AL 441/Nano=30 mg oral aripiprazole on Day 1 followed by oral placebo for 20 days + AL-NCD 662 mg (gluteal) + 441 mg AL (deltoid) on Day 1.
AL 882/Nano=30 mg oral aripiprazole on Day 1 followed by oral placebo for 20 days + AL-NCD 662 mg (gluteal) + 882 mg AL (gluteal) on Day 1.
AL 441/PBO=15 mg oral aripiprazole for 21 days (Days 1-21) + placebo NCD IM injection (gluteal) + 441 mg AL (deltoid) on Day 1.
AL 882/PBO=15 mg oral aripiprazole for 21 days (Days 1-21) + placebo NCD IM injection (gluteal) + 882 mg AL (gluteal) on Day 1.

Table 1: Pharmacokinetic Parameters for Aripiprazole by Treatment Group

PK Parameter Statistics	Treatment Groups			
	NCD Initiation/ AL 441 mg (N=39)[a]	NCD Initiation/ AL 882 mg (N=41)[b]	Oral Initiation/ AL 441 mg (N=40)[c]	Oral Initiation/ AL 882 mg (N=41)[d]
C_{max} (ng/mL)				
N	39	41	40	41
Mean (SD)	268.15 (127.97)	217.53 (102.66)	191.69 (64.10)	220.64 (82.55)
SE	20.49	16.03	10.14	12.89
Geometric Mean	241.14	193.27	180.59	205.06
Median	253.00	199.00	198.50	205.00
Min – Max	81.4 - 732.0	62.5 - 433.0	80.4 - 336.0	71.3 - 403.0
CV (%)	47.72	47.19	33.44	37.42
T_{max} (day)				
N	39	41	40	41
Median	21.0	27.0	16.5	18.0
Min – Max	0.0 - 40.0	0.0 - 56.0	3.0 - 26.0	3.0 - 45.1
AUC_{last} (day*ng/mL)				
N	39	41	40	41
Mean (SD)	9794.6 (3826.4)	11627.2 (5921.8)	6104.9 (2017.9)	9365.5 (5172.7)
SE	612.7	924.8	319.1	807.7
Geometric Mean	8245.2	9461.9	5769.8	7654.1
Median	10000.7	10659.2	6156.0	8564.4
Min – Max	193.4 - 17429.8	96.3 - 25854.8	1717.7 - 12196.5	208.8 - 21954.2
CV (%)	39.07	50.93	33.05	55.22
$AUC_{0\text{-}28}$ (day*ng/mL)				
N	37	39	39	39
Mean (SD)	4256.4 (1703.6)	3570.7 (1935.2)	3371.6 (1110.5)	3911.9 (1661.6)
SE	280.1	309.9	177.8	266.1
Geometric Mean	3931.7	3113.3	3156.8	3566.3
Median	3990.0	2898.3	3631.6	3597.2
Min – Max	1854.8 - 7930.1	1314.7 - 9179.2	836.2 - 5320.3	978.8 - 8409.3
CV (%)	40.02	54.19	32.93	42.47

Abbreviations: AL=aripiprazole lauroxil; CV=coefficient of variation; NCD=NanoCrystal® Dispersion; SD=standard deviation; SE=standard error

[a] 30 mg oral aripiprazole on Day 1 followed by oral placebo for 20 days + AL-NCD 662 mg (gluteal) + 441 mg AL (deltoid) on Day 1.

[b] 30 mg oral aripiprazole on Day 1 followed by oral placebo for 20 days + AL-NCD 662 mg (gluteal) + 882 mg AL (gluteal) on Day 1.

[c] 15 mg oral aripiprazole for 21 days (Days 1-21) + placebo NCD IM injection (gluteal) + 441 mg AL (deltoid) on Day 1.

[d] 15 mg oral aripiprazole for 21 days (Days 1-21) + placebo NCD IM injection (gluteal) + 882 mg AL (gluteal) on Day 1.

Safety Results

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Treatment with a single 662 mg IM dose of AL-NCD coadministered with a single 30 mg oral dose of aripiprazole and either a 441 or 882 mg IM dose of AL (at a separate injection site) or 21 days of 15 mg oral aripiprazole and either a 441 or 882 mg IM dose of AL was generally well tolerated in adult subjects with schizophrenia or schizoaffective disorder.

- The TEAE profile seen with NCD in this study was generally consistent with the known safety profile of aripiprazole and aripiprazole lauroxil
  - Overall, the most common TEAEs were injection site pain (23.0%), headache (9.9%), weight increased (7.5%), insomnia (6.2%), dyspepsia (5.6%), and anxiety (5.0%). All other TEAEs occurred at an overall incidence <5%.
- Most TEAEs were mild to moderate in intensity and nonserious and did not require modification of the study treatment regimen. The overall incidence of severe TEAEs and SAEs was relatively low (each 3.7%) as was the overall incidence of TEAEs leading to study discontinuation (3.1%). The only severe TEAE, SAE, and TEAE leading to study drug discontinuation for >1 subject was road traffic accident (2 subjects; 1.2%)
  - Given the low incidence of severe TEAEs, SAEs, and TEAEs leading to study discontinuation overall, no relationship between the treatment regimen and the occurrence of such events could be discerned
- No study treatment-related deaths occurred during the study (one subject died during the study as a result of injuries sustained in a traffic accident, with this event considered unrelated to study treatment)
- The incidence of injection site pain associated with IM injection of AL-NCD in the gluteal muscle was similar among subjects who received the IM injection of AL in the contralateral gluteal muscle or in the deltoid muscle
- Overall, a low incidence of akathisia was seen in this study (3.7%), with this incidence being lower than that reported in the ARISTADA® prescribing information [Alkermes, Inc., 2016]
- No clinically meaningful trends were observed for laboratory, vital sign, or ECG results
- Overall no consistent effects on weight and BMI were observed across the treatment groups in this study
- No change in disease severity was seen during the study, as assessed by the Investigator using the CGI-S. Overall, all but 2 subjects had CGI-S findings indicative of normal status to mild illness at all on-study timepoints.
- Based on the C-SSRS and TEAEs, there was no suicidal behavior or ideation in any subject

Table 2: Summary of Adverse Events

Subjects with at least 1:	Treatment Group				All (N=161) n (%)
	NCD Initiation/ AL 441 mg (N=39)[a] n (%)	NCD Initiation/ AL 882 mg (N=41)[b] n (%)	Oral Initiation/ AL 441 mg (N=40)[c] n (%)	Oral Initiation/ AL 882 mg (N=41)[d] n (%)	
TEAE	26 (66.7)	28 (68.3)	24 (60.0)	28 (68.3)	106 (65.8)
Drug-related TEAE	21 (53.8)	17 (41.5)	14 (35.0)	18 (43.9)	70 (43.5)
Mild TEAE	14 (35.9)	17 (41.5)	16 (40.0)	17 (41.5)	64 (39.8)
Moderate TEAE	9 (23.1)	11 (26.8)	6 (15.0)	10 (24.4)	36 (22.4)
Severe TEAE	3 (7.7)	0	2 (5.0)	1 (2.4)	6 (3.7)
SAE	3 (7.7)	0	2 (5.0)	1 (2.4)	6 (3.7)
AE Leading to Study Discontinuation	3 (7.7)	0	1 (2.5)	1 (2.4)	5 (3.1)

Overall Sponsor Conslusions

Results from this study demonstrated that:

- The NCD initiation regimen results in rapid achievement of aripiprazole concentrations that:
  1) are comparable in range to the oral aripiprazole initiation regimen;
  2) provide exposure within the first month of treatment initiation comparable to the oral aripiprazole initiation regimen; and
  3) result in persistent aripiprazole concentrations within the therapeutic target range
- Under the conditions of this study, the NCD initiation regimen was well tolerated with a safety profile consistent with the known safety profile of the oral aripiprazole initiation regimen

Overall, these findings suggest that the NCD initiation regimen is an adequate substitute for the 21-day oral aripiprazole initiation regimen, thereby offering an alternative starting regimen for individuals initiating AL therapy

Reviewer Comments

- *<u>Study Design:</u> This was Phase 1 study was to compare the pharmacokinetics (PK) of aripiprazole following administration of an NCD initiation regimen versus an oral aripiprazole initiation regimen*
  - *The study was conducted with the final to-be-marketed formulation of ALKS9072N*
  - *The study was conducted at 662 mg dose of ALKS9072N which was previously determined to be safe and tolerated in schizophrenia patients.*
  - *Adequate numbers (N=161) of adult patients (male and females) between the age of 18-65 year were used who were randomly assigned 1:1:1:1 to the 4 treatment groups.*
  - *PK analysis using a validated method was performed for aripiprazole and its metabolites and appropriate PK parameters (i.e., Cmax, AUC, Tmax etc.) were assessed.*
  - *The study excluded all strong inhibitors of CYP3A4 or CYP2D6 as well as patients who were poor metabolizers of CYP2D6, which minimized the potential for drug interactions and variability of PK due to pharmacogenomics effects.*
  - *Therefore, the overall study design was acceptable.*

- *Protocol deviation: No major or minor protocol deviations were reported.*

- *Data Analysis (i.e., any outliers etc.):*

- *Bioanalytical Method: A validated bio-analytical methodology was used which was acceptable.*

- *Inclusion and Exclusion Criteria: Subjects were adult males and females between the ages of 18 and 65 years. They all had diagnosis of either chronic schizophrenia or schizoaffective disorder, as defined by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). Since Aripiprazole is known to be metabolized via the CYP3A4 and CYP2D6 pathway, the study excluded any subjects who had potent cytochrome P450 (CYP) 3A4 inducers or inhibitors or CYP2D6 inhibitors (prescription medications, over-the-counter [OTC] medications, or dietary supplements) within 30 days prior to admission as well as CYP2D6 "Poor Metabolizer" as determined by pharmacogenetic testing conducted at Screening*

1. *Pharmacokinetic findings: We agree with the sponsor's PK analysis and conclusions from the study.*

Overall Reviewer Conslusions: We agree with the sponsor's overall conclusion

CLINICAL PHARMACOLOGY STUDY REVIEW

Pharmacokinetic Study

Study # ALK9072-B103 **Study Period:** 23-Oct-2015 to 19-Apr-2016

NDA 209830

Title	A Phase 1 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of ALKS 9072N Following Administration to the Deltoid or Gluteal Muscle in Adults with Schizophrenia or Schizoaffective Disorder
Objectives:	**Primary:** To determine the safety, tolerability and pharmacokinetics (PK) of ALKS 9072N 662 mg, administered as a single intra-muscular (IM) injection in the deltoid or gluteal muscle in adults with schizophrenia or schizoaffective disorder **Secondary:** To evaluate the relative bioavailability of ALKS 9072N 662 mg following a single IM injection in the deltoid muscle compared to exposure following administration to the gluteal muscle in adults with schizophrenia or schizoaffective disorder

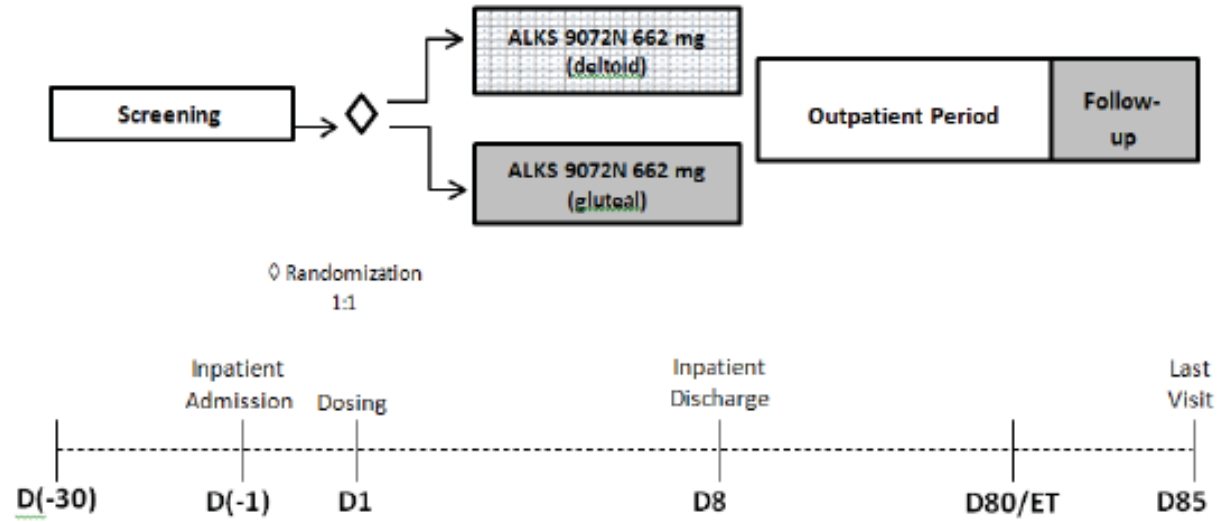
Study Design:

Methodology: This was a multicenter, randomized, open-label, single-dose study of ALKS 9072N (662 mg) following IM injection to the deltoid or gluteal muscle in subjects with schizophrenia or schizoaffective disorder.

Prospective subjects were evaluated for eligibility at a screening visit up to 30 days prior to study drug administration on Day 1. Only subjects who exhibited tolerability to oral aripiprazole (either following test doses or by documented experience) were eligible to enroll in the study. Subjects who successfully completed screening assessments were admitted to an inpatient study facility on Day -1, the day prior to dosing. Eligibility criteria were reviewed to ensure continued eligibility, and baseline assessments were conducted. For eligible subjects who received oral aripiprazole during screening, 28 days elapsed between the last dose of oral aripiprazole and the IM injection of study drug (Day 1). Subjects remained on their regular oral antipsychotic regimens, not including oral aripiprazole, for the duration of the study.

On Day 1, subjects were randomized in a 1:1 ratio to 1 of the 2 treatment groups and received a single 662 mg IM dose of ALKS 9072N in either the deltoid (Group 1) or gluteal (Group 2) muscle. Subjects remained in the inpatient unit for 8 days (Day -1 to Day 7) and were discharged on Day 8, unless additional assessments were medically indicated. Subjects returned to the study center for outpatient study visits between discharge on Day 8 and Day 85.

Study Treatment (including dose, mode of administration, and batch number): Aripiprazole lauroxil, a micron-particle formulation of an extended-release injectable antipsychotic, is a covalent non-ester modification of aripiprazole to form *N*-lauroyloxymethyl aripiprazole. ALKS 9072N is an alternative formulation of aripiprazole lauroxil that is composed of drug particles designed to provide faster dissolution. ALKS 9072N (662 mg; Lots # 467-0002AA and 467-0013AA) was administered as a single IM injection in the deltoid or gluteal muscle.



D=day; ET=early termination

Note: oral aripiprazole test doses were administered on Day -30 and Day -29 (if needed)

Serial blood samples were collected beginning on Day 1, the day of ALKS 9072N administration, and continued through Day 85 to measure plasma concentrations and evaluate the PK of ALKS 9072N and its metabolites.

Route of Administration	Intra-muscular injection—Deltoid and Gluteal
PK Sampling Times and Parameters	**Pharmacokinetics:** The following parameters were calculated, as appropriate, for each analyte using noncompartmental analysis methods: • Maximum plasma concentration (C_{max}) • Time to maximum plasma concentration (t_{max}) • Area under the concentration-time curve from time zero to the last quantifiable time interval (AUC_{last}) • Area under the concentration-time curve from time zero to infinity (AUC_{∞}) • Terminal elimination half-life ($t_{½}$) In addition, the relative bioavailability of ALKS 9072N administered as a deltoid versus a gluteal IM injection was evaluated based on aripiprazole exposure. Samples were collected within 1 hour pre-dose, and 1, 4, and 8 hours (±10 minutes) post-dose on Day 1. On Days 2, 3, 5, and 8, a single sample was collected within ±1 hour of the Day 1 dosing time and after the ECG assessment.
Safety Parameters	Safety and tolerability were assessed throughout the study on the basis of adverse events (AEs); injection site assessment; vital signs (blood pressure, heart rate, respiratory rate, and body temperature) and weight; clinical laboratory parameters (biochemistry [including prolactin], hematology, and urinalysis); electrocardiogram (ECG) parameters; Columbia-Suicide Severity Rating Scale (C-SSRS) responses; and Clinical Global Impression – Severity (CGI-S) responses. Subjects were assessed for movement disorders using the Abnormal Involuntary Movement Scale (AIMS); Barnes Akathisia Rating Scale (BARS); and Simpson Angus Scale (SAS).

	In addition, safety and tolerability were assessed throughout the study on the basis of: • AEs • Injection site assessment • Vital signs (blood pressure, heart rate, respiratory rate, and body temperature) and weight • Clinical laboratory parameters (biochemistry [including prolactin], hematology, and urinalysis) • ECG parameters • C-SSRS responses • Movement disorder measures − Abnormal Involuntary Movement Scale (AIMS) − Barnes Akathisia Rating Scale (BARS) − Simpson Angus Scale (SAS) • CGI-S responses
PK Moieties	Concentrations of Aripiprazole Lauroxil, *N*-hydroxymethyl aripiprazole, aripiprazole, and dehydro-aripiprazole (the primary metabolite of aripiprazole) were quantified in plasma samples
PD Endpoint(s)	NA
PD Parameters	NA
Statistical Methods	**Statistical Methods:** Summary statistics (n, mean, standard deviation [SD], median, minimum, and maximum values for continuous variables, and number and percentage of subjects in each category f categorical variables) are provided for all evaluated variables. Source data for summary tables and statistical analyses are presented as by-subject data listings. **Study Populations:** Safety Population: All subjects who received study drug (ALKS 9072N). Pharmacokinetics Population: All subjects who received study drug and had at least 1 measurable concentration of any of the 4 analytes: aripiprazole lauroxil, *N*-hydroxymethyl aripiprazole, aripiprazole, or dehydro-aripiprazole. **Pharmacokinetic Analyses:** Concentration data are summarized according to protocol-specified nominal sampling times. PK parameters were calculated using noncompartmental techniques, and actual elapsed time from dosing was used to estimate individual plasma PK parameters. Individual subject concentrations and calculated PK parameters are presented in by-subject data listings. The relative bioavailability of ALKS 9072N administered as an IM injection in the deltoid muscle versus in the gluteal muscle was assessed via evaluation of the ratio of deltoid:gluteal for PK parameters of exposure. **Safety Analyses:** Treatment-emergent AEs (TEAEs) were defined as AEs that were newly occurring or worsened following the dose of IM study drug. Reported AE terms were coded using the Medical Dictionary for Regulatory Activities (MedDRA) v17.0. The number and percentage of subjects with TEAEs was summarized overall by severity, as well as by treatment group and by relationship to stu drug. Serious AEs and AEs resulting in discontinuation from the study were summarized. The absolute value and changes from baseline of laboratory test results, vital sign measurements, and ECGs were summarized by treatment group and timepoint. Other safety parameters (eg, subjects with clinically meaningful shifts in BARS, AIMS and SAS, subjects with suicidal behavior and/or ideation assessed by C-SSRS, and subjects with injection site reactions) were summarized by treatment group. Prior and concomitant medications were coded using the World Health Organization Anatomical Therapeutic Chemical (WHO-ATC) Drug dictionary version Mar 2014. The number and percentage subjects using prior and concomitant medications were summarized by treatment group. Data listings are provided for all safety variables. **Sample Size Considerations:** Sample size was based on clinical considerations.

Analytical Method

Method Type	LC/MS/MS	Matrix	Plasma
Analytes	Aripiprazole Lauroxil, *N*-hydroxymethyl aripiprazole Aripiprazole (Parent) Dehydro-aripiprazole (Primary metabolite)		

Validation	▪ Method validated prior to use	☑ Yes ☐ No
	▪ Method validation acceptable	☑ Yes ☐ No
Study Sample Analysis	▪ Samples analyzed within the established stability period	☑ Yes ☐ No
	▪ Quality control samples range acceptable	☑ Yes ☐ No
	▪ Chromatograms provided	☑ Yes ☐ No
	▪ Accuracy and precision of the calibration curve acceptable	☑ Yes ☐ No
	▪ Accuracy and precision of the quality control samples acceptable	☑ Yes ☐ No
	▪ Overall performance acceptable	☑ Yes ☐ No

Study Population:

- 18-65 years patients with diagnosis of either chronic schizophrenia or schizoaffective disorder
- N= 47

Main Criteria for Subject Inclusion:

Subjects with a diagnosis of either chronic schizophrenia or schizoaffective disorder, as defined by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria at Screening, and demonstration of clinical stability, as evidenced by a) no hospitalizations for acute psychiatric exacerbations within 3 months prior to Screening and upon admission; and b) a Clinical Global Impression-Severity Scale (CGI-S) score of ≤3 (mild) at Screening and upon admission were eligible for enrollment. Subjects were to have been receiving a stable oral antipsychotic medication regimen (excluding clozapine) for at least 2 months prior to Screening and have no antipsychotic medication regimen change between Screening and admission.

Table 1: Demography of subjects

Parameter/ Statistic	ALKS 9072N Treatment Group		
	662 mg Deltoid N=23	662 mg Gluteal N=24	Total N=47
Age (years)			
Mean (SD)	47.2 (9.87)	50.0 (9.86)	48.6 (9.87)
Median (Min, Max)	49.0 (28-62)	51.5 (26-64)	50.0 (26-64)
Gender, n (%)			
Male	18 (78.3)	16 (66.7)	34 (72.3)
Female	5 (21.7)	8 (33.3)	13 (27.7)
Race, n (%)			
Black or African American	18 (78.3)	19 (79.2)	37 (78.7)
White	5 (21.7)	4 (16.7)	9 (19.1)
Asian	0	1 (4.2)	1 (2.1)
Ethnicity, n (%)			
Not Hispanic or Latino	22 (95.7)	23 (95.8)	45 (95.7)
Hispanic or Latino	1 (4.3)	1 (4.2)	2 (4.3)
Body Mass Index (kg/m^2)			
Mean (SD)	27.8 (5.29)	29.8 (4.82)	28.8 (5.11)
Median (Min, Max)	26.7 (18.5-39.6)	29.6 (21.9-38.7)	29.5 (18.5-39.6)
Metabolizer Status			
Extensive Metabolizer	11 (47.8)	18 (75.0)	29 (61.7)
Intermediate Metabolizer	11 (47.8)	6 (25.0)	17 (36.2)
Inconclusive	1 (4.3)	0	1 (2.1)

Inclusion Crietria:

1. Willing and able to provide informed consent
2. 18–65 years of age, inclusive, at Screening
3. Met either of the following tolerability criteria upon admission to the inpatient study facility:
   - Demonstrated tolerability to test doses of oral aripiprazole during Screening
   - Had a history of tolerated use of aripiprazole
4. Diagnosis of either chronic schizophrenia or schizoaffective disorder, as defined by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) (American Psychiatric Association 2013) criteria at Screening, and demonstration of clinical stability, as evidenced by the following criteria:
   a. No hospitalizations for acute psychiatric exacerbations within 3 months prior to Screening and upon admission
   b. Clinical Global Impression-Severity Scale (CGI-S) score of ≤3 (mild) at Screening and upon admission
5. Had been on a stable oral antipsychotic medication regimen (excluding clozapine) for at least 2 months prior to Screening and had no antipsychotic medication regimen change between Screening and admission. A medication or dose level change that occurred after Screening and before admission was allowed if tolerability improved before admission
6. Agreed to remain on current antipsychotic regimen (medication and dose level) for the duration of the study, unless a change was medically indicated

Exclusion Criteria:

1. Pregnant, planning to become pregnant, or currently breastfeeding at Screening or upon admission
2. Met any of the following exclusionary medication criteria:
   a. Had received oral aripiprazole within 28 days prior to randomization
   b. Had received AL or IM depot aripiprazole within 6 months prior to admission
   c. Had taken any other extended release (also known as long-acting) injectable antipsychotic within 3 months prior to admission
   d. Was currently being treated with clozapine
3. Had participated in a clinical trial involving any investigational product (ie, drug, device, biologic) within the past 3 months, or was currently participating in a clinical trial involving an investigational product
4. History of psychopathology, other than schizophrenia or schizoaffective disorder, as indicated by any of the following:
   - DSM-5 (American Psychiatric Association 2013) Axis I diagnosis other than chronic schizophrenia or schizoaffective disorder within the 12 months prior to Screening or upon admission
   - DSM-5 (American Psychiatric Association 2013) diagnosis of moderate or severe substance use disorder (except tobacco use disorder), within the 12 months prior to Screening or upon admission
5. In the opinion of the Investigator, the subject was deemed to be a danger to himself/herself or others at Screening or upon admission or met one of the following criteria for elevated suicidal ideation or behavior:

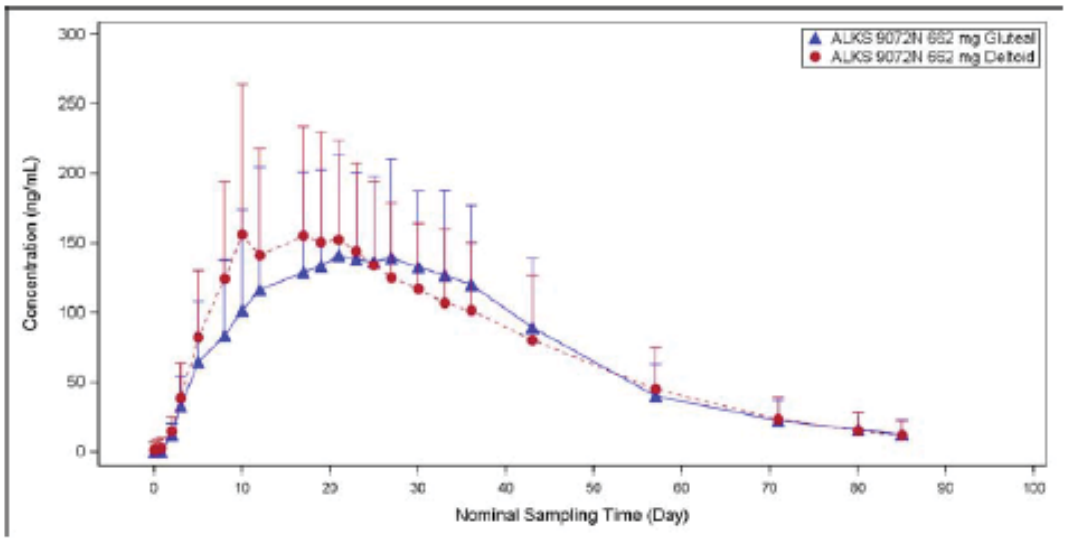
6. History or current evidence of a clinically significant condition or abnormality (including clinical laboratory test results or electrocardiogram [ECG] findings) that, in the opinion of the Investigator, could preclude safe participation in the study, or had any other disease or condition that could prevent, limit, or confound protocol specified assessments including, but not limited to:
    a. Uncontrolled diabetes (hemoglobin A1c [HbA1c] >7%), heart disease, or stroke
    b. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels ≥2 times the upper limit of the laboratory reference range
    c. Thyroid stimulating hormone (TSH) >10% above upper limit of laboratory reference range
    d. An absolute neutrophil count $\leq 1.5\times10^3/\mu L$
    e. A platelet count $\leq 100\times10^3/\mu L$
    f. History of or positive test result for human immunodeficiency virus (HIV) antibody, hepatitis B surface antigen, or antihepatitis C virus antibody
7. History or evidence of neuroleptic malignant syndrome or clinically significant tardive dyskinesia
8. Had a QT interval (corrected using the Fridericia formula; QTcF) >450 ms for men or >470 ms for women at Screening or upon admission
9. Had used potent cytochrome P450 (CYP) 3A4 inducers or inhibitors or CYP2D6 inhibitors (prescription medications, over-the-counter [OTC] medications, or dietary supplements) within 30 days prior to admission
10. Was a CYP2D6 "Poor Metabolizer" as determined by pharmacogenetic testing conducted at Screening
11. Had a positive urine drug test for amphetamines, barbiturates, cocaine, methadone, opiates, or phencyclidine at Screening or upon admission

Results

Following administration of ALKS 9072N, mean aripiprazole concentrations increased slowly and steadily in both groups, then declined through Day 85.Mean aripiprazole concentrations tended to be slightly higher following deltoid administration, but there was overlap in the SDs; thus, no meaningful differences between treatment groups were observed in the aripiprazole concentration-time course.

Figure 1: Mean (SD) Aripiprazole Concentrations Over Time Following Deltoid or Gluteal Administration of ALKS 9072N 662 mg

A. Linear Scale



B. Semi-log Scale

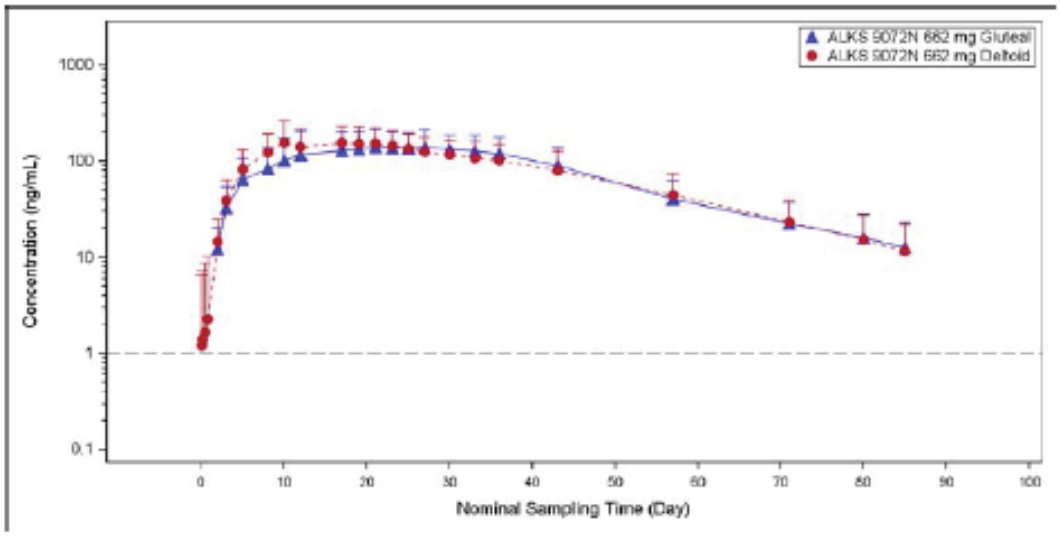


Table 1: Pharmacokinetic Parameters for Aripiprazole Following Deltoid or Gluteal IM Administration of ALKS 9072N

Variable/ Statistic	ALKS 9072N Treatment Group	
	662 mg Deltoid N=23	662 mg Gluteal N=24
C_{max} (ng/mL)		
Mean (SD)	196.1 (97.27)	175.0 (84.95)
%CV	49.61	48.55
Geometric Mean	178.0	159.1
t_{max} (day)		
Median	16.99	25.50
Min, Max	7.0, 29.0	10.0, 41.0
AUC_{last} (day*ng/mL)		
Mean (SD)	6419.0 (2368.80)	6070.2 (2173.42)
%CV	36.90	35.81
Geometric Mean	6016.1	5750.7
AUC_{∞} (day*ng/mL)		
n	22	24
Mean (SD)	6590.8 (2384.09)	6437.2 (2215.52)
%CV	36.17	34.42
Geometric Mean	6193.7	6115.8
$t_{½}$ (day)		
Mean (SD)	14.9 (8.48)	15.2 (6.32)
%CV	56.93	41.47
Geometric Mean	13.2	14.1

%CV=percent coefficient of variation; AUC_{∞}=area under the concentration versus time curve from time zero to infinity; AUC_{last}=area under the concentration-time curve from time zero to the last measurable concentration timepoint; C_{max}=Maximum observed concentration; IM=intramuscular; max=maximum; min=minimum; PK=pharmacokinetic; SD=standard deviation; $t_{½}$=terminal elimination half-life; t_{max}=time to maximum observed concentration

Like aripiprazole, the concentrations of Dehydro-aripiprazole and *N*-hydroxymethyl Aripiprazole were generally similar between the 2 treatment groups.

Relative Bioavailability Assessment (Deltoid vs. Gluteal)

The relative bioavailability of ALKS 9072N from deltoid compared to gluteal administration was evaluated for aripiprazole. Geometric mean ratios were near unity and 90% CIs included 1, indicating that aripiprazole bioavailability following deltoid administration was not significantly different than following gluteal administration for Cmax, AUC∞, and AUClast.

Table 2: Relative Bioavailability Assessment of Aripiprazole Following Deltoid and Gluteal Administration of ALKS 9072N

Variable/Statistic	ALKS 9072N Treatment Group	
	662 mg Deltoid N=23	662 mg Gluteal N=24
C_{max} (ng/mL)		
Geometric Mean	178.0	159.1
GM Ratio	1.12	--
90% CI on Ratio	(0.91, 1.38)	--
AUC_{last} (day*ng/mL)		
Geometric Mean	6016.1	5750.7
GM Ratio	1.05	--
90% CI on Ratio	(0.88, 1.24)	--
AUC_{∞} (day*ng/mL)		
Geometric Mean	6193.7	6115.8
GM Ratio	1.01	--
90% CI on Ratio	(0.85, 1.20)	--

AUC_{∞}=area under the concentration versus time curve from time zero to infinity; AUC_{last}=area under the concentration-time curve from time zero to the last measurable concentration timepoint; CI=confidence interval; C_{max}=maximum observed concentration; GM=geometric mean; GMR=geometric mean ratio; PK=pharmacokinetic
Analysis is based on 1-way analysis of variance. Log-transformed PK parameter is considered as dependent variable and treatment group is considered as independent variable.

Safety Results

Was there any death or serious adverse events? ☐ Yes ☑ No ☐ NA

Based on the results of this study, the following safety conclusions can be made:

- IM administration of ALKS 9072N in the deltoid or gluteal muscle in subjects with schizophrenia was generally safe and well tolerated in this study.
- No subjects died during the study.
- One subject in the deltoid group had an SAE (suicidal ideation) that was assessed by the Investigator as definitely not related to study drug. Based on the C-SSRS and TEAEs, there was no other report of suicidal behavior or suicidal ideation during the study.
- No subject had an AE that resulted in discontinuation from this study.
- TEAEs were reported in 65.2% of subjects in the deltoid group and 79.2% of subjects in the gluteal group. Most TEAEs were mild or moderate in severity.
- The TEAE with the highest frequency during the study was injection site pain, which was reported by 7 subjects (30.4%) in the deltoid group and 5 subjects (20.8%) in the gluteal group, all of which were assessed by the Investigator as related to study drug. Tremor was the only EPS-associated TEAE reported in this study (1 subject, 4.2%, gluteal group).

Table 3: Summary of Adverse Events

Category	ALKS 9072N Treatment Group		
	662 mg Deltoid N=23 n (%)	662 mg Gluteal N=24 n (%)	Total N=47 n (%)
Any TEAEs	15 (65.2)	19 (79.2)	34 (72.3)
Drug-Related TEAEs[a]	10 (43.5)	11 (45.8)	21 (44.7)
Mild TEAEs	8 (34.8)	13 (54.2)	21 (44.7)
Moderate TEAEs	7 (30.4)	4 (16.7)	11 (23.5)
Severe TEAEs	0	2 (8.3)	2 (4.3)
Serious AEs	1 (4.3)	0	1 (2.1)
AEs Leading to Discontinuation	0	0	0

AE=adverse event; SAE=serious adverse event; TEAE=treatment-emergent adverse event.
[a] Adverse events that were possibly, probably, or definitely related to study drug

Overall Sponsor Conslusions

• Plasma profiles of aripiprazole, dehydro-aripiprazole, and *N*-hydroxymethyl-aripiprazole after a single IM injection of ALKS 9072N 662 mg were comparable between deltoid and gluteal administration.

• The relative bioavailability of aripiprazole following deltoid administration of IM ALKS 9072N 662 mg was similar to gluteal administration, thus the 2 injection sites can be used interchangeably.

ALKS 9072N 662 mg administered at either the deltoid or gluteal site resulted in similar PK profiles and bioavailability. Mean exposure was similar from the deltoid site and the gluteal site, and the range of exposures overlapped between the 2 injection sites. ALKS 9072N 662 mg was generally safe and well tolerated. No new safety signal was identified with the deltoid muscle dosing regimen.

Reviewer Comments

1. *Study Design: This was a randomized, open-label, single dose study of ALKS9072N (662 mg) administered as a single intra-muscular (IM) injection in deltoid or gluteal muscle in adults in schizophrenia patients. This parallel dosing study with 47 patients with PK assessment up to Day 8 is an adequate design for comparison of safety, tolerability and PK after an injection into the deltoid muscle vs. the PK after an injection into the gluteal muscle.*
   - *The study was conducted with the final to-be-marketed formulation of ALKS9072N.*
   - *The study was conducted at the 662 mg dose which was previously determined to be safe and tolerated in schizophrenia patients.*
   - *It was a randomized, open-label, single dose study of ALKS9072N with parallel dosing in patients with frequent PK sampling up to 8 days which was adequate to capture the full PK profile.*
   - *Adequate numbers (N=47) of adult patients (male and females) between the age of 18-65 year were used. The two treatment arms were balanced with regards to number of subjects, gender, race etc.*
   - *PK analysis using a validated method was performed for aripiprazole and its metabolites and appropriate PK parameters (i.e., Cmax, AUC, Tmax etc.) were assessed.*
   - *The study excluded all strong inhibitors of CYP3A4 or CYP2D6 as well as patients who were poor metabolizers of CYP2D6, which minimized the potential for drug interactions and variability of PK due to pharmacogenomics effects.*
   - *Therefore, the overall study design was acceptable.*

2. *Protocol deviation: No major or minor protocol deviations were reported.*

3. *Data Analysis (i.e., any outliers etc.): There were no outliers and the PK data from all subjects were included in the analysis.*

4. *Bioanalytical Method: A validated bio-analytical methodology was used which was acceptable.*

5. *Inclusion and Exclusion Criteria: Subjects were adult males and females between the ages of 18 and 65 years. They all had diagnosis of either chronic schizophrenia or schizoaffective disorder, as defined by Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5). Since Aripiprazole is known to be metabolized via the CYP3A4 and CYP2D6 pathway, the study excluded any subjects who had potent cytochrome P450 (CYP) 3A4 inducers or inhibitors or CYP2D6 inhibitors (prescription medications, over-the-counter [OTC] medications, or dietary supplements) within 30 days prior to admission as well as CYP2D6 "Poor Metabolizer" as determined by pharmacogenetic testing conducted at Screening*

6. *Pharmacokinetic findings:* *We agree with the sponsor's PK analysis and conclusions from the study.*

Overall Reviewer Conslusions:

We agree that the exposures of aripiprazole, dehydro-aripiprazole, and N hydroxymethyl aripiprazole after a single IM injection of ALKS 9072N 662 mg were similar between deltoid and gluteal administration. Thus, we agree that the 2 injection sites can be used interchangeably for ALKS 9072N 662 mg injection.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PRAVEEN BALIMANE
06/18/2018

GOPICHAND GOTTIPATI
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