Key Characteristics of the Atypical Long-Acting Injectable Antipsychotic Aripiprazole Lauroxil for the Treatment of Schizophrenia

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INTRODUCTION

- When selecting antipsychotic treatments for schizophrenia, clinicians must consider the risks versus the benefits of available agents in combination with the patient's specific values and preferences[1]
- For long-acting injectable (LAI) antipsychotic choices, LAI pharmacokinetics (PK), site of administration, ease of use, and dosing interval are also considered, enabling tailored treatment approaches for individual patients[2,3]
- We highlight the development of the atypical LAI antipsychotic aripiprazole lauroxil (AL) and summarize the clinical data supporting its key attributes for meeting the treatment needs of patients with schizophrenia

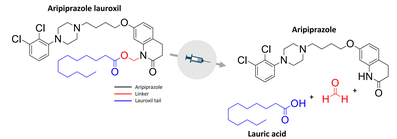
Key Attributes

- Five AL dosing regimens, including the first every-2-month LAI antipsychotic regimen,[4] provide a range of dosing options for patients
  - Clinicians can select an AL regimen to provide plasma aripiprazole exposure in the lower or higher range of the aripiprazole concentrations associated with efficacy, or among regimens with 3 different dosing intervals that provide effective intermediate-range aripiprazole concentrations[3-5]
    - Lower: 441 mg monthly
    - Higher: 882 mg monthly
    - Intermediate: 662 mg monthly, 882 mg every 6 weeks, 1064 mg every 2 months
- AL initiation options are suitable for different settings of care using either a 1-day or a 21-day regimen[6-8]
- The prolonged-release characteristics of AL allow dosing to be resumed after gaps in treatment of up to 6–10 weeks (depending on dosing regimen) without the need for supplementation or reinitiation[5,9]

DEVELOPMENT OF ARIPIPRAZOLE LAUROXIL

- With the goal of lowering aripiprazole solubility and optimizing its prolonged-release characteristics, AL was developed as an inactive prodrug formulation of the aripiprazole molecule using the proprietary LinkeRx technology (**Figure 1**)[6,10,11]

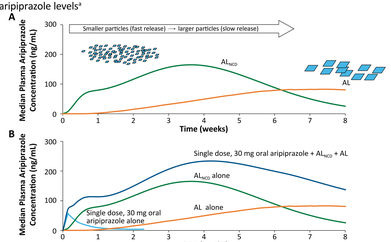
Figure 1. Aripiprazole lauroxil is a prodrug of aripiprazole formulated[a] by reversibly attaching a fatty acid chain (lauroxil tail; blue) to aripiprazole (black) via a linker (red)[b]



[a]The lauroxil tail is reversibly attached to aripiprazole using LinkeRx technology.[6] After injection into plasma, aripiprazole lauroxil dissociates over time into lauric acid plus the active aripiprazole molecule, enabling controlled release and extended exposure to aripiprazole.[6]

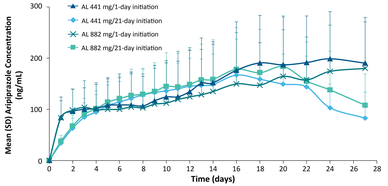
- The AL formulation consists of micron-sized particles, with a slow dissolution rate that provides extended release over a dosing interval of up to 2 months[6]
  - When first approved, AL therapy initiation required 21 days of supplementation with oral aripiprazole to achieve and maintain relevant clinical aripiprazole concentrations
- A NanoCrystal Dispersion formulation of AL (AL_{NCD}), with smaller particles[6] and faster dissolution[7] than AL (**Figure 2A**), was subsequently developed that enabled initiation requiring only 1 day of oral aripiprazole supplementation (AL_{NCD} + 30 mg oral aripiprazole) (**Figure 2B**)

Figure 2. (**A**) Kinetics of AL_{NCD} (smaller particle size) compared with AL (larger particle size); (**B**) AL therapy initiated with the 1-day regimen provides consistent target plasma aripiprazole levels[a]



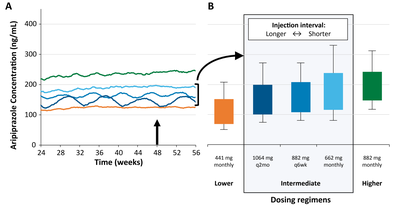
Adapted with permission from Jain et al. *CNS Spectr* (2020).[7]
[a]Plasma levels based on model simulations of aripiprazole levels achieved after administration of AL_{NCD}, AL 1064 mg, or AL 1064 mg plus the 1-day initiation regimen components (AL_{NCD} + a single 30-mg dose of oral aripiprazole) on day 1. Levels of oral aripiprazole based on observed data.
AL, aripiprazole lauroxil; AL_{NCD}, aripiprazole lauroxil NanoCrystal Dispersion.

Figure 3. The 1-day regimen, like the 21-day initiation regimen, results in aripiprazole concentrations that are in the relevant clinical concentration range within 4 days[a]



Adapted from Hard et al. *J Clin Psychopharmacol* (2018).[8]
[a]Mean (SD) aripiprazole concentrations over time (28 days) after 21-day initiation (21 days of 15-mg oral aripiprazole) or 1-day initiation (AL_{NCD} plus a single 30-mg dose of oral aripiprazole) administered with a single AL dose on day 1.
AL, aripiprazole lauroxil; SD, standard deviation.

Figure 4. (**A**) Median simulated steady-state plasma aripiprazole concentrations for weeks 24–56 after initiation[a]; (**B**) average simulated steady-state aripiprazole concentrations for the same regimens,[b] calculated for the injection interval starting at week 48 (arrow in **A**)

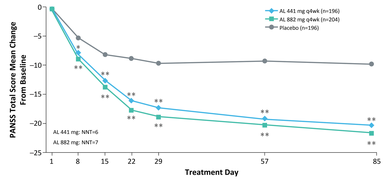


Adapted with permission from Hard et al. *CNS Drugs* (2017) and Sommi et al. *CNS Spectr* (2022).[5,9]
[a]Initiated using 21-day oral aripiprazole.
[b]The AL 441 mg monthly and 882 mg monthly regimens provide plasma aripiprazole exposure in the lower (equivalent to oral aripiprazole 10 mg/d) and higher (equivalent to oral aripiprazole 20 mg/d) ranges, respectively, of aripiprazole concentrations associated with efficacy. The AL 662 mg monthly, 882 mg every-6-week, and 1064 mg every-2-month regimens provide intermediate-range aripiprazole concentrations (equivalent to oral aripiprazole 15 mg/d).
Boxes, 25th to 75th percentiles; whiskers, 10th and 90th percentiles.
q2mo, every 2 months; q6wk, every 6 weeks.

ARIPIPRAZOLE LAUROXIL EFFICACY

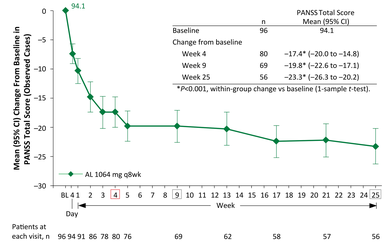
- The efficacy and safety of AL 441 mg and 882 mg monthly regimens were established in a pivotal phase 3 study[12] (**Figure 5**)
- The AL 662 mg monthly, 882 mg every-6-week, and 1064 mg every-2-month regimens and AL_{NCD} were approved based on PK bridging studies and population PK modeling analyses in which their steady-state PK profiles fell between those of the AL 441 mg and 882 mg monthly regimens (**Figure 4**)[3,4,8,9,13,14]
- Efficacy findings from phase 3 and 4 AL clinical trials are presented in **Figures 5–8**

Figure 5. Pivotal study[a]: changes in PANSS total score during 12 weeks of double-blind treatment with AL 441 mg or 882 mg monthly in acutely exacerbated schizophrenia, initiated using the 21-day regimen vs placebo



Adapted with permission from Meltzer et al. *J Clin Psychiatry* (2015).[12]
[a]Change from baseline in PANSS total score vs placebo (LOCF). NNT vs placebo was calculated based on PANSS response (≥30% reduction from baseline PANSS total score) at day 85.[12]
*P<0.004, **P<0.001 vs placebo.
AL, aripiprazole lauroxil; LOCF, last observation carried forward; NNT, number needed to treat; PANSS, Positive and Negative Syndrome Scale; q4wk, every 4 weeks.

Figure 6. ALPINE study[a]: 25 weeks of double-blind treatment with AL 1064 mg every 2 months (paliperidone palmitate used as active control[b]) in acutely exacerbated schizophrenia, initiated using the 1-day regimen



Adapted with permission from Weiden et al. *J Clin Psychiatry* (2020).[9]
[a]Mean (95% CI) change in PANSS total score from baseline to week 4 (primary endpoint, red box) and weeks 9 and 25 (secondary endpoints, gray boxes).
[b]ALPINE included an active control arm (paliperidone palmitate; data not shown); the study was not powered for between-group comparisons.
AL, aripiprazole lauroxil; BL, baseline; CI, confidence interval; PANSS, Positive and Negative Syndrome Scale; q8wk, every 8 weeks.

Figure 7. Therapeutic durability[a]: a post hoc analysis of data from the pivotal study[12] and a 52-week open-label safety study[17] (AL 441 mg or 882 mg monthly)

Adapted with permission from McEvoy et al. *J Clin Psychiatry* (2017).[16]
[a]Change from baseline in PANSS total score (MMRM) in patients with ≥1 PANSS/CGI-S assessment after drug administration in the extension study.
[b]P values reported for change in mean PANSS total score from week 0 to week 64.
[c]A separate analysis comparing change in mean PANSS total score from week 12 (beginning of extension study) to week 64 showed significant reductions in PANSS total score (P<0.0001).
[d]Indicated weeks denote assessment time points.
AL, aripiprazole lauroxil; CGI-S, Clinical Global Impressions–Severity; LS, least squares; MMRM, mixed effects model for repeated measures; PANSS, Positive and Negative Syndrome Scale; q4wk, every 4 weeks; SD, standard deviation; SE, standard error.

Figure 8. Phase 4 switching study[a]: 6-month open-label treatment with AL 441, 662, or 882 mg every 4 weeks (flexible dosing) or AL 882 mg every 6 weeks after switch from risperidone LAI or paliperidone palmitate

Adapted with permission from Miller et al. *Schizophr Res* (2019).[10]
[a]P<0.05 vs baseline.
[b]Change from baseline in CGI-S scores (MMRM; n=51). Mean (SD) CGI-S score at baseline: 3.9 (0.6).
AL, aripiprazole lauroxil; CGI-S, Clinical Global Impressions–Severity; LAI, long-acting injectable; LS, least squares; MMRM, mixed-effects model for repeated measurement; SD, standard deviation; SE, standard error.

ARIPIPRAZOLE LAUROXIL SAFETY AND TOLERABILITY

- AL safety and tolerability was consistent with the known profile of oral aripiprazole (**Table 1**)[12,16,19,20]
  - Akathisia is among the most common adverse events (≥5% of patients) during short-term treatment and is generally reported within the first 4 weeks after initiation[12,16]
  - During long-term AL treatment (up to 3.5 years), mean (SD) body weight gain was 1.2 (6.6) kg from baseline to last assessment; mean (SD) change in prolactin levels was −11.1 (32.9) ng/mL overall (males: −6.7 [16.5] ng/mL; females: −16.5 [45.2] ng/mL)[20]

Table 1. Summary of Key Safety Findings From AL Phase 3 and 4 Studies

Characteristic	12-Week, DB, Placebo-Controlled Study[12]			25-Week, DB, Active-Controlled Study[16]	Combined Long-term OL Safety Studies[a,20]		OL Switching Study[19]
	AL 441 mg q4wk (n=207)	AL 882 mg q4wk (n=208)	Placebo (n=207)	AL 1064 mg q8wk, 1-day initiation (n=99)	AL 441 mg q4wk (n=110)	AL 882 mg q4wk (n=368)	AL 441, 662, or 882 mg q4wk or 882 mg q6wk (n=51)
SAE, n (%)	3 (1.4)	4 (1.9)	4 (1.9)	8 (8.1)	0	18 (4.9)	5 (9.8)
SAE leading to death, n (%)	0	0	1 (0)[b]	0	0	2 (0.5)	0
AE leading to discontinuation, %	6.8	2.9	17.9	10.1	2.7	8.4	3.9
Any AE, %	58.9	57.2	62.3	69.7	52.7	59.0	41.2
AEs occurring in ≥5%[c] of patients in any treatment group, %							
Akathisia	11.6	11.5	4.3	9.1	4.5	4.9	—
Anxiety	2.9	5.3	6.8	—	3.6	6.3	5.9
Diarrhea	2.4	2.4	3.4	—	5.5	3.0	3.9
Dystonia	—	—	—	4.0	—	—	—
Headache	8.2	8.7	8.2	8.1	10.9	5.4	—
Injection site pain	3.4	4.8	1.9	17.2	0.9	4.9	—
Insomnia	9.7	12.0	11.6	—	7.3	14.4	3.9
Nasopharyngitis	—	—	—	—	7.3	4.6	—
Psychotic disorder	—	—	—	—	—	—	7.8
Schizophrenia worsening/ exacerbation	5.8	2.4	10.6	5.1	5.5	4.6	—
Somnolence	—	—	—	4.0	—	—	—
Suicidal ideation	—	—	—	—	—	—	5.9
Weight increased	2.9	2.4	0.5	9.1	9.1	5.2	3.9

[a]From the post hoc analysis of combined 52-week safety study and long-term extension data reported in Lauriello et al, 2020[20]; the long-term extension data are not reported separately elsewhere.
[b]One patient in the placebo group died from homicide; percentage rounded to 0.[12]
[c]Publications did not include values for all AEs listed here. Reported AEs that did not meet the threshold percentage in published tables (eg, ≥5%) are marked "—".[12]
AE, adverse event; AL, aripiprazole lauroxil; DB, double-blind; NCD, NanoCrystal Dispersion; OL, open-label; q4wk, every 4 weeks; q6wk, every 6 weeks; q8wk, every 8 weeks; SAE, serious adverse event.

CONCLUSIONS

- AL was developed using a proprietary prodrug technology with slow dissolution to provide an LAI antipsychotic with several dosage strengths for use over a range of dosing intervals to meet individual medical and quality of care needs
- PK, efficacy, and safety characteristics of AL support its use with multiple approved doses and dosing intervals
- Initiation options, including the only 1-day initiation regimen for an LAI aripiprazole formulation (AL_{NCD} + a single 30 mg oral dose of aripiprazole), can be personalized to the individual patient and are suitable for different settings of care
- Results from randomized controlled trials established the efficacy of the 441 mg and 882 mg monthly and 1064 mg every-2-months regimens in acute exacerbation of schizophrenia,[12,16] with continued therapeutic effect during longer-term treatment[18,20]
- AL safety and tolerability is consistent with the known profile of oral aripiprazole at initiation, during acute treatment, and during maintenance treatment

LIMITATIONS

- For specific limitations associated with the studies that we reviewed here, see the respective primary citation for each study in the Reference section in the supplemental materials, available via the QR code

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AUTHOR DISCLOSURES

LC has served as consultant to AbbVie/Allergan, Acadia, Adamas, Alkermes (including during conduct of this study), Angelini, Astellas, Avanir, Axsome, BioXcel, Boehringer Ingelheim, Cadent Therapeutics, Cerevel, Clinilabs, COMPASS, Eisai, Enteris BioPharma, HLS Therapeutics, Idorsia, Impel, INmune Bio, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Lyndra, MedAvante-ProPhase, Marvin, Merck, Mitsubishi-Tanabe Pharma, Neurelis, Neurocrine, Novartis, Noven, Otsuka, Ovid, Praxis, Recordati, Relmada, Reviva, Sage, Sunovion, Supernus, Teva, University of Arizona, Vanda, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research; received speaker fees from AbbVie/Allergan, Acadia, Alkermes, Angelini, Axsome, BioXcel, Eisai, Idorsia, Intra-Cellular Therapies, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Recordati, Sage, Sunovion, Takeda, Teva, and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and universities and professional organizations/societies; received fees/royalties/publishing income for work with Elsevier (Topic Editor, Psychiatry, *Clinical Therapeutics*), Springer Healthcare (book), Taylor & Francis (Editor-in-Chief, *Current Medical Research and Opinion*, 2022-current), *UpToDate* (reviewer), and Wiley (Editor-in-Chief, *International Journal of Clinical Practice*, through end 2019); owns a small number of shares of common stock (purchased >10 years ago) in Bristol Myers Squibb, Eli Lilly, J&J, Merck, and Pfizer; and has stock options with Reviva.

CUC has been a consultant and/or advisor to or has received honoraria from AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Biogen, Boehringer-Ingelheim, Cardio Diagnostics, Cerevel, CNX Therapeutics, Compass Pathways, Damitsa, Denovo, Gedeon Richter, Hikma, Holmusk, Intra-Cellular Therapies, Jamjoom Pharma, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MediniCell, Merck, MindPax, Mitsubishi Tanabe Pharma, Mylan, Neurelis, Neurocrine, Newron, Noven, Novo Nordisk, Otsuka, Pharmabrain, PPD Biotech, Recordati, Relmada, Reviva, Rovi, Seqirus, SK Life Science, Sunovion, Sun Pharma, Supernus, Takeda, Teva, and Viatris; has provided expert testimony for Janssen and Otsuka; has served on a data safety monitoring board for Compass Pathways, Denovo, Lundbeck, Relmada, Reviva, Rovi, Supernus, and Teva; has received grant support from Janssen and Takeda; has received royalties from UpToDate; and is a stock option holder of Cardio Diagnostics, Kuleon Biosciences, LB Pharma, MindPax, and Quantic.

GWM has served as a consultant for AbbVie, Alkermes, Axsome, Biogen, Corium, Eisai, Ironshore, Intra-Cellular, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Redax, Roche, Sage, Sirona, Sunovion, Supernus, Takeda, and Teva; received speaker fees for AbbVie, Alkermes, Axsome, Corium, Intracellular, Ironshore, Janssen, Lundbeck, Neurocrine, Noven, Otsuka, Sunovion, Supernus, Takeda, and Tris Pharma; and conducted research for AbbVie, Alkermes, Akili, Axsome, Boehringer, Emalex, Idorsia, Janssen, Karuna, Lumos Labs, Medgenics, Neurocrine, NLS-1 Pharma AG, Otsuka, Redax, Relmada, Roche, Sage, Sirtsel, Sunovion, Supernus, Takeda, and Teva.

AJC has served on advisory boards for Acadia, Alkermes, Biogen, BioXcel, Intracellular, and Teva; and on speakers' bureaus for Acadia, Axsome, BioXcel, Intracellular Therapies, Neurocrine, and Teva.

ARH has served on Advisory Boards for Acadia, Alkermes, Biogen, BioXcel, Intra-Cellular, and Teva and on speakers' bureaus for Acadia, Axsome, BioXcel, Intra-Cellular, Neurocrine, and Teva.

PJW is a former employee of Alkermes and has been a consultant for Alkermes, Lyndra, MapLight, and Teva.

BR, JAM, MD, and **CH** are or were employees of Alkermes, Inc., and may own stock/options in the company.

DM is or was an employee of Alkermes Pharma Ireland Ltd. and may own stock/options in the company.

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