

ELECTRONIC SUPPLEMENTARY MATERIAL

Population Pharmacokinetic Analysis and Model-Based Simulations of Aripiprazole for a 1-Day Initiation Regimen for the Long-Acting Antipsychotic Aripiprazole Lauroxil

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ONLINE RESOURCE 1

SUPPLEMENTARY TABLES

Supplementary Table S1 Summary of studies included in the PopPK analysis

Study	Population and planned no. subjects	Dose/treatment duration	Planned PK data
Study 1 ALK9072-B101 (Phase 1)	Adults with schizophrenia N = 70	Single-dose AL _{NCD} IM injection (gluteal) (Variable AL _{NCD} doses) Ascending-dose study to evaluate safety, tolerability, and PK PK samples were taken on days 1 through 15, 17, 19, 21, 23, 25, 27, 30, 33, 36, 43, 50, 57, 64, 71, 78, 85, and 113	84-day PK profile
Study 2 ALK9072-B102 (Phase 1)	Adults with schizophrenia N = 160	Treatment 1: AL 441 mg/1-day initiation: IM AL _{NCD} (gluteal) plus 30 mg oral aripiprazole plus IM AL 441 mg (deltoid) on day 1 followed by 20 days of oral placebo Treatment 2: AL 882 mg/1-day initiation: IM AL _{NCD} (gluteal) plus 30 mg oral aripiprazole plus IM AL 882 mg (contralateral gluteal) on day 1 followed by 20 days of oral placebo Treatment 3: AL 441 mg/21-day initiation: IM placebo (gluteal) plus 15 mg oral aripiprazole plus IM AL 441 mg (deltoid) on day 1 followed by 20 days of 15 mg oral aripiprazole Treatment 4: AL 882 mg/21-day initiation: IM placebo (gluteal) plus 15 mg oral aripiprazole plus IM AL 882 mg (contralateral gluteal) on day 1 followed by 20 days of 15 mg oral aripiprazole PK samples were taken from days 1 through 15, 17, 19, 21, 23, 25, 28, 31, 35, 43, 50, 57, 64, 71, 78, 85, 113, and 141	140-day PK profile
Study 3 ALK9072-B103 (Phase 1)	Adults with schizophrenia or schizoaffective disorder N = 46)	Treatment 1: AL _{NCD} IM injection (deltoid) Treatment 2: AL _{NCD} IM injection (gluteal) PK samples were collected on days 1, 2, 3, 5, 8, 10, 12, 17, 19, 21, 23, 25, 27, 30, 33, 36, 43, 57, 71, 80, and 85	84-day PK profile

Study 4 ALK9072- A105 (Phase 1)	Adults with stable schizophrenia N = 140	Treatment 1: AL 441 mg q4wk Treatment 2: AL 882 mg q6wk Treatment 3: AL 1064 mg q8wk Treatment 4: AL 1064 mg q8wk (alternative formulation) PK samples were taken on days 1, 4, 8, 11, 15, 18, 22, 25, 29, 32, 36, 39, 43, 46, 50, 53, 57, 71, 85, 99, 113, 127, 141, 155, 169, 172, 176, 180, 183, 186, 190, 193, 197, 200, 204, 207, 211, 214, 217, 221, 225, 228, 232, 239, 246, 253, 281, and 309	
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AL aripiprazole lauroxil, *AL_{NCD}* AL nanocrystal dispersion, *IM* intramuscular; *PK* pharmacokinetic

Supplementary Table S2 Estimates of covariate effects in the full model

Covariate effect	NONMEM estimates		
	Point estimate	%RSE	95% CI
Weight on VC/F ^a	1	—	—
Weight on CL/F ^b	0.75	—	—
Weight on AL D	0.571	27.3	0.265, 0.877
Weight on AL ALAG	-0.628	34.1	-1.05, -2.09
Age on CL/F	-0.28	37.9	-0.488, -0.0722
AL _{NCD} injection site on FRAC ^c	0.773	17.4	0.509, 1.04 ^d
AL injection site on D ^c	0.768	6.08	0.676, 0.859
AL injection site on ALAG ^c	1.27	15.7	0.882, 1.67 ^d

AL aripiprazole lauroxil, CI confidence interval, D AL intramuscular duration of absorption, ALAG

AL IM lag time, CL/F apparent clearance of aripiprazole, FRAC Weibull fraction of dose, VC/F

central apparent volume of distribution for aripiprazole

^aFixed as 1.0 (allometric value for weight on VC/F).

^bFixed as 0.75 (allometric value for weight on CL/F).

^cDeltoid estimated in comparison to gluteal.

^dNull included in 95% CI.

Supplementary Table S3 Parameter Estimates for the Final PopPK Model

Parameter	NONMEM Estimates			
	Point Estimate	%RSE	95% CI	CV%
CL/F (L/h)*	1.98	2.54	1.88, 2.07	—
VC/F (L)*	327	4.51	298, 356	—
Weight ON VC/F ^{a,f}	1	—	—	—
MDT1 (h)*	596	3.29	557, 634	—
GAM1	2.2	2.85	2.08, 2.32	—
MDT2 (h)*	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/h)*	0.102	10.9	0.080, 0.124	—
Ka PO ARI (h ⁻¹)*	0.47	14.2	0.339, 0.601	—
D AL (h)*	934	3.86	864, 1005	—
ALAG AL (h)*	106	7.85	89.4, 122	—
FIM AL ^{b,*}	0.571	—	—	—
FPO ARI ^{a,*}	1	—	—	—
FIM AL _{NCD} ^{c,*}	1.12	3.56	1.04, 1.20	—
FIM AL _{NCD} ^d	0.638	—	—	—

ARI(0) (ng/mL)*	0.378	14.8	0.269, 0.488	—
Interindividual variability				
CL/F	0.539	10.80	0.425, 0.653	84.5 ^e
VC/F	0.239	16.80	0.160, 0.318	52.0 ^e
MDT1	0.197	13.00	0.147, 0.247	46.7 ^e
GAM1	0.461	20.80	0.273, 0.649	76.5 ^e
MDT2	0.274	15.10	0.193, 0.355	56.1 ^e
GAM2	0.129	24.00	0.0684, 0.190	35.9
FRAC	0.978	17.90	0.635, 1.32	129 ^e
VP/F (L)	0.686	18.70	0.435, 0.937	99.3 ^e
Q/F (L/h)	2.6	10.90	2.05, 3.15	353 ^e
Ka PO ARI (h ⁻¹)	2.45	16.30	1.67, 3.23	325 ^e
D AL (h)	0.147	21.70	0.0845, 0.210	38.3
ALAG AL (h)	0.895	15.10	0.630, 1.16	120 ^e
FIM AL	0.505	10.80	0.399, 0.611	81.1 ^e
Ari(0)	4.34	10.60	3.44, 5.24	870
Residual variability				
σ^2 prop Studies 1, 2, and 3	0.0359	3.93	0.0331, 0.0387	18.9
σ^2 prop Study 4	0.0207	2.70	0.0196, 0.0218	14.4

AL aripiprazole lauroxil, AL_{NCD} aripiprazole lauroxil nanocrystal dispersion, D AL IM duration of absorption, ALAG AL IM lag time, Ari(0) initial amounts of aripiprazole, CI confidence interval, CL/F apparent clearance of aripiprazole, CV coefficient of variation, FPO oral bioavailability, FIM

AL IM bioavailability, *FIM AL-NCD* AL_{NCD} IM bioavailability, *FRAC* Weibull fraction of dose, *GAM1 and GAM2* Weibull slope factors, *Ka* oral rate of absorption, *MDT1 and MDT2* mean dissolution time for each Weibull, *Q/F* intercompartmental CL for aripiprazole, *RSE* relative standard error, *SE* standard error, *VC/F* central apparent volume of distribution for aripiprazole, *VP/F* peripheral apparent volume of distribution for aripiprazole.

Only diagonal elements of the full Ω block are presented.

*Indicates parameter was estimated on log scale and subsequently that estimates were exponentiated and CIs were calculated using the SE of the exponentiated parameter estimate ($SE \times e^p$).

^aFixed at 1.00.

^bFixed at 57.1% from previous analysis.

^c AL_{NCD} F estimated relative to AL.

^d AL_{NCD} F relative to oral aripiprazole (calculated as 1.24×0.571 [note: more decimal places used in calculation than presented]).

^eCV calculated as $CV_{TP} = \sqrt{e^{\omega_p^2} - 1} \times 100$ rather than square root of $\omega_p^2 \times 100$.

^fPower effect = $VC/F * (\text{weight}/70)1.0$.