Altasciences CLINICAL RESEARCH ALGORITHME PHARMA

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# Single-Dose Pharmacokinetics of ALP2011 in Subjects with Various Degrees of Hepatic Impairment

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## Abstract

The objective of this study was to assess the impact of hepatic impairment on the pharmacokinetics (PK) of ALP2011.
The study was an open-label, multi-center, parallel trial in patients (N = 6-10 per group) with mild, moderate, and severe hepatic impairment (Child-Pugh score: 5-6, 7-9, and 10-15 points, respectively) compared to matched healthy normal subjects. A single 20 mg oral dose was administered in the morning, two hours after a breakfast. Blood samples were collected over 24 hours and were assayed for concentrations of the two isomers. Noncompartmental PK analysis was performed. Pairwise comparisons of the groups (ANOVA) and a regression analysis between hepatic function and the PKs were performed. Safety was monitored throughout the study.
No significant between-group differences were observed for the PKs of the R(-) isomer, as shown by AUCinf (mean 929-1318 ug*h/mL) and $C_{max}$ (mean 168-205 ug/mL). For S(+), pairwise tests revealed significant differences for AUCinf between the control group and the moderate and severe impaired patients (mean 873 vs. 1217-1264 ug*h/mL); however, only a 1.4-fold increase was observed. $C_{max}$ (mean 118-155 ug/mL) was similar between groups. For both isomers, $T_{max}$ (median 1.00-1.67 h) and $T_{½}$ (mean 5.4-6.7 h) values were not affected by hepatic impairment. The drug was well tolerated and the severity of hepatic impairment was not associated with safety concerns.
These results indicate that systemic exposure of ALP2011 is not significantly altered by the presence or severity of hepatic impairment. Impaired hepatic function should not require changes of the posology in this special population.

## Purpose

Since 2000, experimental data in animals and studies conducted in patients have showed that AL2011 may be useful in alcohol dependent patients. Given that ALP2011, in this new therapeutic indication, may now be used to treat individuals with impaired hepatic function, regulatory agencies have recommended conducting a single-dose study to evaluate the impact of hepatic impairment on the pharmacokinetic profile of ALP2011. Consequently, this study was conducted in both healthy subjects (subjects with normal hepatic function) and in subjects with varying degrees of impaired hepatic function (mild to severe hepatic impairment).

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## Study Design

- The study design was designed based on the EMA guidance CPMP/ EWP/ 2339/02 "Guideline on the Evaluation of the Pharmacokinetics of Medicinal Products in Patients with Impaired Hepatic Function".
- This was a multi-center, non-randomized, open-label, single-dose, parallel group study in a subject population comprised of adult male and female volunteers with various levels of hepatic function.
- The degree of impairment was determined using the Child-Pugh classification.
- Subjects with moderate and severe impairment were recruited first, and healthy volunteers were matched by gender, age (+/- 10 years), weight (+/- 15%), and tobacco use, to the extent possible.
- All subjects received a single 20 mg oral dose of ALP2011 under fasting conditions. Blood samples for measurement of R(-) and S(+) ALP2011 isomer concentrations were collected pre-dose and over a 24-hour period post-dose.
- Safety endpoints included the occurrence of adverse events (AEs), clinical laboratory test results, vital signs measurements, 12-lead ECG findings, physical examination findings, and use of concomitant medications.

**Table 1. Child-Pugh Scores**

| | 1 Point | 2 Points | 3 Points |
|---|---|---|---|
| Bilirubin, total, µmol (mg/dL) | <34 (<2) | 34-50 (2-3) | >50 (>3) |
| Albumin, mg/L | >35 | 28-35 | <28 |
| INR | <1.7 | 1.71-2.20 | >2.20 |
| Ascites | None | Suppressed with medication | Refractory |
| Hepatic encephalopathy | None | Grade I-II (or suppressed with medication) | Grade III-IV (or refractory) |

Class A=5-6 points; class B=7-9 points; class C=10-15 points

## Bioanalytical and Statistical Analysis

- Samples were quantified for serum R(-) and S(+) ALP2011 isomers using validated LC-MS/MS method.
- Noncompartmental PK analysis was performed (Phoenix® WinNonlin® 6.3) and a regression analysis was used to evaluate the impact of impaired hepatic function on the relevant PK parameters. When trends observed were significant, an ANOVA was performed to assess individual differences between groups (SAS® 9.4, Proc MIXED).

## Results

### Recruitment

- Healthy subjects were recruited and dosed at Algorithme Pharma, and subjects with mild, moderate and severe hepatic impairment were recruited and dosed at the clinical site of the Centre de recherche du Centre hospitalier de l'Université de Montréal (CRCHUM).

**Table 2. Demographic Data**

| Hepatic function/ impairment | | Normal n=10 | Mild n=10 | Moderate n=10 | Severe n=6 | Overall n=36 |
|---|---|---|---|---|---|---|
| **Age (years)** | Mean (SD) | 48 ( 4) | 56 ( 8) | 50 ( 14) | 52 ( 8) | 52 ( 10) |
| | Min, Max | 44, 56 | 39, 63 | 20, 64 | 39, 62 | 20, 64 |
| **Gender [n (%)]** | Male | 7 ( 70.0) | 5 ( 50.0) | 7 ( 70.0) | 6 (100.0) | 25 ( 69.4) |
| | Female | 3 ( 30.0) | 5 ( 50.0) | 3 ( 30.0) | 0 | 11 ( 30.6) |
| **Weight (kg)** | Mean (SD) | 79.2 ( 14.7) | 78.7 ( 17.8) | 76.8 ( 17.6) | 88.4 ( 18.5) | 79.9 ( 16.8) |
| | Min, Max | 56.8, 94.4 | 44.3, 113.2 | 46.3, 101.4 | 63.9, 114.2 | 44.3, 114.2 |
| **BMI (kg/m²)** | Mean (SD) | 26.58 ( 2.50) | 29.54 ( 6.41) | 26.52 ( 5.54) | 30.73 ( 4.76) | 28.08 ( 5.14) |
| | Min, Max | 21.60, 29.46 | 19.17, 39.08 | 19.10, 36.06 | 25.60, 36.86 | 19.10, 39.08 |
| **Child-Pugh Score** | Mean (SD) | NA | 5.30 ( 0.48) | 7.70 ( 0.82) | 10.33 ( 0.52) | 7.38 ( 2.06) |
| | Min, Max | NA | 5.00, 6.00 | 7.00, 9.00 | 10.00, 11.00 | 5.00, 11.00 |

NA: Not Applicable

## R(-) Isomer

- The results showed similar $C_{max}$ for subjects with hepatic impairment (mean Cmax ranged 183-205 ng/mL) compared to healthy subjects (mean $C_{max}$ 168 ng/mL).
- No overall group effect was noted for the exposure (AUC), (mean $AUC_{0-\infty}$ ranged 929-1318 ng*h/mL).
- Median $T_{max}$ was similar for all groups (range 1.00-1.67 hours).
- No significant differences in elimination half-life of the drug between healthy volunteers and hepatic-impaired subjects were observed in all pairwise comparisons, with a $T_{½}$ ranging 5.57-6.64 hours among groups.

**Table 3. Summary of Plasma R(-)-Isomer Pharmacokinetic Parameters**

| | Hepatic Function | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Normal Function | | Mild Insufficiency | | Moderate Insufficiency | | Severe Insufficiency | |
| PK parameter | Mean | CV% | Mean | CV% | Mean | CV% | Mean | CV% |
| $C_{max}$ (ng/mL) | 168 | 17.3 | 200 | 38.3 | 205 | 22.8 | 183 | 32.2 |
| $T_{max}$ (h)[a] | 1.33 | 0.75-2.50 | 1.50 | 0.50-2.50 | 1.00 | 0.50-2.10 | 1.67 | 1.00-4.10 |
| $AUC_{0-T}$ (ng*h/mL) | 843 | 12.7 | 985 | 38.7 | 1149 | 36.2 | 1197 | 26.2 |
| $AUC_{0-\infty}$ (ng*h/mL) | 929 | 10.8 | 1049 | 37.5 | 1239 | 36.1 | 1318 | 26.8 |
| $AUC_{0-T/\infty}$ (%) | 90.56 | 2.5 | 93.47 [b] | 2.6 | 92.72 | 1.2 | 91.03 | 3.9 |
| $Cl_{TOT}/F$ (L/h) | 21.7 | 10.9 | 21.4 | 34.6 | 17.4 [b] | 23.7 | 16.5 | 37.2 |
| $V_D/F$ (L) | 179 | 19.7 | 167 | 31.2 | 158 | 24.2 | 152 | 23.2 |
| $\lambda_z$ (1/h) | 0.1244 | 16.2 | 0.1275 | 17.3 | 0.1120 | 17.7 | 0.1087 | 23.1 |
| $T_{half}$ (h) | 5.70 | 15.8 | 5.57 | 15.0 | 6.36 | 16.6 | 6.64 | 20.7 |

a median (range)
b significant between-group difference with normal group (p >0.05)

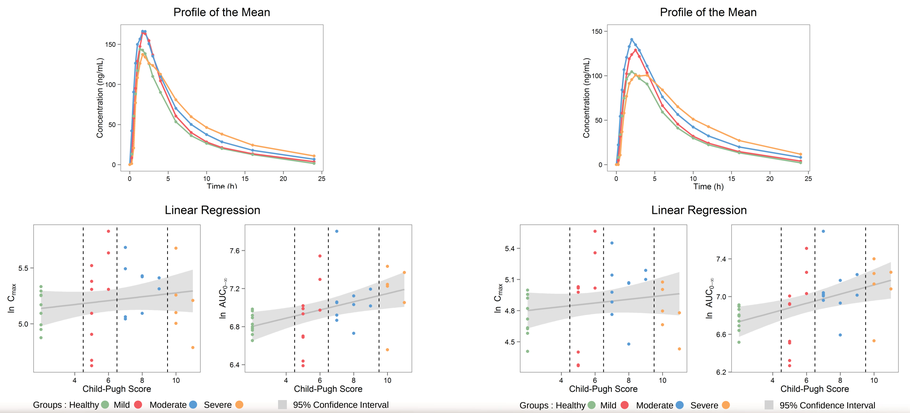
## S(+) Isomer

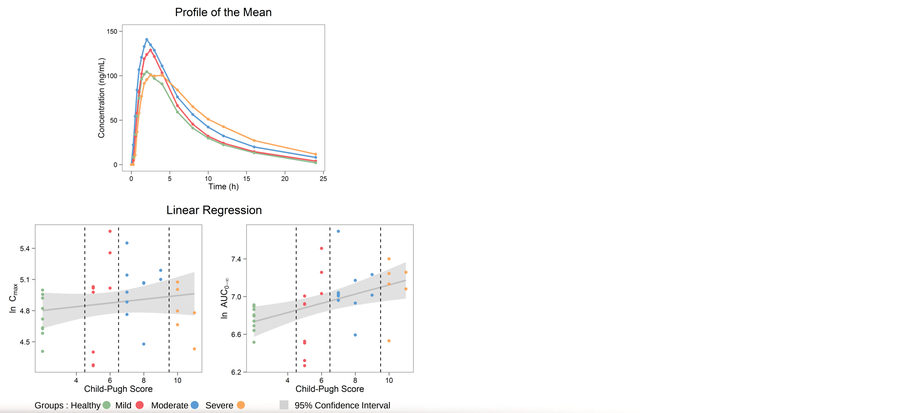
- The results showed similar $C_{max}$ for subjects with hepatic impairment (mean Cmax ranged 123-155 ng/mL) compared to healthy subjects (mean $C_{max}$ 118 ng/mL).
- Significant differences were observed between the healthy subjects (mean $AUC_{0-\infty}$ 873 ng*h/mL) and the moderate and severe impaired patients (mean $AUC_{0-\infty}$ ranged 1217-1264 ng*h/mL), however, only a 1.4-fold increase was observed.
- Median $T_{max}$ was similar for all groups (range 1.67-2.08 hours).
- No significant differences in elimination half-life of the drug between healthy volunteers and hepatic-impaired subjects were observed in all pairwise comparisons, with a $T_{½}$ ranging 5.36-6.64 hours among groups.

**Table 4. Summary of Plasma S(+)-Isomer Pharmacokinetic Parameters**

| | Hepatic Function | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Normal Function | | Mild Insufficiency | | Moderate Insufficiency | | Severe Insufficiency | |
| PK parameter | Mean | CV% | Mean | CV% | Mean | CV% | Mean | CV% |
| $C_{max}$ (ng/mL) | 118 | 18.8 | 145 | 41.7 | 155 | 25.1 | 123 | 22.6 |
| $T_{max}$ (h)[a] | 1.67 | 0.75-4.00 | 1.83 | 1.33-3.03 | 1.83 | 0.75-3.00 | 2.08 | 1.33-6.00 |
| $AUC_{0-T}$ (ng*h/mL) | 795 | 14.0 | 927 | 43.3 | 1140 [b] | 32.0 | 1132 | 26.1 |
| $AUC_{0-\infty}$ (ng*h/mL) | 873 | 11.8 | 994 | 41.3 | 1217 [b] | 31.6 | 1264 [b] | 25.5 |
| $AUC_{0-T/\infty}$ (%) | 90.81 | 3.0 | 92.43 | 3.6 | 93.59 | 1.8 | 89.51 | 4.3 |
| $Cl_{TOT}/F$ (L/h) | 23.2 | 12.9 | 23.3 | 39.8 | 17.6 [b] | 26.0 | 17.1 | 35.8 |
| $V_D/F$ (L) | 180 | 19.8 | 181 | 38.8 | 153 | 23.3 | 159 | 25.7 |
| $\lambda_z$ (1/h) | 0.1320 | 15.3 | 0.1286 | 12.5 | 0.1160 | 12.5 | 0.1074 | 19.3 |
| $T_{half}$ (h) | 5.36 | 15.3 | 5.46 | 11.4 | 6.06 | 12.0 | 6.64 | 17.6 |

a median (range)
b significant between-group difference with normal group (p >0.05)




## Safety

- The majority of AEs were mild or moderate in severity, and all AEs were transient in nature (lasting less than 24 hours) and resolved prior to subject discharge. The most commonly reported AE was hypertension, experienced by three subjects. No AEs led to discontinuation from the study.
- Overall, increase in severity of hepatic impairment did not result in significant increase in incidence of AEs.
- There were no SAEs and no deaths. No clinically significant effects on laboratory values, vital signs, ECGs, or physical examinations were noted during this study.

## Conclusion

The study results demonstrate that systemic exposure, as indicated by $C_{max}$ and AUCs, to orally administered ALP2011 is not significantly altered by the presence of hepatic impairment, even in severely impaired patients.

Adjustment of the ALP2011 dosage regimen in patients with impaired hepatic function is concluded to be unnecessary, unless other factors warrant it, as there were no significant changes in systemic exposure of ALP2011.