**Electronic Supplementary Material**

***Clinical Pharmacokinetics***

**Pharmacokinetics of Ampreloxetine, a Norepinephrine Reuptake Inhibitor, in Healthy Subjects and Adults with Attention-Deficit/Hyperactive Disorder or Fibromyalgia Pain**

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**Compliance with Ethical Standards**

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**Supplementary Table 1**. Summary of Plasma PK Parameters for Ampreloxetine: Day 1 (MAD Study)

|  |  |  |  |
| --- | --- | --- | --- |
| **Dose Level****(mg)** | **Cmax****(ng/mL)** | **Tmaxa****(hr)** | **AUC0-24****(ng\*hr/mL)** |
| 4 (Fasted) | Mean | 2.54 | 10 | 40.4 |
|  | SD | 0.86 | 8.00,14.0 | 11.2 |
|  | n | 6 | 6 | 6 |
|  |  |  |  |  |
| 4 (Fed) | Mean | 2.09 | 8.00 | 35.2 |
|  | SD | 0.61 | 6.00, 14.0 | 10.4 |
|  | n | 5 | 5 | 5 |
|  |  |  |  |  |
| 10 | Mean | 5.82 | 10 | 104 |
|  | SD | 2.22 | 8.00, 14.0 | 41 |
|  | n | 6 | 6 | 6 |
|  |  |  |  |  |
| 20 | Mean | 9.57 | 11 | 167 |
|  | SD | 3.58 | 6.00, 14.0 | 63 |
|  | n | 6 | 6 | 6 |
|  |  |  |  |  |
| 20 | Mean | 12.9 | 8 | 225 |
| (Older age group) | SD | 1.9 | 6.00, 10.0 | 39 |
|  | n | 6 | 6 | 6 |
|  |  |  |  |  |
| 40 | Mean | 31.9 | 8 | 573 |
|  | SD | 11.4 | 6.00, 8.00 | 206 |
|  | n | 6 | 6 | 6 |

a Median (min, max).

*AUC0-24* area under the curve 0-24 hours, *Cmax* maximum concentration, *MAD* multiple-ascending dose, *max* maximum, *min* minimum, *PK* pharmacokinetic, *Tmax* time at maximum concentration.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Descriptor – Mean (min, max)** | **All subjects** | **SAD/MAD** | **Phase 2** **(ADHD)** | **Phase 2** **(FM)** |
| **Number of subjects (n)** | 499 | 68 | 192 | 239 |
| **Age (years)** | 38.7 (18, 65) | 36.8 (18, 64) | 30.8 (18, 45) | 45.5 (19, 65) |
| **Body weight (kg)** | 80.6 (43.1, 157) | 74.4 (51.6, 96.0) | 81.5 (48.5, 136) | 81.6 (43.1, 158) |
| **Height (cm)** | 168.3 (137, 199) | 167.3 (149, 184) | 173.5 (150, 199) | 164.5 (137, 191) |
| **Baseline creatinine clearance (ml/min)** | 100.5 (45.2, 201) | 123.2 (69.8, 200) | 113.0 (67.3, 201) | 83.9 (45.2, 154) |
| **Body mass index (kg/m2)** | 28.4 (18.6, 44.6) | 26.6 (19.9, 32.8) | 27.0 (18.7, 34.9) | 30.1 (18.6, 44.6) |
|  |  |  |  |  |
| **Sex (M, F), n** | 175 M, 324 F | 40 M, 28 F | 119 M, 73 F | 16 M, 223 F |
| **Smoker/Non-smoker, n** | 82 S, 417 NS | 0 S, 68 NS | 36 S, 156 NS | 46 S,193 NS |
|  |  |  |  |  |

**Supplementary Table 2:** Summary of Covariates for Population PK Analysis

*ADHD* attention-deficit/hyperactivity disorder, *F* female, *FM* fibromyalgia, *M* male, *MAD* multiple-ascending dose, *NS* non-smoker, *S* smoker, *SAD* single-ascending dose.

**Supplementary Fig. 1: a.** Model-predicted ampreloxetine plasma concentrations; **b.** Individual predicted plasma concentrations plotted versus observed plasma concentrations; **c.** Weighted residuals.



*Cp* plasma concentrations.