Background

We previously determined the maximum tolerated dose (MTD) of SEP-432 to be 300mg/day. The main goals in the present study were to characterize the CSF and plasma pharmacokinetic profile of SEP-432 in CSF and plasma will also be described.

Methods

This study was conducted in healthy male and non-pregnant, non-nursing female volunteers. Subjects were screened by medical history, physical exam, electrocardiogram (ECG), and routine labs, and could not have any clinically relevant abnormalities, unstable medical conditions, or any significant chronic disease, psychiatric disorder, or history of substance abuse. Subjects were screened to ensure that they had no conditions, surgeries, or medications that would complicate lumbar puncture; this included an X-ray of the lumbar spine to rule out any anatomical abnormalities, and a careful history for any recent febrile illnesses or infections/inflammations near the lumbar puncture site. This study was approved by the institutional review board (IRB) IntegReview in Austin, Texas.

Results

As shown in the following table, both SEP-432 and duloxetine significantly (p<0.05) decreased DOPAC relative to placebo; SEP-432 having a greater effect than duloxetine (82% and 58% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively). SEP-432 also had a statistically significant effect than duloxetine (39% and 28% decreases in CSF respectively).

Results (cont.)

As seen in the figure below, the plasma PK decline follows a multi-compartmental model, i.e., a rapidly declining initial phase, followed by a slower elimination phase. The CSF exposure of SEP-432 was 22% that of plasma, while SEP-432 was 46% of plasma (ratio of CSF/plasma AUC0-24). Figure 3 shows the mean CSF SEP-432 (300 mg) plasma and CSF Concentrations over 24 Hours (Day 14)

Conclusions

At its MTD, SEP-432 showed significant monoamine biomarker effects consistent with a dual NE, 5HT reuptake inhibitor property, but not centrally. The comparator duloxetine produced similar changes in monoamines and metabolites over 24-hours and the pharmacokinetic profile of SEP-432 in CSF and plasma will also be described.

References