

<b>Pfizer Inc.</b>	<b>CP-448187 (elzasonan)</b>
<b>Mechanism of Action</b>	5-Hydroxytryptamine 1B receptor (5-HT <sub>1B</sub> ) antagonist <a href="http://www.iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=2">http://www.iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=2</a> <a href="http://www.ncbi.nlm.nih.gov/gene/3351">http://www.ncbi.nlm.nih.gov/gene/3351</a>
<b>Overview</b>	CP-448187 is a potent (K <sub>i</sub> = 0.13 nM), modestly selective [ $>100$ -fold for other 5-HT and non-5-HT receptors, except for 5-HT <sub>1A</sub> (K <sub>i</sub> = 0.20 nM), dopamine reuptake (~10-fold), and hERG (~25-fold)], functional antagonist of the human and guinea pig 5-HT <sub>1B</sub> receptor.
<b>Safety/Tolerability</b>	CP-448187 has been studied in humans at single and multiple doses ranging from 0.5 mg to 60 mg QD. The most common treatment-emergent adverse effects were insomnia, dizziness, headache, nausea, asthenia, and somnolence. The dose of 3 mg QD used in Phase 2 studies was associated with maximal mean increases in QTcF of between 1.6 and 5.9 msec.  Nonclinical toxicology data support clinical studies up to 1 year in duration.
<b>Additional Information</b>	At 3 mg QD for 7 days, CP-448187 demonstrated 70 – 80% 5-HT <sub>1B</sub> receptor occupancy for all brain regions via a PET ligand study. An apparent antidepressant effect was seen with CP-448187 in Phase 2 at 3 mg QD, with faster onset and reduced sexual dysfunction compared to SSRIs, despite the inability to escalate dose, and potential efficacy, due to QTc changes. The most frequent adverse event of dizziness is hypothesized to be due to the interaction of CP-448187 with 5-HT <sub>1A</sub> receptors.
<b>Suitable for and Exclusions</b>	Clinical trials of up to 3 – 6 months duration at 3 mg QD where the potential benefit justifies the risks and adverse events (Aes) noted above. Patients with conduction abnormalities on ECG, familial long QT syndrome, or taking drugs with the potential to prolong the QT interval should be excluded.
<b>Clinical Trials</b>	<a href="http://clinicaltrials.gov/ct2/results?term=elzasonan">http://clinicaltrials.gov/ct2/results?term=elzasonan</a>
<b>Publications</b>	<a href="http://dmd.aspetjournals.org/content/38/11/1984.full.pdf">http://dmd.aspetjournals.org/content/38/11/1984.full.pdf</a> <a href="http://www.ncbi.nlm.nih.gov/pubmed?term=CP-448%2C187%20">http://www.ncbi.nlm.nih.gov/pubmed?term=CP-448%2C187%20</a>