Bristol-Myers Squibb	BMS-562086 (pexacerfont)
Mechanism of Action	Corticotropin-releasing factor 1 (CRF_1) receptor antagonist http://iuphar-db.org/DATABASE/ObjectDisplayForward?familyId=19&objectId=212 http://www.ncbi.nlm.nih.gov/gene/1394
Overview	Pexacerfont is a potent and selective CRF_1 antagonist which is orally bioavailable and brain penetrant; IC_{50} = 7.2 ± 0.9 nM (n = 4). It is specific for CRF_1 and has more than 1,000-fold less affinity for CRF_2, and > 100-fold less affinity for the CRF-binding protein. Pexacerfont was active in the defensive withdrawal and elevated plus maze models of anxiety in rats (1 - 10 mg/kg, p.o.). The lowest effective dose of pexacerfont in the defensive withdrawal model resulted in ~50% occupancy of brain CRF_1 receptors. Doses as high as 30 mg/kg p.o. had no effect on mild stress-induced elevations of plasma corticosterone and doses as high as 100 mg/kg did not lead to overt side effects such as ataxia or alteration of locomotor activity.
Safety/Tolerability	Pexacerfont has been evaluated in an extensive battery of non-clinical studies. The liver, thyroid gland, pituitary gland, mammary gland, testis, and the female reproductive tract were the primary target organs in rats whereas the testis was the only target organ in dogs given 180 mg/kg/day for 1 year. The most noteworthy preclinical findings included: 1) testicular toxicity in rats (after 2 weeks of treatment) and dogs (after 1 year of treatment) at ≥ 17x the mean human AUC at 100 mg; NOEL for testicular effects in several studies in both species ranged from 8-12x (based on several studies in both species; 2) mammary glandular hyperplasia in male and female rats after 3 and 6 months and 1 year of treatment; exposure multiples of the human AUC at 100 mg (proposed daily human dosing) at the lowest effect levels were 14-17x at 3 months and 2x at 6 months and 1 year; 3) altered estrous cyclicity in rats at ≥ 5x the human AUC and reduced fertility in male and female rats at ≥ 30x the human AUC. NOEL for fertility in males and females were 8-11x; and 4) nonselective developmental toxicity in rats at ≥ 24x the human AUC at 100 mg; NOEL was 6x. Pexacerfont was not a selective developmental toxicant and was nongenotoxic. Pexacerfont was generally well tolerated in over 500 subjects treated in 8 Phase 1 and 3 Phase 2 studies. In Phase 1 studies, single doses of pexacerfont were administered between 5-900 mg, and multiple doses ranged between 50-400 mg/day. In the Phase 2 clinical studies, pexacerfont was dosed at 100 mg/day in approximately 210 subjects for up to 8 weeks in female subjects. The most common treatment-emergent AEs in the Phase 2 studies were headache, nausea, vomiting, diarrhea and upper respiratory tract infections. There was no evidence that pexacerfont had any clinically relevant effects on vital signs, ECGs, clinical laboratory values, or physical examination findings. The incidence of SAEs was low and similar to placebo in the Phase 2 studies. No unexpected safety findings were observed and no deaths occurred.

Additional Information	The pexacerfont development program was terminated by BMS in 2008 after the lack of any efficacy signal in Phase 2 studies in major depressive disorder, generalized anxiety disorder and irritable bowel syndrome. A spermatogenesis study in healthy males was initiated but ended early due to the overall program termination. An external DMC reviewed the data gathered from the spermatogenesis study and the board concluded it was safe to proceed with testing in males.
Suitable for and Exclusions	Suitable for chronic dosing. Women of childbearing potential should have a negative pregnancy test prior to treatment and use effective forms of birth control during treatment. Results of spermatogenesis study should be reviewed when considering enrolling male subjects.
Clinical Trials	http://clinicaltrials.gov/ct2/results?term=BMS-562086++or+pexacerfont
Publications	http://www.ncbi.nlm.nih.gov/pubmed?term=BMS-562086%20or%20pexacerfont%20 http://pubs.acs.org/doi/pdf/10.1021/jm900025h