| Bristol-Myers Squibb | BMS-830216 |
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| **Mechanism of Action** | Melanin-concentrating hormone 1 ($MCH_1$) receptor antagonist<br>http://iuphar-db.org/DATABASE/ObjectDisplayForward?familyId=37&objectId=280<br>http://www.ncbi.nlm.nih.gov/gene/2847 |
| **Overview** | BMS-830216 is an orally bioavailable, phosphate prodrug of BMS-819881, a novel, selective and potent antagonist of the $MCH_1$ receptor that has been tested in human subjects. Potent inhibitor of receptor signaling (Ki = 10 nM) with a relatively slow off-rate. Brain to plasma ratios (0.66 in rats; 3-8 in monkeys) demonstrated CNS penetration. $MCH_1$ receptor occupancy in rats was 40-60% at 6 hour after a single 3 mg/kg dose. Reductions in food intake and body weight (BW) in both lean and diet induced obese (DIO) male Sprague-Dawley rats (at 3 mg/kg, 5.5% at 10 days in lean rats and 4.9-6.0% at 30 days in DIO rats). BW loss was a function of reduced adipose tissue. No indications of any overt effects on motor or sensory function nor any abuse potential. |
| **Safety/Tolerability** | No genotoxicity; no ion channel, cardiovascular, respiratory or neurologic liabilities; in repeat-dose toxicity studies ≤ 4 weeks in rats/monkeys, effects were minimal and only in rats with NOAELs that provided > 1x safety margins relative to the maximum clinical exposure. A potential phototoxicity liability was identified. |
| **Additional Information** | Generally safe/well tolerated at all doses in SAD and in MAD for up to 28 days; no BMS-830216-related SAEs and most AEs were mild to moderate and manageable; indications of mild photosensitivity. Dose-proportional increases in exposure; even longer $t_{1/2}$ in obese patients than in HVs (190 to 230 hour versus 77 to 143 hour); similar metabolite/parent ratio in both obese and HVs. The projected efficacious trough concentration (556 ng/ml) achieved at 150 mg daily dose.<br><br>Estimated availability of 8.5 kg of GLP grade API and 3.75 kg of GMP grade API; specifications in place to generate formulated tablet rather than drug-in-capsule used to date. To enable use, estimate 6-12 month duration plus resources for analytical release testing, stability, etc. |
| **Suitable for and Exclusions** | With 28-day (daily) treatment duration (and extended systemic exposures due to long $t_{1/2}$),<br>no BMS-830216-related decreases in mean body weight relative to baseline and no discernible trends that would suggest a clinically meaningful reduction in food intake. |
| **Clinical Trials** | http://clinicaltrials.gov/ct2/results?term=BMS-830216 |
| **Publications** | Two abstracts/presentations to be delivered at the 2012 American Chemical Society and the 2012 Obesity Society annual meetings |