<table>
<thead>
<tr>
<th>Janssen (J&amp;J)</th>
<th>JNJ-31001074/Bavisant</th>
</tr>
</thead>
</table>
| **Mechanism of Action** | Histamine Type 3 (H3) receptor antagonist  
IUPHAR link for target: [http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=264&familyId=33](http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=264&familyId=33)  
| **Overview** | JNJ-31001074 potent and selective brain-penetrating and orally active small molecule H3 receptor antagonist. This compound shows considerable affinity for the human H3 receptor and lacks any measurable affinity for 50 other neurotransmitter and neuropeptide receptors up to concentrations 1000 times higher than its human H3 receptor affinity. In animals, this compound has been shown to promote wakefulness and attention, reduce sleeping, increase cognitive performance and reduce alcohol consumption. In humans, the compound occupies central H3 receptors at well-tolerated oral doses. H3 antagonists activate multiple neurotransmitters, such as histamine, acetylcholine and norepinephrine. They therefore have potential applications in a broad array of CNS disorders characterized by impaired cognition, impaired attention and/or excessive sleepiness or substance abuse. |
| **Safety/Tolerability** | The preclinical safety of the compound has been evaluated in GLP safety pharmacology; short-, medium- and long-term toxicology studies; as well as in reproduction, juvenile toxicity and abuse potential studies. Carcinogenicity studies are ongoing. Adequate safety margins were established to support long-term clinical trials. Human single and multiple ascending dose studies suggest an acceptable safety margin, with sleep-wakefulness as the primary target affected and no maximum tolerated dose being identified, even at very high doses. Dose-dependent insomnia was the most prominent adverse event. No noteworthy cardiovascular effects were observed. |
| **Additional Information** | The compound shows good oral availability; has a dose proportional PK profile, which has not exhibited a food-effect; and is suitable for once-daily dosing. The compound is metabolized via several metabolic pathways. It may have mild PK interaction potential with some CYP-enzyme modulators.  
Studies suggest the compound is long acting, which supports once-daily dosing. Most likely a Biopharmaceuticals Classification System (BCS) Class I drug: high solubility, high permeability  
Human PET receptor occupancy suggests doses of 3 mg achieve ~90% receptor occupancy. Lower doses, particularly in augmentation, may be both tolerable and potent.  
Phase 2a and 2b studies in adult ADHD have been completed. The 4-week proof of concept (N = 156) evaluated doses of 10 and 30 mgs of JNJ-31001074 and placebo (PBO). The 6-week dose-finding study (N = 420) evaluated 3 doses of JNJ-31001074 (1 mg, 3 mg and 10 mg), PBO, and 2 active comparators. Overall, efficacy was not robust enough or with sufficient risk/benefit ratio to warrant further development for broad indication.  
Pharmacokinetic data are available in the pediatric (ADHD, ages 6–17 years) and adult and elderly (healthy volunteer) populations.  
No particular formulation or manufacturing challenges have been observed for the development of a solid oral formulation with this compound. |
| Suitable for and Exclusions | Studies of ADHD should be excluded.  
Suitable for studies in alcohol and other substance use disorders.  
Toxicology package supports chronic dosing. |
|-----------------------------|------------------------------------------------------------------------------------------------|
| Additional Characteristics: | CNS penetrant  
This drug is amenable to exploration/use in pediatric populations. Studies in pediatric populations for which there is no adult population will be considered. Studies for diseases/conditions that have a pediatric and adult population will also be considered if studies in a pediatric population are scientifically justified. |
| CNS Penetrance/Pediatric Diseases |                                                                                      |