A Phase I, First-In-Human, Healthy Volunteer Study to Investigate the Safety, Tolerability, and Pharmacokinetics of CVN424, a Novel GPR6 Inverse Agonist for Parkinson’s Disease *

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Online Supplement: Complete Eligibility Criteria

Screening for eligible subjects must be completed within 28 days prior to randomization or first dose.

Inclusion Criteria
Subject eligibility is determined according to the following criteria prior to entry into the study:

1. In the opinion of the Investigator, the subject is capable of understanding and complying with protocol requirements.

2. The subject signs and dates a written informed consent form (ICF) and any required privacy authorization prior to the initiation of any study procedures.

3. Subject is a healthy male or female adult who is 18 to 50 years of age inclusive at the time of ICF and study drug dosing.

4. Subject weighs at least 45 kg (99 lbs) and has a BMI between 18.0 and 30.0 kg/m\(^2\), inclusive at Screening.

5. A male subject who is nonsterilized and sexually active with a female partner of childbearing potential agrees to use adequate contraception from signing of the ICF throughout the duration of the study and for 12 weeks after last dose.

6. A female subject with no childbearing potential, defined as the subject has been surgically sterilized (hysterectomy, bilateral oophorectomy or tubal ligation) or who are postmenopausal (defined as continuous amenorrhea of at least 2 years and FSH>40 IU/L).

Exclusion Criteria
Any subject who meets any of the following criteria will not qualify for entry into the study:

1. Subject has received any investigational compound within 30 days prior to the first dose of study medication, or within 5 half lives, whichever is greater.

2. Subject is a study site employee or an immediate family member of a study site employee.

3. Subject has evidence of CS neurologic, cardiovascular, pulmonary, hepatic, hematopoietic disease, renal, metabolic, gastrointestinal, urologic, immunologic, endocrine disease, serious allergy, allergic skin rash, psychiatric disorder, or other abnormality that may impact the ability of the subject to participate or potentially confound the study results.

4. There is any finding in the subject’s medical history, physical examination, or safety laboratory tests giving reasonable suspicion of a disease that would contraindicate taking
CVN424, or a similar drug in the same class, or that might interfere with the conduct of the study

5. Subject has a known hypersensitivity to any component of the formulation of CVN424.

6. Subject has a positive urine result for drugs of abuse at Screening or Inpatient Check-in (Day -1).

7. Subject has a history of drug abuse (defined as any illicit drug use) or a history of alcohol abuse within 1 year prior to the Screening Visit or is unwilling to agree to abstain from alcohol and drugs throughout the study.

8. Subject has taken any excluded medication, supplements, or food products listed in the Excluded Medications and Dietary Products table as listed in the Supplementary Table “Excluded Medications and Dietary Products”.

9. If subject is female of childbearing potential (e.g., premenopausal, not sterilized).

10. If subject is male and intends to donate sperm during the course of this study or for 12 weeks thereafter.

11. Subject has previously had a seizure or convulsion (lifetime), including absence seizure and febrile convulsion.

12. Subject has current or recent (within 6 months) gastrointestinal disease that would be expected to influence the absorption of drugs (i.e., a history of malabsorption, any surgical intervention known to impact absorption [e.g., bariatric surgery or bowel resection], esophageal reflux, peptic ulcer disease, erosive esophagitis, or frequent [i.e., more than once per week] occurrence of heartburn).

13. Subject has a history of cancer or other malignancy, with the exception of basal cell carcinoma that has been in remission for at least 5 years prior to Day 1.

14. Subject has a positive test result for hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) antibody or a human immunodeficiency virus infection at Screening.

15. Subject has used nicotine-containing products (including but not limited to cigarettes, electronic cigarettes, pipes, cigars, chewing tobacco, nicotine patch or nicotine gum) within 28 days prior to Inpatient Check-in (Day -1) or a positive urine cotinine test at Screening or Inpatient Check-in (Day -1).

16. Subject has poor peripheral venous access.

17. Subject has donated or lost 450 mL or more of his or her blood volume (including plasmapheresis) or had a transfusion of any blood product, within 45 days prior to Day 1.

18. Subject has a Screening or Inpatient Check-in (Day -1) abnormal (CS) ECG. Entry of any subject with an abnormal (NCS) ECG must be approved and documented by signature by the Investigator or medically qualified sub-investigator.

19. Subject has a supine blood pressure outside the ranges of 90 to 140 mm Hg for systolic and 60 to 90 mm Hg (males) and 50 to 90 mm Hg (females) for diastolic, confirmed with repeat per PI discretion, at the Screening Visit or Inpatient Check-in (Day -1).

20. Subject has a resting heart rate outside the range 40 to 90 bpm, confirmed with repeat per PI discretion, at the Screening Visit or Inpatient Check-in (Day -1).
21. Subject has a QT interval with Fridericia’s correction method (QTcF) >430 ms (males) or >450 ms (females) or PR outside the range of 120 to 220 ms, confirmed with one repeat testing, at the Screening Visit or Inpatient Check-in (Day -1) Visit.

22. Subject has abnormal Screening or Inpatient Check-in (Day -1) laboratory values that suggest a CS underlying disease or subject with the following lab abnormalities: ALT and/or AST >1.5 the ULN, confirmed with one repeat testing.

23. Subject has a risk of suicide according to the investigator’s clinical judgment (e.g., per Columbia-Suicide Severity Rating Scale) or has made a suicide attempt in the previous 2 years.

**Excluded Medications and Dietary Products**
Use of the agents in the Supplementary Table “Prohibited Medications and Dietary Products” is prohibited from the time points specified until completion of all study activities.
### Prohibited Medications and Dietary Products

<table>
<thead>
<tr>
<th>28 days prior to Inpatient Check-in (Day -1)</th>
<th>7 days prior to Inpatient Check-in (Day -1)</th>
<th>72 hours prior to Inpatient Check-in (Day -1)</th>
</tr>
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<tbody>
<tr>
<td>Prescription medications (including oral contraceptives)</td>
<td>OTC medications, including antacids, proton-pump inhibitors, and H2 receptor antagonists (a)</td>
<td>Products containing caffeine or xanthine (e.g., tea or coffee)</td>
</tr>
<tr>
<td>Nicotine-containing products</td>
<td>Vitamin supplements</td>
<td>poppy seeds</td>
</tr>
<tr>
<td>Nutraceuticals (e.g., St. John’s wort, ginseng, kava kava, ginkgo biloba, Chinese herbs, and melatonin)</td>
<td>Alcohol-containing products</td>
<td></td>
</tr>
<tr>
<td>Immunization/Vaccines (b)</td>
<td>Known strong inhibitors/inducers of CYPs 3A4/5 (c)</td>
<td></td>
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</tbody>
</table>

CYP= cytochrome P-450, OTC=over the counter.

(a) Occasional use of acetaminophen (~1 g/day) or other medication as approved by sponsor’s Medical Monitor on a case-by-case basis is allowed except on Day 1.

(b) Inclusive of but not limited to H1N1 and flu vaccinations.

(c) e.g., chloramphenicol, clarithromycin, ketoconazole.