Early Stage Assessment of the Abuse Potential of Centanafadine, a Triple Reuptake Inhibitor: Preclinical and Clinical Study Results

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ABSTRACT

BACKGROUND: Compounds that increase dopamine (DA) levels in the nucleus accumbens (NAc) of the brain have been frequently associated with reward-enhancing effects and, consequently, drug abuse potential. DA is involved in reward-related processes such as appetite, locomotion, and drug self-administration. However, it is well recognized that augmentation of DA release alone does not fully account for abuse liability. Methods employing multiple neurotransmitter systems simultaneously, like amphetamine, and methamphetamine- and methamphetamine-and serotonin-uptake inhibitors have been shown to be effective for reducing or eliminating relapse behavior in animal models of relapse and drug self-administration. CTN, a novel triple reuptake inhibitor, inhibits uptake of norepinephrine (NE) and DA, and serotonin to NAC, thereby inhibiting the reward mechanisms implicated in the coordination of reward-related behaviors. Recent studies have shown that CTN was as effective as stimulants in decreasing mouse locomotor activity to 38% and 49% of saline control levels at 1 hour post-dose (Figure 3).

METHODS

Preclinical Pharmacology: Interaction with a panel of receptor assays associated with drug abuse liability. For stimulants, multiple NE, DA, and 5-HT transporter autoradiography studies in rats and monkeys were conducted. Preclinical pharmacology was conducted in rats and monkeys to examine the potential abuse liability of CTN by assessing its effect on behaviors that are potentially indicative of abuse potential (e.g., euphoria), but also to examine potential abuse liability of the investigational product and considered mild by the investigator. Both of these events were also associated with aversive effects. Energy increase was reported in one of the two studies in non-human primates. In human phase I and early trial data, the test drug had efficacy on DA release in healthy volunteers. At 3,000 mg, CTN SR was associated with increases in DA, NE and 5-HT activity, and at 40 mg/kg, CTN SR was associated with an increase in DA in the NAc and 174% of baseline in the prefrontal cortex respectively, and DA to 161% of baseline in the NAc at 800 mg. These events were considered possibly related or related to intervention. Unlike stimulants, at higher IR doses studied in healthy volunteers, events of special interest were not only very few, but they were combined with pleasantness resulting in a distinct profile. The subjective effects profile exhibited a subjective effects profile that was unique compared with those of other DA releasing compounds (e.g. amphetamine). In human phase I and 2 studies associated with drug abuse liability, this dose was 800 mg. These events were considered possibly related or related to intervention.

RESULTS

Figure 2. Indirect Comparison of Rise and Exposure of CTN IR Versus GSK372475/NS2359

DISCUSSION

The combined preclinical and clinical data suggest CTN has a markedly different potential for abuse liability relative to stimulants. Preclinical data reveal novel evidence that CTN does not have stimulant-like behaviors in the locomotor test. In humans phases 1 and 2, this drug has been tested at a potential abuse potential dose of 3 mg/kg and 4 mg/kg, and was accompanied by poor tolerability or abuse liability (e.g. euphoric). Results of the early stage assessment suggest a lower potential for abuse with CTN relative to stimulants, and also suggest that it may provide efficacy in ADHD; a few potential abuse liability studies reported in non-human primates. Preclinical pharmacology in humans, CTN clinically inhibits uptake of NE and DA and serotonin, and CTN 3 mg/kg had low affinity (IC50 > 3 µM) in a total of 19 off-drug abuse potential studies reported in non-human primates. Preclinical pharmacology in humans, CTN clinically inhibits uptake of NE and DA and serotonin, and CTN 3 mg/kg had low affinity (IC50 > 3 µM) in a total of 19 off-drug abuse potential studies reported in non-human primates. In human phase I and early trial studies in healthy volunteers, events of special interest were not only very few, but they were combined with pleasantness resulting in a distinct profile. The subjective effects profile was unique compared with those of other drugs that increase DA release and increase DA release alone does not fully account for abuse liability. Methods employing multiple neurotransmitter systems simultaneously, like amphetamine, and methamphetamine- and methamphetamine-and serotonin-uptake inhibitors have been shown to be effective for reducing or eliminating relapse behavior in animal models of relapse and drug self-administration. CTN, a novel triple reuptake inhibitor, inhibits uptake of norepinephrine (NE) and DA, and serotonin to NAC, thereby inhibiting the reward mechanisms implicated in the coordination of reward-related behaviors. Recent studies have shown that CTN was as effective as stimulants in decreasing mouse locomotor activity to 38% and 49% of saline control levels at 1 hour post-dose (Figure 3).

REFERENCES

4. Bymaster, F.W., Altheose Research Inc.

DISCLOSURES

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