Human abuse potential study design and interpretation for CNS active drugs

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Conflict of interest statement

Employee of Grünenthal USA
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General overview

- Abuse potential assessment of a new chemical entity (NCE) is based on comprehensive analysis of chemistry, pharmacology, clinical data, and the public health risk associated with the drug, human abuse liability studies play a key role in this assessment.

- Human Abuse Potential (HAP) studies are Phase I studies and consist of pharmacology assessments that provide unique information relevant to central nervous system-active drugs:
  - opioids,
  - stimulants,
  - depressants,
  - cannabinoids,
  - hallucinogens

- HAP study is an important component of product labeling and scheduling recommendations of new drugs
  - This paradigm has been implemented to evaluate abuse deterrent formulations
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
Vyvanse contains lisdexamfetamine, a prodrug of amphetamine, a Schedule II controlled substance.
9.2 Abuse
A randomized, double-blind, placebo-control, cross-over, abuse liability study in 38 patients with a history of drug abuse was conducted with single-doses of 50, 100, or 150 mg of Vyvanse, 40 mg of immediate-release d-amphetamine sulphate (a controlled II substance), and 200 mg of diethylpropion hydrochloride (a controlled IV substance). Vyvanse 100 mg produced significantly less “Drug Liking Effects” as measured by the Drug Rating Questionnaire-Subject score, compared to d-amphetamine 40 mg; and 150 mg of Vyvanse demonstrated similar “Drug-Liking Effects” compared to 40 mg of d-amphetamine and 200 mg of diethylpropion.

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
APTIOM is not a controlled substance.
9.2 Abuse
In a human abuse study in recreational sedative abusers APTIOM showed no evidence of abuse. In Phase 1, 1.5% of the healthy volunteers taking APTIOM reported euphoria compared to 0.4% taking placebo.

9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
POTIGA is a Schedule V controlled substance.
9.2 Abuse
A human abuse potential study was conducted in recreational sedative-hypnotic abusers (n = 36) in which single oral doses of ezogabine (300 mg [n = 33], 600 mg [n = 34], 900 mg [n = 6]), the sedative-hypnotic alprazolam (1.5 mg and 3.0 mg), and placebo were administered. Euphoria-type subjective responses to the 300-mg and 600-mg doses of ezogabine were statistically different from placebo but statistically indistinguishable from those produced by either dose of alprazolam. Adverse events reported following administration of single oral doses of 300 mg, 600 mg, and 900 mg ezogabine given without titration included euphoric mood (18%, 21%, and 33%, respectively; 8% from placebo), hallucination (0%, 0%, and 17%, respectively; 0% from placebo) and somnolence (18%, 15%, and 67%, respectively; 15% from placebo).
Overview

Study objectives

Population selection

Study design
  Population size
  Selection of test drug doses
  Selection of positive comparator
  Selection of negative comparators
  Selection of measures

Analysis and interpretation of measures
Introduction

- Regulatory recommendations on HAP:

- Sponsors are encouraged to proactively interact with FDA in planning and conducting such studies, often by the end of PhII and to submit protocols to FDA for review and advice on design, as well as safety issues, before beginning the study.
Overview

• Study Objectives
  • To provide information on the relative abuse potential of a new drug in humans
  • To contribute to predicting the likelihood of abuse when the drug becomes available.

• In practical terms the goal of HAP studies is to
  1) Rule out potential for abuse (unscheduled vs. scheduled – placebo vs. Test drug)
  2) Aid in scheduling placement (relative abuse potential – Test vs. Control)
Abuse Potential Assessment Decision Tree

1. Chemistry?
2. Binding?
3. Receptor Function?
4. AEs in animals?
5. PK in animals?
6. CNS-active?
7. Effects in animals?
8. Reward effects in animals?
9. Physical dependence in animals?
10. Study plans?
11. Abuse AEs in healthy humans?
12. Abuse AEs in patients?
13. Physical dependence in humans?
14. Human abuse potential study?
15. Reward effects in humans?
16. Abuse AEs in larger patient population?
17. Submission complete?
18. NDA info shows abuse?
19. Reports of actual abuse outside U.S.?
20. Label appropriate?

Presentation by Sun at 2013 ISCTM dinner workshop;
Adapted from Bonson & Sun, Draft Decision Tree on Assessment of Abuse Potential,
poster presented at the Science of Abuse Liability Meeting, Nov 2011, Washington, DC
Population selection

- Healthy volunteers with recent or current history of using a drug in the pharmaceutical class of the test drug for non-medical purposes.
- The subjects in the study should have experience with drugs with similar psychoactive properties, regardless of the pharmacologic mechanism of action.

- Example of inclusion criteria:
  - History of recreational XXX use (defined as non-therapeutic use at least 10 times in the subject’s lifetime and at least once in the last 12 weeks).
  - The subjects should be able to reliably differentiate between placebo and the active control on subjective measures.
Study Design

- Phase 1, randomized, double-blind, double-dummy, placebo- and active-controlled, crossover, single dose study.

**Eligibility assessment**

**Screening**
- 1 visit
  - Positive control
  - Placebo

**Pre-Qualification**

**Treatment**
- 6-8 visits
  - 2-3 strengths NCE
  - 2-3 strengths positive control
  - Placebo

**Follow-up**
Study Design

• Within-subjects, repeated Williams square design is recommended.

• The washout period of a crossover designed study should be at least five times the maximum t1/2 of the longest acting drug in the study.

• Sample size:
  • In past studies between 12 and 25 subjects has been used although in recent studies approximately 40 subjects have been used.
Dose Selection

• Typically 2-3 doses of the test drug are selected
  • Range from minimally effective to supra-therapeutic dose, if safety is known and precautions are taken to deal with safety concerns.
  • A dose run-up pilot study in a drug abuser population can provide an empirical basis for dose selection.
  • Challenge: selection of supra-therapeutic dose
Selection of Positive Control

• The positive control should have measurable abuse potential previously established through experimental studies and epidemiological data.

• The positive control should be a drug of abuse in the same pharmacological class as the test drug, preferably with the same indication as the test drug.

• Preferably the positive control would mimic time-course profile of the test drug.

• Typically 2-3 doses of the positive control are selected.

• Within a given study, a positive control should have its anticipated effects on the parameters of abuse potential that are being studied. Failure to demonstrate the expected effects would invalidate the study.
Examples of positive controls per drug class

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Positive control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid</td>
<td>Hydromorphone, Morphine, Oxycodone</td>
</tr>
<tr>
<td>Stimulants</td>
<td>D-amphetamine, Mixed amphetamine salts, Phentermine, Methylphenidate</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>Dronabinol</td>
</tr>
<tr>
<td>Perceptual disturbances / Hallucinogens</td>
<td>Ketamine, Zolpidem</td>
</tr>
<tr>
<td>Depressants</td>
<td>Diazepam, Alprazolam, Zolpidem, Lorazepam, Triazolam</td>
</tr>
</tbody>
</table>
Selection of negative control

- Placebo is considered as a negative control
- Additional negative controls might provide important information for scheduling although it is typically not recommended by the Agency
Data collection

- Subjective Effects
  - visual analog scales (VAS) or rating scales
- Pharmacological effects
- Behavioral and cognitive performance assessment
- Safety
- Pharmacokinetics
Outcome measures

• The primary method for evaluating the subjective effects of drugs is through the use of standardized questionnaires.

• To accommodate abuse liability assessment of new test drugs with novel and diverse mechanism of action and new formulations multifarious scales have been developed and applied

  • Ratings of liking (“at the moment” and “overall”) and other subject-rated effects
  • Disposition to take the drug again,
  • Drug identification;
  • Subject-rated strength of drug effect
  • Price value assessment
  • Addiction Research Center Inventory (ARCI)
  • Measurement of relevant physiological effects
  • Behavioral and cognitive performance assessment
  • Assessment of mood state changes using Profile of Mood States (POMS)
Outcome Measurements

- Up to 3 primary measures are recommended
  - VAS Drug liking “at this moment” (bipolar)
    
    At this moment my liking for this drug is:

    0
    Strong disliking

    50  neutral

    100
    Strong liking

- VAS Take Drug Again
- Drug identification

- Timing of the assessments
  - “At the moment” vs. “at the end of the day” measures
## Interpretation of subjective effects measures

<table>
<thead>
<tr>
<th>Scale interpretation</th>
<th>Scale description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Balance</td>
<td>VAS Drug Liking, VAS Overall Drug Liking</td>
</tr>
<tr>
<td>Positive</td>
<td>VAS High, VAS Good Effects, VAS Take Drug Again ARCI MBG</td>
</tr>
<tr>
<td>Negative</td>
<td>VAS Bad effects, VAS Sick</td>
</tr>
<tr>
<td>Unknown</td>
<td>VAS Any effects</td>
</tr>
<tr>
<td>Dissociative effects</td>
<td>VAS Floating, VAS Detached</td>
</tr>
<tr>
<td>Simulant / sedative effects</td>
<td>VAS Alertness/Drowsiness ARCI Benzedrine Group (BG) ARCI Pentobarbital-Chlorpromazine-Alcohol Group (PCAG)</td>
</tr>
<tr>
<td>Other</td>
<td>Drug Similarity</td>
</tr>
<tr>
<td>Psychomotor effects</td>
<td>Divided Attention Test,</td>
</tr>
</tbody>
</table>
Parameters of interest

- Subjective effects are assessed in terms of *onset, peak, duration of activity and offset of the effect*
  - Peak effect (Emax and/or Emin)
  - Time to the peak effect (tEmax)
  - Partial area under the curve (AUE)
    - Early drug effect – (AUE 0-1h)
    - Duration of the effect – (AUE 0-8h)
Interpretation of subjective effects measures - review of time course profile

- VAS Drug Liking (at the moment)

Partial AUE (0-1)
Partial AUE (0-8)

Strong Liking
Neutral
Strong Disliking

Time to $Emax$ ($T_{max}$)

Time post drug administration (h)

Placebo
Positive control
Statistical Analysis

• Repeated measure analysis of variance (ANOVA)
• Non-parametric analysis if assumption of data normality is not met
Analysis of subjective effects measures

- Study is validated by showing a significant difference in response between positive control treatment and placebo.
- The abuse potential of the test drug is assessed by comparing responses of the test drug with those of placebo and with those of the positive control.
Safety assessments

- Adverse events, particularly abuse potential related AEs, collected throughout the trial provide important information about abuse potential of the test drug in comparison to the positive control and placebo.
Conclusions

✓ Human abuse potential (HAP) studies play a key role in abuse potential assessments of new test drugs
  • an important component of product labeling and scheduling recommendations

✓ HAP studies are recommended late in product development to assure comprehensive drug characterization is available as it forms basis for HAP study design

✓ Sponsors are encouraged to proactively interact with FDA in planning and conducting such studies, often by the end of Phase II and to submit protocols to FDA for review and advice on design, as well as safety issues, before beginning the study.
Thank you