Human Abuse Liability (HAL) Studies: Not Your Traditional Phase I Study

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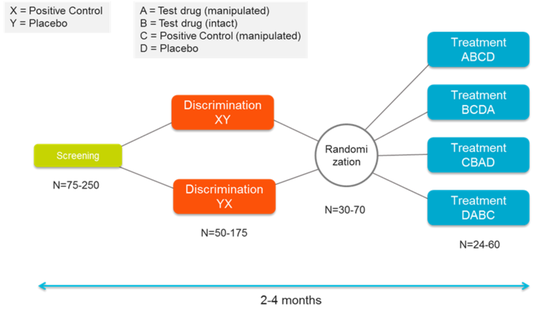
INTRODUCTION

Abuse potential refers to the likelihood for a drug to be used in nonmedical situations for its positive psychoactive effects, eg, euphoria, hallucinations, mood changes, etc. Human abuse liability (HAL) studies are required for drugs that affect the central nervous system, drugs similar to known drugs with abuse potential, and drugs with positive psychoactive effects. This poster discusses what a HAL study is, what challenges the study team faces, with a focus on challenges to medical writers.

HAL STUDY DESIGN

- Design: double-blind, active and placebo control, crossover design
- Subject population: generally healthy, nondependent, recreational drug users
- Test drug: Can be a new molecular entity (NME) or abuse-deterrent formulation (ADF)

Generic HAL study schematic diagram



ABUSE POTENTIAL OUTCOME MEASUREMENTS

Pharmacodynamics (Primary)

- Drug liking (most common primary measure)
- Take drug again assessment
- Ability to identify similarity of effects to other psychoactive drugs
- Subject-rated strength of drug effect
- Behavioral and cognitive performance assessment

(subjective)

- Measurement of relevant physiological effects, eg, pupillometry (objective)

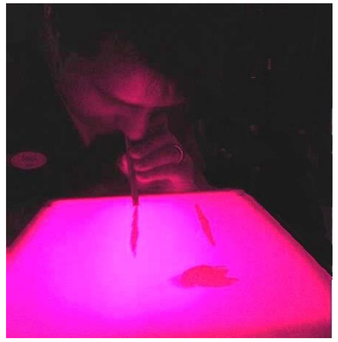
Pharmacokinetics

- T_{max}
- Early exposure
- Duration of exposure

Safety

- Adverse events associated with abuse potential e.g., mood –related AEs

MEASUREMENT OF SUBJECTIVE PD EFFECTS: VISUAL ANALOG SCALES



BIPOLAR VAS

At this moment, my liking for this drug is:

0	50	100
Strong disliking	neutral	strong liking

UNIPOLAR VAS

I am feeling high

0	100
Not at all	extremely

CHALLENGES OF HAL STUDIES

- HAL studies are more complex and require more time and resources than other Phase 1 studies, as well as specialized expertise.
- Specialized subjective assessment scales may require training of clinic staff and subjects, and feasibility of multiple assessments in the clinic can be challenging.
- A vast amount of data is generated , thus data management needs are extensive, and interpretation of data and reporting is more involving.
- Statistical challenges include unique analyses, further complicated by the lack of composite endpoints and the subjective endpoints.
- Interpreting numerical results of subjective scales to evaluate overall abuse potential is a challenge, ie, statistical significance vs clinical significance.
- Steep learning curve for team members new to HAL studies.
- In general, HAL studies are more challenging for NMEs than for ADFs, due to absence of comparable studies.

MEDICAL WRITING CHALLENGES

Protocol

- As HAL studies are likely to be new to most Sponsors, medical writer should be able to provide a robust rationale for study design.
- The complexity of study design increases risk of conflicting information within different sections of the protocol, eg, time points.
- Nature and time required for resources complicate schedules of assessment—ensuring feasibility in the clinic can be a challenge.

Clinical Study Report

- Numerous PD measures and PD parameters along with several treatments and multiple comparisons, e.g. between treatments and following different manipulation methods and routes of administration, etc, can result in an overwhelming amount of data
- High data volume may require creation of numerous in-text tables, increasing time commitment and quality control (QC) needs
- Discussion of abuse potential requires weighing of favorable and unfavorable drug effects, and results may not be consistent across PD measures.

In general, few resources exist to guide new medical writers of protocols and CSRs on HAL studies.

ADDRESSING MEDICAL WRITING CHALLENGES

- For Sponsors, engage teams and MWs with prior HAL study experience
- Engage subject matter experts to assist with protocol development, data interpretation and presentation to minimize volume of in-text data
- Protocol writers should interact closed with experienced clinic staff to ensure feasibility of assessments.
- During SAP development, have the key endpoints, comparisons, and measures of abuse potential for the particular study clearly outlined.
- Have pre-CSR discussions to determine the key results for presentation in the CSR vs to be presented in end-of text tables.
- Consider programming in-text tables and/or design end-of-text tables that can be easily pasted into the CSR to minimize QC issues.
- Build and maintain an up-to date library of previous HAL studies organized by study design for easy reference.
- A general understanding by the medical writer of HAL study design and assessments prior to protocol development and CSR writing is essential.

CONCLUSIONS

- HAL studies present additional challenges compared to traditional Phase 1 studies, primarily greater complexity and unique design and assessments.
- A general understanding by the medical writer of HAL study design and assessments is essential.
- For beginning medical writers, resources are limited and engaging with subject matter experts is essential.
- For established writers, increased efficiencies of the writing process can help with the additional challenges of writing for HAL studies.

REFERENCES

1. FDA Guidance for Industry: Assessment of Abuse Potential of Drugs (Draft)
2. FDA Guidance for Industry: Abuse-Deterrent Opioids-Evaluation and Labeling

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