Investigator's Brochures 2019

Exercises for Aaron Bernstein PhD, IB Presentation, Dec. 4, 2019— iJOBS & AMWA-NY

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I. Multiple Choice Questions

1. Which of the personnel or department representatives are involved in creating an IB?

a. Medical Writer
b. Clinical MD
c. Clinical Research Associate
d. Nonclinical Pharmacologist
e. DMPK Scientist
g. Toxicologist
h. Chemistry, Manufacturing and Controls (CMC)
i. Clinical Pharmacologist
j. Safety Scientist

2. What is the estimated number of weeks to complete the final version of an initial IB?

a. 2-6
b. 6-10
c. 8-12
d. 5-9
e. 3-7

3. Name two roles of the Medical Writer in writing the IB.

a. Preparing the nonclinical portions of the IB
b. Preparing the Clinical Pharmacology section of the IB
c. Preparing the first and subsequent drafts of the IB
d. Preparing the DMPK Section
e. Managing review and approval process

4. Which are true statements about the guidelines for preparing a Changes Page of an IB?

a. Inclusion of data cut-off date in the "List of Serious Adverse Events Considered to be Expected for Regulatory Reporting Purposes"
b. Maximum length is 2 pages
c. Consideration of including cut-off dates for analyses and key safety information (eg, death, serious adverse events) for late-stage IB revisions
d. Placement of Changes Page is after title page in all versions of IB
e. A detailed description is provided of all changes vs previous IB

5. What is an acceptable time delay in updating the IB, assuming few or nonextraordinary adverse event reports (SAEs, critical toxicology data, etc.?)

a. 6 months
b. 1 year
c. 18 months
d. 2 years
d. 3 years

6. **Which of the following types of nonclinical studies/data should be included in the IB in their respective sections of the IB Guidelines**?

   a. **Section 4.1: All nonclinical studies**
   b. **Section 4.1: Comparative data from other compounds still in development**
   c. **Section 4.1: Nonclinical pharmacokinetics**
   d. **Section 4.2: Studies/data not relevant to study of investigational drugs in humans, eg, those establishing methodology**
   e. **Section 4.3: Toxicology and Safety Pharmacology**

II. True or False Questions

1. **The main intended readers are the trial subjects__**
2. **An IB is not required for a planned clinical trial of a marketed product for an indication not yet approved by labeling __**
3. **The purpose of including nonclinical information in an IB for a clinical (human subjects) trial is to alert investigators about possible relevant safety concerns, pharmacokinetics, and expected therapeutic benefit in human subjects __**
4. **The balance of nonclinical and clinical trial information remains constant through the various revisions of an IB __**

(continued on next page)

5. **In the IB, it is common practice to include the exact composition of the physicochemical formulation use, including list of excipients__**
6. **A high-level outline of the Clinical Development Plan should be provided in Section 2, Introduction__**
7. **A review by each area of study (eg, toxicology, PK, pharmacology) of an updated revision of versions 3 and onward of an IB should continue to be reviewed by the appropriate functional area__**

III. What to Look for in Source Material

A. A Preclinical Study Abstract

Instructions:

Abstract A: Carefully read the questions you should keep in mind while reading the abstract. Answer them after you have read the abstract.

The objective of these questions is to figure out which pieces of information will be useful, helpful, or crucial to the investigator who will run a trial with human subjects.

As a medical writer, you will be putting together in the IB the kind of information that would appear in a prescribing information brochure to guide the healthcare professional and patient. The IB serves that function for an investigational drug. The information you select may also help guide the content of the study protocol.

1. What is an important finding in the abstract that should appear in the IB to guide the investigators? (For example, was high blood pressure a problem? If "yes," the clinical study might include frequent BP readings)

   _____
   _____
   _____

2. **Looking at the other statements in the abstract, which body system or systems would the IB be likely to be recommend that the investigator pay special attention?**

   _____
   _____
   ___

Which additional or unusual tests might be written into the IB and protocol to detect similar toxicity or toxicities in a human subject that was or were found in an animal model?

a) **In IB, suggest performing PK studies to obtain half-life in human subjects**

b) **Suggest including multiple urine analyses**

c) **Cite detection of methemoglobinemia, and obtain information from arterial blood gas and CO-oximetry panel. Note: Arterial blood with elevated methemoglobin levels**

d) **Blood has a characteristic chocolate-brown color as compared to normal bright red oxygen-containing arterial blood**
("eMedicine – Methemoglobinemia" retrieved 2008-09-13. Cited by Wikipedia., Nov. 17, 2019.)

_____
_____
____

4. From reading this abstract, which tests would probably not be recommended to be given to study subjects?

_____
_____
__

Disposition and metabolism of the Sulfonylurea Oncolytic Agent LY295501 in Mouse, Rat, and Monkey. William J. Ehlhardt, Joseph M. Woodland, John E. Toth, et al. Drug Metabolism and Disposition. June 1997, 25 (6) 701-708.

The disposition and metabolism of LY295501 was studied in mice, rats, and monkeys. This novel diaryl sulfonylurea oncolytic agent is structurally related to sulofenur and shows excellent activity in a broad range of mouse antitumor models. The compound is well absorbed, giving plasma concentrations greater than 200 µg/ml after oral doses of 30–100 mg/kg, where it appears to be completely bound (>99.9%) to plasma proteins. The high degree of protein binding may be a factor in its relatively long half-life, which ranges from about 8 hr in rats and 15 hr in mice to 50 hr in monkeys. While more material was excreted in feces than in urine from mice and rats given single oral doses of [14C]LY295501, urine was the major route of elimination in monkeys. Three major metabolites—all formed *via* oxidation of the saturated part of the benzodihydrofuran moiety—were characterized in the urine of mice, rats, and monkeys. It is interesting that two of these metabolites are derived from opening of this saturated ring, an unusual metabolic process which represents a significant part of the metabolism of LY295501. As with sulofenur, metabolites of 3,4-dichloroaniline formed after metabolic cleavage of the sulfonylurea linkage were also found in urine. Unlike sulofenur, these do not seem to have major toxicological significance, but their formation does explain the minor methemoglobinemia observed in toxicology studies of LY295501. Even though only trace amounts of LY295501 were found in urine, LY295501 is the predominant drug-related material in plasma, along with small amounts of other, relatively nonpolar, metabolites.

B. Abstract of a Preclinical Overview

Instructions:

Abstract B: Carefully read the questions you should keep in mind while reading the abstract. Answer them after you have read the abstract.

1. **After carefully reviewing the abstract of this preclinical overview article, which information is most relevant to investigators conducting clinical (human) studies. That information should appear in the IB you are writing for an early Phase 2 protocol.**

   _____

   _____

2. **From reading the abstract, what kind of endpoints would be appropriate for evaluating this drug in clinical trials?**

   _____

   _____

Preclinical overview of nabumetone: Pharmacology, bioavailability, metabolism, and toxicology. FR.Mangan Ph D; JD Flack PhD; D Jackson MD, FRCP (Edin.). The American Journal of Medicine, Volume 83, Issue 4, Supplement 2, 30 October 1987, Pages 6-10.
https://doi.org/10.1016/0002-9343(87)90585-7

Nabumetone is a novel nonacidic nonsteroidal anti-inflammatory drug (NSAID) developed by Beecham Pharmaceuticals. After absorption, nabumetone undergoes extensive metabolism, the main circulating material being 6-methoxy-2-naphthylacetic acid, (BRL 10720). This, unlike nabumetone, is a potent inhibitor of prostaglandin synthesis and is considered to be the active anti-inflammatory metabolite. Nabumetone is active in all standard laboratory models of inflammation and has a greater ratio of active to gastric irritant doses (therapeutic ratio) in the rat than any other NSAID tested. The lack of effect on the gastric mucosa in all species has been a notable feature of the toxicology studies. In humans, relative bioavailability is similar after administration of different dose levels, the mean terminal plasma half-life of BRL 10720 being about 24 hours, allowing for once-daily dosing. The half-life of BRL 10720 does not change on repeated dosing, and no unexpected or irreversible accumulation occurs in elderly patients.

Lessons Learned:

Please write down 1 or 2 learnings from these two presentations that you value highly and exchange with another person.

Thank you for your attention. We hope you've enjoyed our presentation and have learned something useful.

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