Investigator's Brochures (IBs)

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Investigator's Brochures (IBs)

- What and Why of an Investigator's Brochure
- Section by Section Review
- Roles and Responsibilities, Timelines
- Updating the Investigator's Brochure

What is an Investigator's Brochure?

An Investigator's Brochure is a compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects.

Source: *ICH E6 Guideline for Good Clinical Practice, Section 7, Investigator's Brochure*

Purpose of an Investigator's Brochure?

"…to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of a clinical study protocol, such as:

- The dose, dose frequency, dosing interval
- Methods of administration
- Safety monitoring procedures
- Measures to treat anticipated possible adverse events

Source: *ICH E6 Guideline for Good Clinical Practice, Section 7, Investigator's Brochure*

General Considerations

- First version of an IB: mostly non-clinical data. Subsequent IB versions, non-clinical data should be made more succinct as clinical data become available.
- The exact content and format of an IB will depend on many factors (e.g. stage of clinical development and number of indications to be covered).
- For marketed products with planned clinical trials *outside approved labeling* an updated IB is required.
- A new IB needs to be prepared if the new indication is very different to the existing indication.

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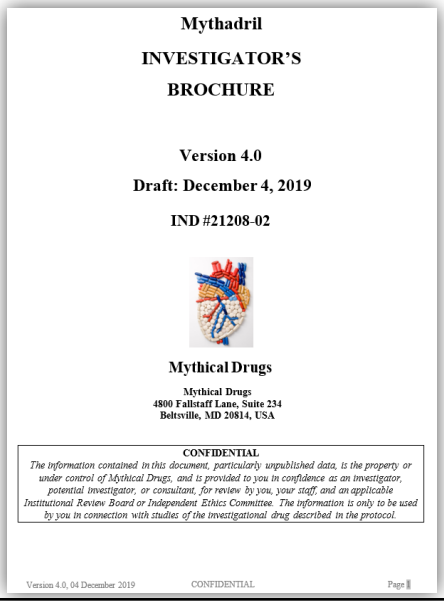
Title Page



Mythadril

INVESTIGATOR'S

BROCHURE

Version 4.0

Draft: December 4, 2019

IND #21208-02

Mythical Drugs

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Version 4.0, 04 December 2019 CONFIDENTIAL Page

Table of Contents

TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE *(Example)*

- Confidentiality Statement (optional)
- Signature Page (optional)

1. Table of Contents
2. Summary
3. Introduction
4. Physical, Chemical, and Pharmaceutical Properties and Formulation
5. Nonclinical Studies

5.1 Nonclinical Pharmacology

5.2 Pharmacokinetics and Product Metabolism in Animals

5.3 Toxicology

6. Effects in Humans.

6.1 Pharmacokinetics and Product Metabolism in Humans

6.2 Safety and Efficacy

6.3 Marketing Experience

7. Summary of Data and Guidance for the Investigator

NB: References on 1. Publications
2. Reports

These references should be found at the end of each chapter.

Appendices (if any)

Section 1. Overall Summary

1.	**Overall Summary**
1.1	**Medical Need and Scientific Rationale**
1.2.	**Physicochemical Properties and Clinical Formulation**
1.3	**Nonclinical Studies**
1.3.1	Nonclinical Pharmacology
1.3.2	Nonclinical Pharmacokinetics and Metabolism
1.3.3	Toxicology and Safety Pharmacology
1.4	**Effects in Humans**
1.4.1	Clinical Pharmacokinetics
1.4.2	Pharmacodynamics
1.4.3	Efficacy
1.4.4	Safety
1.5	**Guidance for the Investigator**

- Brief (1-2 pages)
- Subsections reflect the order of the main sections of the IB

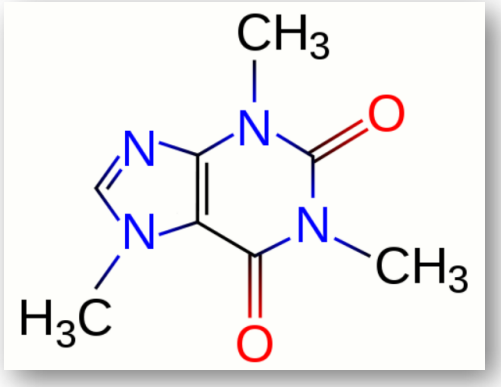
Section 2. Introduction

2.	**Introduction**
2.1	**Medical Need**
2.2	**Scientific Rationale**
2.3	**Clinical Development Plan**
2.4	**References**

- Brief (1-2 pages)
- Provides the following information:
  - Chemical name and generic name (tradename should be mentioned here if applicable; however, generic name should be used througout the other IB sections)
  - Anticipated indication along with background on the disease being treated
  - Unmet medical need addressed by this drug
  - Rationale for conducting research with this drug
  - High level outline of the clinical development plan

Section 3. Physicochemical Properties and Clinical Formulation

3.	**Physicochemical Properties and Clinical Formulation**
3.1	**Physicochemical Properties**
3.2	**Clinical Formulation**
3.3	**References**



Section 4. Nonclinical Studies

4.	**Nonclinical Studies**
4.1	**Nonclinical Pharmacology**
4.2	**Nonclinical Pharmacokinetics and Metabolism**
4.3	**Toxicology and Safety Pharmacology**
4.4	**References**

- For a first version of the IB (aim for 20 pages).
- Provide minimal descriptions of methodology in the text. Details can be provided in tables in appendices.
- Discuss results in an integrated manner, not study-by-study.
- Include interpretation and critical analysis of data.

Example Toxicology Summary

4.3 Nonclinical Toxicology

The nonclinical toxicity of the anti-cancer drug Mythadril was extensively profiled. Mythadril was studied in genotoxicity assays, reproductive toxicology studies as well as repeat-dose oral toxicity studies, in which mice, rats, and dogs were given Mythadril for up to a maximum of six months. Mythadril was found to be genotoxic in three in vitro assays and in one in vivo micronucleus assay. Mythadril was studied at exposures of 400 mg/kg/day which greatly exceeds the proposed clinical exposure. At all doses studied, Mythadril did not affect fertility and did not cause malformations. Effects noted in rats (delayed skeletal ossification) and rabbits (fetal mortality) occurred only at maternally toxic doses. The repeat dose no-adverse-effect-level of Mythadril determined for each species investigated far exceeds the proposed clinical Mythadril exposure and duration of treatment.

Section *5. Effects in Humans*

Section 5. Effects in Humans (Con't)

- The organization and extent of information depends on the stage of development of the product.
- A tabulated list(s) of all clinical pharmacology and/or clinical therapeutic studies in the clinical development program should be provided.
- For first IBs, retain Section 5 heading and state that no clinical studies have yet been conducted.
- The information should be provided in an integrated manner (not study by study).

Section 5. Effects in Humans (Con't)

Study	Study Phase – Population	Number Treated	
		Mythadril	Placebo
Healthy Subjects			
HTD34526	Phase 1 - Tolerability, PK of single ascending oral doses	N = 6 (300 mg/day) N = 6 (500 mg/day) N = 6 (680 mg/day)	N=14
FTG12258	Phase 1 - Food effect (PK), tolerability, safety	N = 9 (100 mg/day) N = 8 (500 mg/day)	NA
TEX12257	Phase 1 - Excretion balance, PK, metabolism, tolerability	N = 6 (200 mg)	NA
TRT12893	Phase 1 - Ketoconazole drug interaction, PK, safety	N = 7 (50 mg) N = 7 (300 mg)	NA
Metastatic Colorectal Cancer			
UGI35879	Phase 3 – Stage 4 mCRC in US Patients	N = 131 (400 mg/day) N = 133 (500 mg/day)	N = 95
AGM 55578	Phase 3 – Stage 3/4 mCRC in Japanese Patients	N = 10 (400 mg/day) N = 11 (500 mg/day)	N = 95
Breast Cancer			
ARD12181	Phase 2 - Intermediate, ruxolitinib pre-treated	N = 97 (400 mg/day)	NA
TES13519	Phase 1 - Effect of 14-day repeated oral doses of Mythadril on ventricular repolarization, compared to placebo in adult patients with advanced solid	N = 59 (500 mg/day)	N = 60
Special Populations			
YUP13449	Phase 1 - Renal Impairment in Volunteers	N = 36 (300mg)	NA
WFD13450	Phase 1 - Hepatic Impairment in Volunteers	N = 17 (300mg)	NA
SFT12893	Phase 1 - Ketoconazole drug interaction, PK, safety	N = 7 (300 mg)	NA

Example Summary of Efficacy in Humans

5.3 Efficacy Results

A total of 1987 adults with clinically documented nasopharyngitis suspected or proven to be due to Gram-positive pathogens were randomized into two identically designed, randomized, double-blind, multicenter, multinational, non-inferiority trials (GET I and GET II) comparing a single 1200 mg intravenous dose of Mythical Drug to intravenous vancomycin (1 g or 15 mg/kg every 12 hours) for 7 to 10 days.

The primary endpoint in both trials was early clinical response (responder), defined as cessation of cough and absence of fever 48 to 72 hours after initiation of therapy. Table 5 provides the efficacy results for the primary endpoint in GET I and GET II in the primary analysis population.

Table 5. Clinical Response Rates in Nasopharyngitis Trials

	Mythical Drug n /N (%)	Vancomycin n /N (%)	Difference (95% CI)
GET I	413/475 (86.9)	297/479 (72.9)	14.1 (-0.5, 8.6)
GET II	432/503 (85.9)	228/502 (65.3)	20.6 (-3.7, 5.0)

Example Summary of Safety in Humans

Table 6. Identified Serious Adverse in Trials with Mythical Drug

Report Serious Adverse Event	Mitigation Strategy
Pancreatitis	Specific eligibility and withdrawal criteria in study protocols. Risk communication via informed consent form for subjects.
Gastrointestinal events Vomiting Diarrhea	Specific GI eligibility criteria Risk communication via informed consent form for subjects Stopping of study medication in the event of GI intolerability
Pneumonia	Risk communication via informed consent form for subjects Stopping of study medication in the event of GI intolerability
Appendicitis	Risk communication via informed consent form for subjects Stopping of study medication in the event of GI intolerability
Atrial fibrillation/atrial flutter,	Risk communication via informed consent form for subject Regular ECGs
Anaphylactic shock	Risk communication via informed consent form for subject Immediate treatment with subcutaneous epinephrine

Section 6. Guidance for the Investigator

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Roles and Responsibilities

Coordinating Author: Medical Writer
- Plans and maps-out the process
- Prepares first and subsequent drafts of the IB
- Manages review and approval process

Contributing Authors: Preparing contributions according to direction of company guidance and Coordinating Author
- Clinical Physician (Medically Qualified)
- Clinical Research Associate
- Nonclinical Pharmacologist
- Nonclinical Pharmacokineticist
- Toxicologist
- Chemist
- Clinical Pharmacologist
- Safety Scientist

Approximate Timelines

	Elapsed Time from Receipt of Last Contribution
First draft of IB (incorporating informal author review)	2 weeks
Team review (5 working days)	3 weeks
Second draft (team comments incorporated)	5 weeks
Formal functional review (5 working days)	6 weeks
Final Word version of IB (comments from functional review incorporated)	8 weeks
E-mail approval and publishing in pdf format (final IB ready to use)	9 weeks

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Updating the IB

Update the IB at Least Once a Year

- The ICH E6 guideline on GCP specifies: "The IB should be reviewed at least annually and revised, as necessary."

However…

- EU Commission Directive 2005/28/EC, Section 4, Article 8 (3) states:
  - "The investigator's brochure shall be **validated and updated by the sponsor at least once a year**"
- This Directive is law in each of the EU member states, making the annual IB update a legal requirement.

Summary of Changes

Edition 11 Changes

Section	Summary of Changes
Section 4.1.1. Antimicrobial Spectrum of Activity	Updated with surveillance data from 2015.
Section 4.1.2. Mechanisms of Action	Updated with additional data on mechanism of action and activity against non-dividing bacteria.
Section 4.1.4. In Vitro Pharmacodynamics	Updated with antibiotic combination data.
Section 4.1.6. Animal Models of Infection	Updated with data from additional studies.
Section 4.2. Pharmacokinetics and Drug Metabolism in Animals	Section abbreviated given the availability of human data.
Section 5.2.3. Pharmacokinetics in Special Populations	Updated with transporter study results.
Section 5.2.4. Drug-Drug Interaction Studies	Added results of newly completed study (Study XXXXX) to assess the drug-drug interaction potential of a single 1200 mg dose of MYTHICAL DRUG on the pharmacokinetics of S-warfarin following a single dose was conducted in 36 healthy subjects.
Section 5.2.5. Laboratory Coagulation Test Interference	Added results of newly completed Phase I study (Study XXXXX) investigating the effects of a single 1200 mg IV dose of Mythical Drug on the results of multiple coagulation tests in healthy volunteers.
Section 5.2.8. Mythical Drug New Formulation	Added results of newly completed Phase I study (Study XXXXX) evaluating the pharmacokinetics and safety of a new formulation of of MYTHICAL DRUG in healthy adult subjects.
Section 5.4.1. Safety from Pooled Phase 3 ABSSSI Clinical Trials with Single-dose Mythical Drug	Presentation of safety data abbreviated. Reference made to safety information provided in Section 6. Summary of Data and Guidance for the Investigators.
Section 5.4.2. Safety from Completed and Ongoing Postapproval Studies	Added safety data from recently completed and ongoing postapproval studies. Updated safety data from the ongoing pediatric study,

Questions?

Thank you for your participation!

Follow-up Questions?

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