Advanced Drug Delivery Reviews 63 (2011) 511–517

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Comparative requirements for exploratory clinical trials — eIND, eCTA and microdosing☆

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ARTICLE INFO

Article history:
Received 29 January 2010
Accepted 18 October 2010
Available online 26 October 2010

Keywords:
Safety assessment
Exploratory
Clinical trial
Microdosing
eIND
eCTA
Toxicology
Toxicity study
First-in-human
Translational medicine

ABSTRACT

Exploratory clinical trials provide a strategy for rapid human entry of investigational drugs. Such clinical studies are typically conducted during early clinical development in phase I as first-in-human studies, have no therapeutic intent, are not intended to examine clinical tolerability and involve a small number of human subjects at limited dose/exposure. Early decision data derived from such clinical studies may include PK, PD and/or biomarker-based translational medicine endpoints as well as PK/PD modeling approaches. This review critically discusses the various exploratory clinical trial strategies, their advantages and disadvantages as well as the regulatory safety requirements. In this respect, strategies for exploratory Investigational New Drugs (eIND), exploratory Clinical Trial Applications (eCTA) and microdosing are highlighted and compared in view of the new ICH M3(R2) guideline including options for biotechnology-derived pharmaceuticals such as monoclonal antibodies.

Contents

1. Introduction

Exploratory clinical trials are typically conducted during early clinical development in phase I as first-in-human (FIH) studies, have no therapeutic intent, are not intended to examine clinical tolerability (i.e. maximum tolerated dose, MTD), are based on limited preclinical safety data and involve a small number of human subjects at limited systemic dose/exposure, primarily by oral or *i.v.* route of administration. Despite these restrictions, early access to human data can be advantageous for certain drug candidates to provide insight into human physiology/pharmacology, knowledge of drug candidate characteristics and therapeutic target relevance to disease. Exploratory clinical trials can be used to investigate a variety of parameters such as PK, PD and/or other biomarkers, which include PET receptor binding and displacement, as well as other imaging or diagnostic modalities. The subjects included in these studies can be patients from

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "New Strategy for Drug Development with Exploratory IND Studies: Scientific Basis and Future Directions".

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doi:10.1016/j.addr.2010.10.010

selected populations or healthy volunteers (HV). The dosing duration of exploratory clinical trials is generally limited to 2 weeks, however, may also consist of one single dose only.

Traditionally, upon identification of a promising preclinical drug candidate a scaled-up synthetic process for a pilot plant cGMP synthesis of up to 10 kg of the drug substance (DS) is developed. The subsequent time frame required for the various preclinical development activities supporting FIH dosing, including regulatory toxicology studies often consuming the largest fraction of DS, is very compound and company dependent but typically would be around 1.5–2 years [1]. It is therefore a need for a more efficient, less resource/DS intense and more rapid way to test drug candidates in humans earlier and to decide on further clinical development of drugs based on early exploratory data in humans rather than solely based on animal data. By testing and comparing (multiple) drug candidates for selection in humans, improved drugs would enter more traditional, full development sooner with less overall expenditure of limited financial and animal resources. Such early decision data may include PK, PD and/or biomarker-based translational medicine endpoints as well as PK/PD modeling approaches. The review of Sistare and DeGeorge provides an overview on these endpoints including their utility (Table 1 in [2]).

The generally accepted traditional paradigm of safety assessment and dose selection for FIH clinical trials involves repeated dose toxicity studies in rodents and non-rodents with either rodent and/or non-rodent being considered as the pharmacologically relevant (i.e. pharmacologically responsive) species. These toxicity studies are generally expected to identify both (high) dose levels leading to toxicity (including identification of target organs) and (low) dose levels leading to no toxicity (No-Observed Adverse Effect Level, NOAEL) both in rodents and non-rodents (Fig. 1). However, only recently several more flexible regulatory toxicology approaches did emerge to support specifically designed FIH trials (Fig. 1). Along these lines, the identification of NOAELs is not anymore required for first human entry into patients with late stage or advanced cancer failing on accepted therapies [3] whereas identification of toxicity is not required for exploratory clinical trials where stringent limits in systemic exposure would be acceptable to the sponsor [4]. Furthermore, in case toxicity is (intended to be) identified in one species only (typically the rodent), further exploratory clinical paradigms would be applicable [4]. Even in cases where no pharmacologically relevant *in vivo* preclinical safety model could be identified, human entry was pursued for several monoclonal antibodies (mAbs) not cross-reacting with target homologues in animal species, thus, in the absence of relevant *in vivo* toxicology data (ie. without signs of potentially expected on-target toxicity and, thus, also without relevant NOAEL) (Fig. 1).

An overview on relevant guidance documents for exploratory clinical trials (eIND, eCTA) and FIH dose selection as well as for standard Investigational New Drug (IND, in US)/Clinical Trial Application (CTA, in Europe) approaches is provided in Table 1. A decision tree on the different types of exploratory clinical trials based on the new ICH M3(R2) guideline [4] is outlined in Fig. 2.

2. Microdosing

The type of exploratory clinical strategy requiring the lowest amount of DS and most limited preclinical safety testing (Table 2), however, being most limited in human dose, is clinical microdosing, also known as phase 0. Microdosing is performed to assess PK, distribution and/or imaging endpoints in clinical trials at sub-pharmacological doses/exposures, typically at first human entry. No therapeutic efficacy or safety data can be obtained from microdosing studies. The concept is to dose max. 100 μg of an investigational drug and less than 1/100th of the dose that is calculated to yield a pharmacological effect in humans (i.e. pharmacologically active dose, PAD), based on animal data or human *ex vivo* data. This approach mainly refers to low molecular weight (LMW) compounds and is outlined in guidance documents from ICH [4], EMEA [5], FDA [6] and recently the Belgian FAMHP [7]. As outlined in the respective regulatory documents (Table 1) such trials require only very limited preclinical safety testing (Table 2). Anticancer pharmaceuticals devoid of genotoxicity might be as well explored as a microdose in healthy volunteers.

There are essentially three analytical technologies that can be used to acquire data from microdose studies with LMW drugs: imaging by positron emission tomography (PET; mainly ^{11}C or ^{18}F labeling of DS) and bioanalytical determinations either by standard liquid chromatography massspectrometry/mass spectrometry (LC-MS/MS) or by accelerator mass spectrometry (AMS; mainly ^{14}C labeling). AMS is able to detect ^{14}C-labeled drugs and metabolites in biological samples with up to sub-attomole ($<10^{-18}$ mol) sensitivity [8]. AMS, depending on the specific radiotracer activity of the drug, delivers several orders of magnitude improvement in sensitivity compared to most LC-MS/MS methods while considerably limiting radiation exposure to study subjects.

Developing novel imaging probes, such as PET tracers, is resource intensive with an early clinical development path that is often longer than that of a drug. Co-development of an imaging agent with an exploratory drug candidate is not feasible without safety testing. Therefore, the FDA, recognizing this restriction, introduced the eIND/microdosing approach [6]. For studies in which trace amounts of an imaging agent are required, the inclusion of that imaging agent into a clinical trial is feasible. In practice, however, this limits the use of novel

		Preclinical toxicity	
		Identified	**Not identified**
NOAEL	**Identified**	**Standard IND / CTA**	**Multiple dose exploratory trial**
	FIH starting dose:	NOAEL-based	Dose predicted to give 1/50 AUC @ NOAEL in more sensitive species
	FIH max. dose:	Generally based on clinical safety	Exposure limited to 1/10 of lower AUC @ highest dose tested
	Guidance:	FDA guidance for FIH dosing in HV	ICH M3(R2)
	Not identified	**Oncology IND / CTA** (in patients with late stage cancer)	**Human entry only on case-by-case basis** (reported for certain mAbs*)
	FIH starting dose:	STD_{10}/HNSTD-based	MABEL-based
	FIH max. dose:	Generally based on clinical safety	On case-by-case
	Guidance:	ICH S9	-

Fig. 1. Overview on general options for FIH clinical trials considering the outcome of repeated dose toxicity studies in rodents and non-rodents. *Based on personal communication: FIH dosing was endorsed by US or EU regulatory authorities for several mAbs not cross-reacting with target homologues in animal species, thus, in the absence of relevant *in vivo* pharmacology/toxicology data.