Regulatory Toxicology and Pharmacology 65 (2013) 334–343

Contents lists available at SciVerse ScienceDirect

Regulatory Toxicology and Pharmacology

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

Target organ toxicities in studies conducted to support first time in man dosing: An analysis across species and therapy areas

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ARTICLE INFO

Article history:
Received 5 December 2012
Available online 17 February 2013

Keywords:
First time in man
Target organ toxicities
Pre-clinical studies
Toxicity profile
Candidate drugs

ABSTRACT

An analysis of target organ toxicities in first time in man (FTiM) toxicity studies for 77 AstraZeneca candidate drugs (CDs) was conducted across a range of therapy areas. In the rodent, the most frequently affected organ was the liver followed by adrenal glands, kidney, spleen, bone marrow and thymus. In non-rodent, liver and thymus were the most frequently affected organs, followed closely by the testis and GI tract. The profile of affected organs was largely similar across the therapy areas of respiratory and inflammation, cardiovascular/gastrointestinal and CNS/pain. The oncology/infection therapy area differed with a larger range of organs affected. For the 75 CDs for which both rodent and non-rodent studies were conducted, new target organs were identified in non-rodents for 43 of the CDs. Notably, the changes seen only in non-rodents included organ systems of high relevance for human risk assessment such as the liver, male reproductive tissues and CNS. Additionally, profiles were similar for those CDs that progressed into human trials and those that did not. Overall, our data provide new insights into drug toxicity profiles in pre-clinical species and additionally confirm the value of using non-rodents as a second species in toxicity testing to support human safety.

1. Introduction

Before a new small molecule candidate drug can enter human clinical trials for the first time, safety and tolerability must be assessed in pre-clinical rodent and non-rodent toxicology studies, both as a regulatory requirement and, more importantly, to assess, limit and manage risk to human volunteers or patients. Pre-clinical studies conducted prior to the initial phase 1 clinical investigations are required to characterise the target organ toxicity, to determine dose dependency and relationship to exposure. Information from these studies is used to estimate initial safe starting doses and dose ranges for initial human trials, as well as to provide clinicians with key information to help develop suitable monitoring and patient exclusion strategies for these trials. For most indications early trials are carried out in healthy volunteers where starting doses and dose escalation strategies are usually based on no observed adverse-effect dose levels (NOAELs) in these pre-clinical studies (FDA Guidance for Industry, 2005). For life threatening indications such as some infection and oncology developments, most Phase I studies are conducted in patients with advanced and/or metastatic disease and the safe starting dose for these studies is usually based on toxicological findings observed in the most sensitive pre-clinical species (Senderowicz, 2010).

Preclinical toxicology packages performed by pharmaceutical companies before commencing human Phase 1 clinical trials with a small molecule are specified in regulatory guidance (ICH Guidelines M3(R2) and S9, 2009) and, as such, the designs often have a high degree of similarity. In general, toxicology studies of up to one month of duration are suitable to support single or multiple dosing for a similar duration in Phase I clinical trials in human volunteers or patients (ICH Guideline M3(R2), 2009), although for oncology Phase I trials in advanced cancer, dosing can continue beyond the duration of toxicology cover according to the patient's response (ICH Guideline S9, 2009). Consequently, it is common practice within pharmaceutical companies to support initial Phase I studies in humans with toxicology studies of up to one month of duration in two species.

Several publications have addressed the utility of pre-clinical toxicology studies in assessing the safety risks for the intended human patient or volunteer populations (e.g. Olson et al., 2000; Greaves et al., 2004).There have been a few published analyses over the years describing the most common target organs identified in regulatory toxicology studies conducted to support first into human dosing of potential new drugs (Baldrick, 2008; Ballet, 1997; Greaves et al., 2004; Heywood, 1981) but the database is sparse. In addition, despite these analyses, there is little published on proposed new chemical entities that were intended for testing in humans but failed to reach this stage because of significant toxicity identified in the nonclinical studies (Greaves et al., 2004).

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http://dx.doi.org/10.1016/j.yrtph.2013.02.002

Here, we present the results of an analysis of target organ toxicities identified in studies conducted to support the first clinical trial in humans for a total of 77 AstraZeneca small molecule candidate drugs (CDs) across a range of therapy areas and targets. In addition, we present an assessment of target organs across the different therapy areas and also between those CDs that progressed into humans and those that did not. Finally, we analyze the role of the non-rodent species in detecting toxicities that may not be detected in rodents and their significance.

2. Materials and methods

A total of 155 GLP rodent and non-rodent toxicity studies, conducted to support 77 small molecule candidate drugs (CDs) intended for first time in man (FTiM) dosing, were analysed for the profile of target organs. Of these 77 potential CDs, 59 progressed into FTiM clinical trials, whilst the remaining 18 compounds were not progressed further. The majority of these studies (95%) were conducted during the period 2000–2010 (the remaining studies were run during 1996–1999). Target organ toxicity was primarily defined as compound-related histopathological changes; other changes such as altered organ weights or clinical pathology findings, in the absence of associated histopathological changes, were not considered to be evidence of target organ toxicity for the purpose of this analysis. However the central nervous system was identified as a target organ where notable in-life observations (e.g. convulsions) were seen even in the absence of histopathological change. Single or multiple findings within a tissue, or the severity of the findings, were not discriminated in the analysis.

For the majority of CDs, a single rodent and a single non-rodent GLP study were conducted prior to FTiM, although for 3 CDs additional rodent or non-rodent studies were conducted to explore further dose levels or to assess reversibility of target organ toxicities. Any additional target organs identified from these studies are included in the analysis. The majority of studies were of one month of duration of with the following exceptions: 14 day studies in rodents/ non-rodents were conducted for 2 compounds; 1 month rodent / 14 day non-rodent studies were conducted for 1 compound with 14 day rodent / 1 month non-rodent studies for 1 further compound. For 2 additional CDs, 1 month rodent data, only, was analysed. A summary of included study details are as shown in Table 1.

The rodent and non-rodent species used in the majority of studies were rats (Wistar-derived) and beagle dogs, respectively (Table 1), with mice, cynomolgus monkeys or marmosets used in the remaining studies. The majority of the studies used the oral route for compound administration, except for 2 compounds for which inhalation studies were conducted. To enable a full evaluation of potential effects on reproductive organs, in particular to assess effects on spermatogenesis, the animals in the majority of studies commenced dosing at an age that ensured that they were sexually mature at study termination, with the following exception: the 6 studies in cynomolgus monkeys used sexually immature animals. The dosing route, age and species are detailed in Table 1, but were not discriminated in the analysis.

The majority (>95%) of the studies used one control and 3 drug-treated groups. The dose levels selected for use on all studies were based on data from appropriate dose range finding studies. The

Table 1
Summary of included studies.

Study design	Comments	
Total studies conducted	78 rodent plus 77 non-rodent studies (for 77 CDs)	
Study duration		
2 weeks	3 rodent plus 3 non-rodent studies	
3 weeks	1 non-rodent study	
1 month	75 rodent plus 73 non-rodent studies	
Species		
Rat	75 studies (70 Han Wistar, 2 Sprague Dawley, 3 Alpk:APfSD)	
Mouse (CD-1)	3 studies	
Dog (beagle)	70 studies	
Primate (marmoset)	1 study	
Primate (cynomolgus)	6 studies	
Route of administration		
Oral	76 rodent plus 75 non-rodent studies	
Inhalation	2 rodent plus 2 non-rodent studies	
Treatment groups		
Control + 1 test group	1 non-rodent study	
Control + 2 test groups	1 non-rodent study	
Control + 3 test groups	74 rodent plus 73 non-rodent studies	
Control + 4 test groups	4 rodent plus 1 non-rodent studies	
Control + 5 test groups	1 non-rodent study	
Number of animals/group		
Rat 10 male + 10 female	75 studies (1 study with 11/sex, 1 with 6/sex)	
Mouse 10 male + 10 female	3 studies	
Dog 3 male + 3 female	70 studies	
Marmoset 3 male + 3 female	1 study	
Cynomolgus 3 male + 3 female	6 studies (1 study with 2/sex)	
Age of animals at start of dosing		
Rat	5–6 weeks	4 studies
	7–10 weeks	63 studies
	>10 weeks	8 studies
Mouse	7–10 weeks	3 studies
Dog	<10 months	9 studies
	>10 months	61 studies
Marmoset	14 to 33 months	1 study
Cynomolgus	1 to 3 years	6 studies