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Applications and Benefits of Healthy Volunteer Trials to Accelerate Oncology Drug Development

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PURPOSE

Phase I drug development for oncology compounds is traditionally conducted directly in patient populations. Oncology molecules have historically been cytotoxic, meaning their safety and risk:benefit profile makes them unviable for dosing in healthy subjects. While this ensures reduced nonclinical requirements, rapid access to patient data and an earlier assessment of efficacious potential, it can also present challenges. For example, patients recruited in Phase I trials typically are at end of life care and will be taking multiple co-medications and have multiple co-morbidities (e.g. liver and kidney function may vary greatly among the recruited subjects). Practically, recruiting patients into Phase I studies can also be problematic, requiring multiple clinical sites and protracted recruitment times for what would traditionally be single site, quickly recruited healthy volunteer studies.

In recent years, however, a deeper understanding of cancer aetiology has improved the drug target specificity of oncology compounds and led to the genesis of molecular targeted agents (MTAs), with a more favorable safety profile than traditional chemotherapy molecules, creating potential to dose safely in healthy volunteers. To determine if a MTA is a candidate for this pathway to accelerated development, investigators must consider its mutagenic, teratogenic and cytotoxic potential, along with its overall toxicity potential.

Oncology drug development therefore now has the potential to use healthy volunteers in Phase I trials to address some of the disadvantages of patients. Published data on clinicaltrials.gov indicates that a wide range of clinical pharmacology study types have recently been performed in health volunteer populations (Figure 1). This poster describes two case studies of a first in human (FIH) and relative bioavailability study, demonstrating how oncology compounds can successfully be transitioned into healthy volunteers and the concomitant drug development benefits.

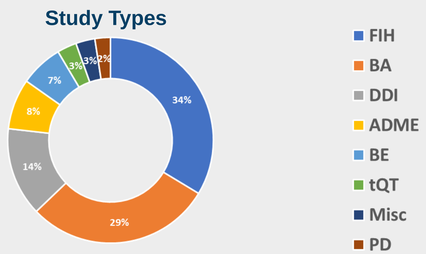


Figure 1: Breakdown of oncology phase I study types in healthy volunteers as recorded on clinicaltrials.gov

METHODS

Prior to initiating clinical trials in humans, a nonclinical package is required in line with regulatory guidance. Unsurprisingly requirements for healthy volunteers are more extensive than oncology patients, so some additional nonclinical studies may be required prior to beginning a first in human in healthy volunteers (Table 1). Data from clinical studies in patients can also be used to justify the use of healthy volunteers in later studies, for example a relative bioavailability study to identify a lead formulation prior to Phase II

Study type	Data provided	Healthy Volunteer	Patient
Safety pharmacology	Mechanism of action	X	X
	Vital organ function	X	X
Pharmacokinetics	AUC, C_{max}, $T_{1/2}$	X	X
	Metabolic and plasma protein binding	X	
Toxicology	NOAEL	X	
	Recoverability	X	X
	2 week repeated dose study	X	
	Single dose study		X[a]
	Male fertility (as part of general tox study)	X	X
	Photosafety (as required)	X	X
	Combination drug product tox (as required)	X	X
Genotox	Assay for gene mutation	X	
	Chromosome damage in mammalian systems	X	

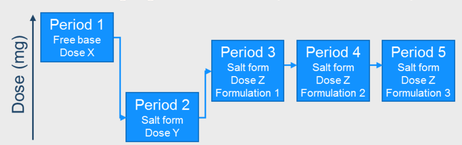
Table 1: Types of nonclinical studies required for first in human studies in healthy volunteers versus patients, [a]assuming a once every 2 to 3 week dosing schedule for the first in human

Case study 1: A first in human study to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of oral ME-401 a Pi3K δ110 inhibitor. This FIH study used a leapfrog SAD design as an efficient use of subjects, and assessed inhibition of basophil activation to demonstrate proof of pharmacological effect (PoPE). Another feature of this study was to allow assessments of the relative bioavailability of alternative formulations to optimize exposure.[1]

Figure 2: Case study 1 study design Case

Case study 2: A five period sequential study to assess the relative bioavailability of 3 novel hydrobromide (HBr) salt formulations of oral CO-1686, an epidermal growth factor (EGF) inhibitor, versus the reference freebase (FB) formulation. Phase I studies had identified that the FB form exhibited non-linear systemic exposure and variable pharmacokinetics. A HBr salt form was identified to improve exposure. An integrated program design allowed real-time adjustment of tablet dose strength in response to emerging clinical data prior to subsequent dosing periods.[2]

Figure 3: Case study 2 study design



RESULTS

Case study 1: Following single doses of ME-401, no serious or severe adverse events were recorded. Plasma exposure increased linearly up to 60 mg, following which there was supra-proportional increase in exposure. Percentage inhibition of basophil activation was measured at baseline and following single oral dose of ME-401 (Figure 4). The EC90 was predicted to be achieved following single daily 60 mg doses.[1]

Case study 2: The HBr salt exhibited a twofold increase in relative bioavailability compared to the FB form, as well as a twofold reduction in variability (Figure 5). All formulations of CO-1686 were safe and well tolerated following single oral doses.[2]

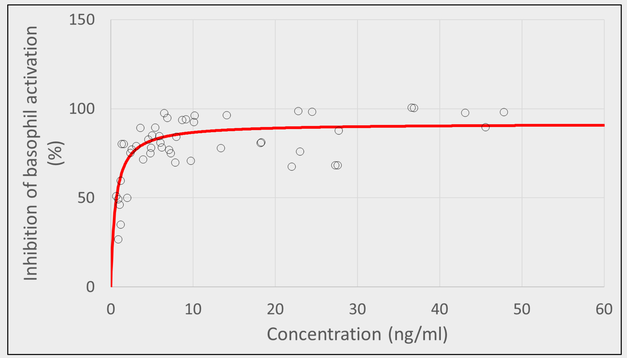


Figure 4: Percentage inhibition of basophil activation, corrected for baseline, as a function of ME-401 plasma concentration

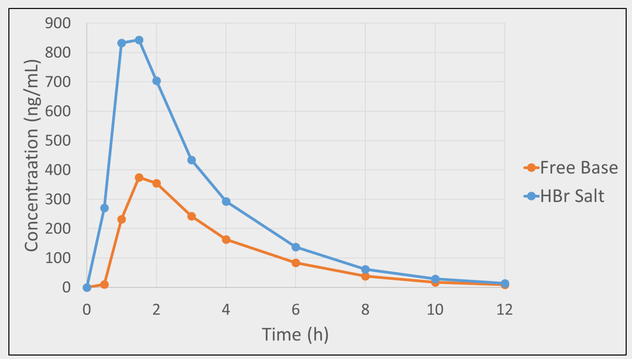


Figure 5: Geometric mean plasma data following oral dosing of rociletinib free base and HBr salt

CONCLUSIONS

Clinicaltrials.gov indicates that FIH and bioavailability studies are the most common trials performed with oncology drugs in healthy volunteers (Figure 1). The case studies described here confirm the benefits achievable from this approach:

Case study 1: Single doses of ME-401 up to 150 mg were safe and well tolerated and generally exhibited linear pharmacokinetics (PK) up to 60 mg. Based on PK and PD data a recommended dose of 60 mg was identified for use in patients trials based on the fitted Emax model [1], allowing rapid progression with confidence into patient trial, with drug product available for patient trials within 12 months of starting formulation work.

Case study 2: A HBr salt form successfully demonstrated improvements in exposure and variability compared to the FB form, and a formulation suitable for further development was identified.[2]. The use of healthy volunteers allowed for rapid formulation assessment and screening, with a suitable formulation identified in less than 5 months.

REFERENCES

[1] Safety, Pharmacokinetics, and Pharmacodynamics of ME-401, an Oral, Potent, and Selective Inhibitor of Phosphatidylinositol 3-Kinase P110δ, Following Single Ascending Dose Administration to Healthy Volunteers, Moreno, Ofir et al. Clinical Therapeutics, 2018

[2] A Phase I Program to Assess the Pharmacokinetics of a New Salt Form of CO-1686 and Prototype Formulations in Healthy Volunteers, McDermott, John et al. AAPS, 2015

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