Received: 2 June 2021 | Revised: 3 September 2021 | Accepted: 14 September 2021

DOI: 10.1111/bcp.15092

ORIGINAL ARTICLE

Healthy volunteers in first-in-human oncology drug development for small molecules

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[Correction added on 3 August 2022, after first online publication: The copyright line was changed.]

This review provides tools to consider the inclusion of healthy volunteers (HVs) in first-in-human (FIH) oncology clinical trials with small molecules, including targeted and immunomodulatory agents, a strategy that was not envisioned with classic chemotherapy. To enable an FIH oncology trial in HVs compared to cancer patients (CPs), a robust nonclinical package must be generated, which includes toxicokinetic and pharmacokinetic studies, as well as more extensive safety pharmacology, toxicology and genotoxicity studies. This strategy could provide an early clinical characterization of the pharmacokinetic parameters and clinical safety profile in the absence of comorbidities and concomitant medication. It also avoids the ethical issue of administrating subtherapeutic doses to CPs, and could potentially help to accelerate the timelines of clinical drug development for patient care. That being said, stakeholders involved in these studies need to proceed with caution, fully understand the regulatory guidance and thoroughly evaluate the benefits and risks. This paper serves to address the regulatory guidance and other considerations needed when using healthy volunteers in early oncology trials.

KEYWORDS
first-in-human, healthy volunteers, nonclinical, oncology, pharmacokinetic, phase 1, safety, toxicity

1 | BACKGROUND

First-in-human (FIH) phase 1 clinical studies have traditionally been conducted in healthy volunteers (HVs) in the majority of the therapeutics areas, but for oncology drugs with cytotoxic or highly immunosuppressive or immunogenic mechanisms of action, these studies have usually included cancer patients (CPs) with advanced, unresectable tumours, for which there is no curative therapy and in whom the disease has progressed beyond the standard-of-care treatment.

The classic FIH dose-finding studies in CPs have been single-arm, open-label studies, starting at subtherapeutic doses, with multiple dose escalation cohorts, driven by the dose-limiting toxicities (DLTs) observed in the first cycle until the maximum tolerated dose (MTD) and recommended phase 2 dose (RP2D) are reached.

During the cytotoxic agents' era, rule-based designs have most commonly been selected, such as the classic 3 + 3 design and even the accelerated titration design. Model-based design, in particular the continuous reassessment method (CRM), was incorporated as an

alternative to improve the MTD determination, but its implementation was slow compared to the 3 + 3 design.[1–3]

For targeted and immunomodulatory agents, although rule-based designs have continued to be selected to start clinical drug development, it has been observed that target modulation and establishment of the optimal biological dose is generally more precise than MTD to select the RP2D. This has supported the introduction of more innovative and well-modelled designs such as the modified toxicity probability interval (mTPI), the Bayesian optimal interval (BOIN), the Bayesian logistic regression model (BLRM) and i3 + 3, among others.[4–9] Likewise, the inclusion of clinical pharmacology and pharmacometrics endpoints have become key drivers for dose optimization and selection of the appropriate dose and regimen of administration, which should continue after phase I and throughout the clinical development in order to mitigate safety risks while maintaining efficacy, prior to the pivotal trials.[10,11]

As selected agents have a more favourable safety profile, depending on the mechanism of action and the nonclinical toxicology package of the investigational medicinal product (IMP), they provide the option of going beyond the classic design and using HVs for FIH oncology trials.[12–14] In fact, as far back as 2012, Iwamoto et al described 35 studies including HVs in the development of 30 oncology drugs.[15] However, performing early phase oncology studies in HVs is still uncommon. Unfavourable safety profiles and risk of life-threatening and fatal consequences, as occurred in 2006 with the immunomodulatory agent TGN1412 (anti-CD28 monoclonal antibody that stimulates T cells), hinder the inclusion of HVs. In the TGN1412 case, eight HVs who were enrolled in the phase I clinical trial rapidly developed severe cytokine release syndrome and acute respiratory distress requiring intensive supportive care.[16]

To mitigate and manage the risk associated with FIH clinical studies and weigh the option to enrol HVs *vs* patients, in 2007 the European Medicines Agency (EMA) published a guideline to implement appropriate strategies to start and conduct early clinical trials, which was revised in 2017.[17] The guideline provides an overview to assure the quality aspects of the IMP and the requirements to move from nonclinical (selection of relevant animal models) to early clinical development (identification of the starting dose, dose escalation methods, definition of the maximum exposure and design of the FIH). The parts of the guideline that are relevant to dose-finding studies in CPs or HVs with oncology small molecules are highlighted in this paper.

2 | METHODS

This article provides insights into the options, regulatory requirements, advantages and disadvantages of including HVs in early phase drug development with oncology small molecules (targeted and immunomodulatory agents).

An electronic search of the International Conference on Harmonisation (ICH), the Food and Drug Administration (FDA) and EMA websites, and the PubMed database was performed to obtain the essential regulatory guidance and key literature to discuss the topic of this paper using the following main search terms: healthy volunteers, phase 1, first-in-human, pharmacokinetics in oncology, small molecules, cancer or oncology drug. Also, **ClinicalTrials.gov** was reviewed to search for FIH trials with oncology small molecules (targeted and immunomodulatory agents) in HVs. A limited number of registered studies were located at ClinicalTrials.gov[18] and are listed in Table 1.

What is already known about this subject

- Inclusion of healthy volunteers has rarely been considered for first-in-human (FIH) trials evaluating oncology therapeutics.
- Generally, inclusion of healthy volunteers in clinical trials with oncology compounds has been limited to clinical pharmacology studies.
- Development of noncytotoxic therapeutics with a favourable safety profile provides an opportunity for considering conduct of oncology FIH trials in healthy volunteers.

What this study adds

- This paper sheds light on the key elements that should be considered when evaluating the appropriateness of inclusion of healthy volunteers in FIH trials with oncology small molecules, and highlights the advantages and disadvantages of initiating FIH oncology trials in healthy volunteers prior to moving to cancer patients.

2.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY, and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20.[19]

3 | RESULTS

3.1 | Nonclinical regulatory requirements for assessing the possibility of including HVs in studies with oncology drugs

Excluding the specific case of microdosing clinical studies (which have reduced requirements for supporting nonclinical data and which still have relatively limited use in drug development),[20–25] all clinical trials require a package of nonclinical studies to support an understanding of pharmacology, pharmacokinetics and toxicology before the

TABLE 1 Examples of first-in-human trials with small oncology molecules (targeted and immunomodulatory agents) in healthy volunteers

NCT ID	Drug	Mechanism of action	Phase I	Drug development indication
NCT04508179 (recruiting)	7HP349	Activator of both the **VLA-4**/**VCAM-1** and **LFA-1**/**ICAM-1** cell adhesion axes	Phase 1, placebo-controlled, within-cohort randomized, double-blind, single and multiple ascending dose study of the safety, tolerability and pharmacokinetics of 7HP349 in normal healthy male subjects	Solid tumour
NCT02629692 (recruiting)	K0706	Novel BCR-ABL1 tyrosine kinase inhibitor (TKI)	Safety, tolerability, pharmacokinetics and activity of K0706 – healthy (for part A) – chronic myeloid leukaemia (for part B and C)	Chronic myeloid leukaemia
NCT00996671 (completed)	GSK2256098	Focal adhesion kinase (FAK) inhibitor	Randomized, single-blind, placebo-controlled dose-escalation study to evaluate safety, pharmacokinetics, pharmacodynamics and preliminary food effect following single oral dose of GSK2256098 in healthy subjects	Cancer
NCT02798978 (completed)[56]	GSK1795091	Toll-like receptor (TLR4) agonist	Phase I, two-part (part 1 single-dose escalation and part 2 a parallel group) study to determine the safety, tolerability, pharmacodynamics (PD) and pharmacokinetics (PK) profile of toll-like receptor (TLR4) agonist (GSK1795091) in healthy subjects	Solid tumour
NCT01960374 (completed) [57]	Selumetinib	ATP-independent inhibitor of mitogen-activated protein kinase (MEK or MAPK/ERK kinase)	Dose-escalation study to assess safety, tolerability and PK in Japanese and non-Japanese Asian healthy male volunteers	Solid tumour approved for neurofibromatosis type 1

Source: ClinicalTrials.gov[18]

exposure of human subjects (ICH M3[R2]).[26] However, appropriate study packages can vary greatly depending on the type of compound (small or large molecules, cellular or gene therapies) and the intended trial subject population. For HVs, who stand to gain no benefit from the investigational treatment, the threshold of acceptable risk is low and the nonclinical testing requirements are more extensive than for CPs. For CPs, particularly those with severe disease and/or short life expectancy, the benefits of the potential new treatment plus the desire to expedite such treatments mean that nonclinical testing requirements can be less extensive (ICH S9).[27]

Key nonclinical endpoints where the data requirements differ for FIH studies with a small molecule in HVs compared to CPs, comprise those which support safety and are summarized in Table 2. In particular, for clinical studies in HVs, nonclinical studies need to establish the No Observed Adverse Effect Levels (NOAELs) or Minimal Anticipated Biological Effect Level (MABEL) in the case of high-risk compounds.[27,28] The pivotal toxicology studies are designed to provide the NOAELs and toxicokinetic (TK) information on corresponding systemic exposures at these doses. Information on the minimum pharmacologically active dose (PAD) is generated in nonclinical pharmacology studies using appropriate animal models of the disease indication. The NOAELs and minimum PAD are used to calculate the acceptable starting dose for the FIH HVs study, and the TK data can be used to inform potential dose escalation/stopping criteria either alone or alongside physiologically-based pharmacokinetic (PBPK) modelling. However, a recent publication has shown that the calculation of a starting dose using state-of-the-art modelling, such as PBPK, is more frequently used for biologics compared to small molecules. Only 15% of the examined studies were found to have used a PBPK approach to calculate the starting dose.[29] A review of performance of PBPK modelling from in vitro and in vivo nonclinical data to predict human exposure in FIH trials for 116 candidate small molecules revealed moderate predictive values, with 59-78% of maximum observed plasma concentration (C_{max})and 58-64% of area under the plasma concentration-time curve (AUC) predictions were within 2-fold of actual values.[30] In contrast, pivotal toxicology studies to support dosing in CPs do not need to establish a NOAEL, and a dose corresponding to 1/10th of the severely toxic dose in 10% of rodents (STD_{10}) or 1/6th of the highest nonseverely toxic dose (HNSTD) in nonrodents can be used to calculate the starting clinical dose. Nonclinical safety pharmacology evaluations are more comprehensive to support HVs clinical studies, comprising a core battery of tests for potential effects on the cardiovascular system (using in vitro electrophysiology and in vivo assessments in telemetered animals),

TABLE 2 Nonclinical data required to support clinical studies in healthy volunteers *vs* cancer patients

Study type	Healthy volunteers	Cancer patients
Safety pharmacology	In vitro electrophysiology (evaluation for potential human ether-a-go-go-related gene channel inhibition), assessment of cardiovascular effects following dosing in the nonrodent (usually conscious, telemetered animals) and assessments for effects on the respiratory system (generally via whole-body or nose-only plethysmography in rodents) and central nervous system (generally in rodents using a functional observational battery/ Irwin test). Effects on other organ systems (eg, renal, gastrointestinal tract etc) should be considered, as appropriate (ICH S7A[31]/S7B[58])	Detailed clinical observations following dosing and appropriate electrocardiographic measurements in nonrodents are generally considered sufficient (ICH S9)[27]
Pharmacokinetics (PK) and toxicokinetics (TK)	Minimum package[26]: – plasma protein binding and in vitro metabolism studies (eg, using hepatocytes or microsomes) and TK evaluation in the toxicology studies – PK studies in toxicology species (rodent and nonrodent) are also generally performed Other studies can include[26]: – identification of cytochrome P450 (CYP) enzymes contributing to metabolism, evaluation of CYP induction plus determination of permeability and evaluation as a potential substrate or inhibitor of P-glycoprotein and breast cancer resistance protein Caco-2 monolayers	Evaluation of limited PK parameters (C_{max}, AUC, $t_{1/2}$) in the toxicology species to support dose selection, dosing schedule and escalation during phase I studies[27]
General toxicology	Toxicology (and TK) in two species (rodent and nonrodent) with no observed adverse effect levels (NOAELs) established to support calculation of the starting dose for the clinical study[26]	For small molecules, testing in two species (rodent and nonrodent) but NOAEL or NOEL are not essential to support clinical dosing. Calculation of starting dose based on 1/10th the severely toxic dose in 10% of rodents (STD 10) or 1/6th the highest nonseverely toxic dose (HNSTD) in nonrodents.[27]
	Minimal anticipated biological effect level (MABEL) in case of high-risk compounds[27,28]	
Genetic toxicology	A standard battery of tests is performed. Negative results are needed in either (option 1) a reverse mutation test in bacterial cells (Ames test) and a mammalian cell test (cell mutation, chromosome aberration or micronucleus test) or (option 2) an Ames test plus a combined endpoint in vivo study (eg, rodent micronucleus test and comet assay) ICH S2(R1)[32] Any positive results must be investigated further for biological relevance	Not considered essential to support clinical trials. If studies are conducted and positive results obtained in vitro, further in vivo testing may not be warranted.[27]

the central nervous system (by assessment of neurobehavioral effects in rodents) and the respiratory system (via whole-body or nose-only plethysmography in rodents) (ICH S7A).[31] This compares to only post-dose observations of clinical signs and electrocardiographic measurements in nonrodents being sufficient to support clinical trials in CPs.

Another key difference in the nonclinical data requirements for small molecules is that genotoxicity assessments should be conducted prior to FIH clinical studies in HVs, but are not needed to support clinical development in CPs. Initial dosing in HVs needs to be supported by sufficient data to show a lack of biologically relevant genotoxicity with

negative results from at least an in vitro assessment for potential mutagenicity in bacterial test strains and either (1) an in vitro genotoxicity assessment in mammalian cells (in a gene mutation test, chromosome aberration test or micronucleus test) or (2) a combined endpoint in vivo genotoxicity assay (eg, a rodent combined COMET and micronucleus test) needed prior to HV clinical trials (ICH S2 [R1]).[32] If positive results are obtained in the genotoxicity tests, further investigation of the biological relevance of these findings is needed, eg, via mechanistic studies and relevant genotoxicity assessments in vivo, prior to dosing HVs. In contrast, for CPs if genotoxicity studies have been conducted and show positive results, these do not preclude dosing in the clinical study. Hence, careful attention should be paid to both the design of the nonclinical testing package and the assessment of the subsequent data when HVs are to be included in studies with oncology drugs.

3.2 | Study design considerations for FIH trials in HVs

Administration of IMP to humans for the first time is a critical step due to uncertainties surrounding the behaviour of the drug with respect to the nature, severity and the time course of the adverse events in humans, which can be different from those in animals.

To mitigate the risk of delayed adverse events and cumulative toxicities, which can worsen with repeated dosing due to accumulation of the drug, the most conservative and commonly adopted approach for an FIH trial in HVs is a thorough characterization of the safety and PK profile of a single dose in a single ascending dose (SAD) part before proceeding to multiple-doses in the multiple ascending dose (MAD) part of the study.[33] In contrast, a repeat-dose phase 1 is considered an appropriate design for oncology trials in CPs. Another important element to consider while designing FIH studies in HVs is inclusion of placebo, which is critical to avoid bias in the assessment and interpretation of the safety data, but such a design would be considered inappropriate for FIH oncology trials with CPs.[34,35] The use of placebo in oncology trials in HVs is essential to assess the pharmacodynamic (PD) effects of the drug under investigation to control for baseline variation in the PD endpoints.

Sentinel dosing in the first cohort of the SAD or in all cohorts of the trial for high-risk, first-in-class substances, or compounds with unknown mechanism of action is an additional precautionary safety measure to consider for FIH trials in HVs. Under this approach, dosing starts with treating only two subjects simultaneously, one on active drug and a second one on placebo, thereby exposing one subject to active treatment initially. Dosing the remainder of subjects in the cohort can be resumed following a satisfactory review of at least 24 hours of post-dose safety data from the sentinel subjects.[17]

Duration of dosing in the MAD for the FIH trial in HVs must not exceed the duration of Good Laboratory Practice (GLP) animal repeated-dose toxicity studies conducted in two mammalian species, which initially comprise 14- or 28-day studies, whereas dosing in oncology trials continues until disease progression or unacceptable toxicities.[26]

For an oncology drug to be evaluated in a phase 1 HVs study, a SAD design would be a standard approach, while MAD would be more appropriate to be conducted in the target population in view of the risk of toxicity on cumulative exposure and the lack of accurate evaluation of target effects in HVs.

An example of an FIH with a small molecule targeted drug used in HVs prior to a study in CPs is a SAD study initiated by GlaxoSmithKline in HVs with the oral compound GSK2256098 (NCT00996671)[18] (see Table 1). The objectives of this study were to assess the safety, PK, PD and food effect of the investigational drug in HVs before proceeding to CPs.[36]

GSK2256098 is a potent, ATP-competitive inhibitor of focal adhesion kinase (FAK) activity. FAK is a nonreceptor tyrosine kinase required for cancer cell growth, proliferation, survival, migration, angiogenesis, invasion and mesenchymal transformation,[37] and its overexpression has been reported in several solid tumours[38,39] and hematologic cancers.[40,41]

In this example, the HVs in the SAD study were randomized to receive either active drug (GSK2256098) or placebo.[18] The starting dose was selected as 20 mg and the highest exposure in the study was defined as not to exceed the exposure at the NOAEL in the most sensitive species and gender (male dog, 6 mg/kg/d). The data from this FIH study in HVs supported the selection of the starting dose and dosing regimen in the phase 1 study in CPs, where the starting dose of GSK2256098 was selected to be 80 mg, oral twice daily. Doses were escalated until the MTD was determined and the highest dose used in this study was 1500 mg.[42]

3.3 | Dosing selection for FIH studies in HVs

Calculating the safe starting dose for investigational anticancer small molecules for FIH trials in HVs follows the same recommendations as for investigational nonanticancer small molecules, which are outlined in the FDA Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers.[43]

In contrast to oncology trials in CPs where the goal is to identify a starting dose that is expected to have a minimal pharmacological effect and is safe to use, the starting dose for HVs is a dose expected to result in an exposure lower than the PAD, unless a robust scientific rationale such as supportive toxicology data or clinical safety data from other compounds of the same class are available for higher doses or the potential side effects are readily monitored and reversible.[17]

The starting dose for small molecules is related to either the NOAEL or PAD converted into a human equivalent dose (HED), depending on the level of uncertainty regarding the human relevance of findings observed in nonclinical studies and the knowledge of the intended target. Generally, the NOAEL derived from appropriate animal studies, which might not necessarily be the most sensitive species, is the most common method used to calculate a safe starting dose for small molecules, unless the PAD was shown to be lower than the NOAEL. To further limit the potential for adverse reactions in HVs,

safety factors are generally applied in the calculation of the starting dose. Safety factors that are taken into account are, for example, the novelty of the mode of action of the drug. A lower HED may be selected based on the novelty of drug. If the toxicology findings are minimal or easily monitored in HVs, a higher dose or a more aggressive dose-escalating schedule may be applied. Other considerations are the shape of the dose-response curve, the expected exposure in humans and the relevance of the animal models.

An example calculation of a clinical starting dose for a SAD is illustrated in Table 3. The conversion factors used for deriving the HED from NOAELs in nonclinical species[43] are listed in Table 4.

In this fictional example, the NOAEL from the pivotal 4-week, repeat-dose toxicity studies in rats and dogs were 800 and 40 mg/kg/d, respectively. The dog was identified as the most sensitive species because the HED for the dog NOAEL (22 mg/kg/d) was less than the HED for the rat NOAEL (129 mg/kg/d). After dividing by a 10× safety factor (2 mg/kg), the maximum recommended starting dose (MSRD) for a 60-kg human was 120 mg.

Furthermore, in a relevant animal pharmacological model study where multiple ascending doses of the IMP ranging from 1 to 10 mg/kg/d were administered for 14 consecutive days in rats, the lowest dose that showed significant pharmacological activity was 1 mg/kg/d, which was considered as a PAD. As shown is Table 3, the pharmacologically active HED (PAHED) for a 60-kg human was 9.7 mg/kg. Because the PAHED (9.7 mg/kg) is lower than the MSRD (120 mg/kg), the starting dose will be selected based on the PAHED.

It was noted in a recent review of 41 clinical studies with non-oncology small molecules that in about 25% of studies exposure at the highest clinical dose was greater than that seen at the NOAEL (the common predefined ceiling exposure), although no adverse findings of concern were reported in any of the cases.[29] This illustrates that exceeding the NOAEL is possible, although only in a careful, stepwise and rational way.

3.4 | Maximum exposure dose in HVs

In FIH studies in CPs, if the expected benefits outweigh the risks, exposure may not limit the dose-escalation or the highest dose investigated in a clinical trial.[27] In contrast, it is an EMA requirement for clinical trials in HVs that the projected exposure at the highest dose must not exceed that reported at the NOAEL in the most sensitive animal species and the maximum dose should be predefined in the protocol for each part of the study.[17] The maximum exposure in HVs should be within the estimated human PD dose range. However, if scientifically justified and the safety profile of the IMP is deemed acceptable, doses exceeding the PD dose range may be approved by the regulators, for example in thorough QT studies in HVs, a supratherapeutic dose needs to be reached for a QT waiver.

The maximum exposure is usually justified based on all available nonclinical and clinical data, including PK, PD, findings in toxicology studies and exposure at the expected therapeutic dose range. Additionally, the maximum exposure should take into account when the target is fully saturated and no further therapeutic benefit is to be expected by increasing the dose. A specific requirement of the EMA is that when the exposure cannot be adequately estimated, the maximum dose is to be predefined in the protocol. It is noteworthy that while this is an EMA-specific requirement, the FDA and other agencies may accept a protocol where the maximum dose is not predefined and dose escalation is solely guided by safety and PK findings or safety findings only (authors' experience).

3.5 | Dose escalation in HVs

To ensure safety of the subjects during dose escalation in HVs, safety data from a minimum number of subjects of a cohort must be reviewed at the end of each dose level prior to proceeding to the next higher dose/exposure level. When dose exposure limit (AUC and/or C_{max}) is one of the dose escalation stopping criteria defined in the protocol, PK data must also be included in the review to verify that the exposure limit was not exceeded in any individual participant and to ensure the predicted exposure at the next selected dose level will not exceed the limit defined in the protocol. Ideally, PD data may also be included in the review, which can be informative when characterising the dose/exposure PD effect relationship.

While dose escalation for FIH oncology trials in CPs is generally determined by MTD, this approach is considered to be inappropriate

TABLE 3 Example of starting dose calculation

Maximum recommended starting dose (MSRD)

Species	NOAEL (mg/kg/d)	BSA conversion factor	HED (mg/kg/d)	Safety factor	MSRD (mg/kg/d)	Human weight (kg)	MSRD (mg/d)
Rat	800	6.2	129	10	13	60	780
Dog	40	1.8	22	10	2	60	120

Pharmacologically active dose (PAD)

Species	PAD (mg/kg/d)	BSA conversion factor	PAHED (mg/kg/d)	Human weight (kg)	PAHED (mg/d)
Rat	1	6.2	0.16	60	9.7

Abbreviations: BSA, body surface area; HED, human equivalent dose; MSRD, maximum recommended starting dose; NOAEL, number of observed-adverse-effect level; PAD, pharmacologically active dose; PAHED, pharmacologically active human equivalent dose.

TABLE 4 Conversion of animal doses to human equivalent doses based on body surface area

Species	To convert animal dose in mg/kg to dose in mg/m^2, multiply by K_m	To convert animal dose in mg/kg to HED[a] in mg/kg, either:	
		Divide animal dose by	Multiply animal dose by
Human	37	...	...
Child (20 kg)[b]	25	...	...
Mouse	3	12.3	0.08
Hamster	5	7.4	0.13
Rat	6	6.2	0.16
Ferret	7	5.3	0.19
Guinea pig	8	4.6	0.22
Rabbit	12	3.1	0.32
Dog	20	1.8	0.54
Primate:			
Monkey[c]	12	3.1	0.32
Marmoset	6	6.2	0.16
Squirrel monkey	7	5.3	0.19
Baboon	20	1.8	0.54
Micro-pig	27	1.4	0.73
Mini-pig	35	1.1	0.95

Abbreviation: HED, human equivalent dose.

Source: US Food and Drug Administration (FDA) Guidance for Industry. Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers.[43]

[a]Assumes 60 kg human. For species not listed or for weights outside the standard ranges, HED can be calculated from the following formula: animal dose in mg/kg $\times$ (animal weight in kg/human weight in kg)$^{0.33}$.

[b]This K_m value is provided for reference only since healthy children will rarely be volunteers for phase 1 trials.

[c]For example, cynomolgus, rhesus and stumptail.

for HVs trials because MTD definition takes into consideration the potential therapeutic dose and the expected benefit/risk balance, which are not applicable for HVs where there is no potential benefit. For HVs, it is common that the maximum fold increase in dose/exposure, the maximum number of cohorts as well as dose escalation stopping criteria, including safety, exposure (C_{max} and/or AUC) and PD if feasible, are predefined in the protocol.

Dose increments from one dose level to the next are guided by the dose/exposure-toxicity or the dose/exposure-effect relationship based on the nonclinical studies and then adapted following review of emerging clinical data from previous cohorts. Factors that warrant a cautious dose-escalation scheme can include a small therapeutic window (eg, low ratio of toxic dose to therapeutic dose) in nonclinical data, poor translatability of animal model, unknown reliability of monitoring potential adverse events in humans before serious, irreversible effects develop and nonlinear PK potentially resulting in supraproportional increases in exposure, particularly in the higher dose levels of SAD and MAD.[17]

In general, dose increments for a SAD part of an FIH SAD/MAD trial in HVs, are predetermined in the protocol, although the EMA guidelines do not provide limitations on the dose escalation steps.[17] Often doses are increased by fixed intervals on either a logarithmic scale (eg, 25 mg, 50 mg, 100 mg, 200 mg), which is the most commonly used approach, or a linear scale (eg, 25 mg, 50 mg, 75 mg, 100 mg) when very slow escalation is warranted for safety reasons.[33] Usually, the rate of escalation in the SAD is 3- to 5-fold at subpharmacological, nonefficacious doses, then is slowed to 1.5- to 2-fold at suprapharmacological doses, where in the MAD part the starting dose and the dose increments are determined following review of safety and PK data from the SAD.

For FIH oncology trials, various dose increment approaches can be proposed based on the study design, for example modified Fibonacci sequence (eg, 50 mg, 75 mg, 125 mg, 200 mg) in the traditional 3 + 3 design, 40% dose increments in the accelerated titration 3 + 3 design or 100% dose increments in single patient cohorts and then 40% dose increments when cohorts are reverted to 3 + 3 in the accelerated design. In the model-based design, dose levels are predefined at baseline for single patient cohorts, but with successive patients the model is recalculated according to Bayesian principles.[1,44]

A comparison of FIH trials for small molecule oncology therapeutics in HVs and CPs is summarized in Table 5.

4 | DISCUSSION

The decision as to which population should be considered for an oncology FIH trial (HVs *vs* CPs) is highly complex and the benefit/risk should be carefully weighed, taking into consideration the mechanism

TABLE 5 Comparison of first-in-human trials for small molecule oncology therapeutics in cancer patients *vs* healthy volunteers

	First-in-human in cancer patients	First-in-human in healthy volunteers
Study design	Open label, nonrandomized Multiple doses until disease progression or inacceptable tolerability Sentinel dosing not required Dose escalation is mainly driven by safety parameters (DLT). PK/PD may support decisions Maximum number of cohorts to be evaluated is determined by MTD Dose increment approaches can be used depending on the trial design selected Study population includes both males and females, although pregnancy is to be avoided in all cases	Double-blinded, randomized, placebo controlled A SAD study followed by a MAD study Number of doses is predefined in the protocol (a single dose in the SAD and up to 28 days of repeated doses in the MAD Sentinel dosing in at least the first cohort of the SAD or all cohorts for first-in-class investigational drugs In general, dose escalation stopping criteria determined by safety and PK parameters (maximum exposure (AUC and/or C_{max}) Maximum number of cohorts to be evaluated is predefined in the protocol Dose increments of the SAD are predefined on a logarithmic or linear scale, which can be revised following review of the safety and PK data from the earlier cohorts Dose increments of the MAD are determined after the review of the safety and available PK/PD data from the SAD Generally, gender is limited to males only or males and females of nonchild-bearing potential or on contraceptives Rarely, females of child-bearing potential are included because of restrictions that might be imposed by the sponsor or ethics based on either lack or nonsupportive reproductive toxicology data[59]
Starting dose	1/10th the severely toxic dose in 10% rodents (STD10) or 1/6th of the highest nonseverely toxic dose in nonrodents (HNSTD)	– ≤1/10th of the human equivalent dose calculated from no observed adverse effect level in the most sensitive species for HVs or – pharmacologically active human equivalent dose (PAHED) calculated from pharmacologically active dose (PAD) in a relevant pharmacological animal model
Study population	CPs with solid tumour and/or hematologic malignancies, which may be restricted to patients with specific tumour type or a specific molecular biomarker during the dose escalation and expansion cohorts, depending on the mechanism of action and the generated emerging data/early signals of clinical antitumor activity[44,60]	Healthy volunteers
Study duration	Relatively long, precise patient selection	Short, rapid subject accrual
Primary objectives	Safety and tolerability Define DLT, MTD and RP2D	Safety and tolerability PK parameters
Secondary objectives	PK/PD Efficacy	PD
Tissue biopsies	Recommended for targeted therapy and immunotherapy[52]	Not required/not possible
Regulatory requirements, genotoxic studies	Not required	In vitro studies are essential and in vivo studies are desirable

Abbreviations: AUC, area under the plasma concentration-time curve; CP, cancer patient; DLT, dose-limiting toxicity; HV, healthy volunteer; MAD, multiple ascending dose; MTD, maximum tolerated dose; PD, pharmacodynamics; PK, pharmacokinetics; RP2D, recommended phase 2 dose; SAD, single ascending dose.

of action, toxicology findings and pharmacokinetic profile of the drug, relevance of the animal model and other factors such as route of administration. To this point, inclusion of HVs in trials assessing clastogenic therapeutics, drugs for which irreversible toxicology findings have been reported and/or adverse effects that cannot be properly monitored in the clinic, or even compounds with intrathecal or intrauveal route of administration, would not be acceptable.

In FIH oncology trials in CPs, once the RP2D has been determined and is considered to be a safe dose to use in a large patient population, safety concerns could potentially arise due to higher exposures than expected. This could be a result of intrinsic factors such as impaired renal and hepatic function, genetic polymorphism, ethnicity, gender and age, or extrinsic factors such as drug-drug and food-drug interactions. If safety allows, it would be of great benefit to identify toxicities associated with exceeding the exposure at MTD in HVs before proceeding to CPs, as it can be easier to manage adverse events in HVs with no comorbid disease and no concomitant medications and also to guide dose decision in CPs. This can be achieved through the safety evaluation of either a single supratherapeutic dose(s) of the IMP in HVs or a single therapeutic dose of the IMP in the presence of a strong inhibitor of the enzyme that is primarily involved in the metabolism of the IMP, resulting in an exposure in excess of that at the therapeutic dose. However, the threshold for acceptable toxicities is far lower in HVs than in CPs, which can be viewed as a major limiting factor in the decision to include HVs in oncology programs. Baldrick et al., has shown in 25% and 12% of examined FIH protocols for small molecules and biopharmaceuticals, respectively, that exposure at the top dose level was greater than that seen at the NOAEL,[29] suggesting that an adaptive top dose approach (based on emerging human safety data) may be acceptable to the regulators and doses well above those expected to be needed should be studied (when safety allows, ie, adverse events are tolerable, not severe and expected safety issues can be adequately monitored and treated) in phase I trials to identify toxicities and to identify the highest dose that is reasonably well tolerated.[44]

Besides safety and PK, additional secondary or exploratory clinical pharmacology endpoints that involve single or multiple doses could be easily integrated in an FIH study in HVs. Food-drug interaction[45] is frequently assessed in one cohort of the SAD part in a crossover design provided the dose chosen and the expected exposure are equal to or lower than that which was reached in a previously conducted SAD cohort where all relevant data has been reviewed and no dose-stopping criteria were met. A drug-drug interaction to assess the impact of multiple doses of an IMP on the PK of a CYP 450 substrate(s) could also be evaluated in one of the MAD cohorts given that the number of doses/total exposure do not exceed the limit approved by the regulators.[46,47] Similarly, impact of age, gender and ethnicity on the pharmacokinetics of the IMP can be studied in parallel to the SAD part, which would guide dose adjustment, if required, in the patient population as drug development proceeds into larger-scale patient studies.

Starting the development of oncology drugs in HVs would help to reduce the number of doses administered to CPs by avoiding the administration of subtherapeutic doses.[48] To note, with molecular targeted agents (MTA) the MTD is reached less frequently than with classic chemotherapy. Recent evidence suggests that higher doses are not necessarily translated to antitumour activity, which may imply that the risk of subtherapeutic exposure in patients is decreasing. However, Ferte et al[49] conducted a review of 317 phase 1 oncology trials reported in the literature between January 1997 and January 2009 and did not observe any increase in signs of antitumour activity at early doses. In contrast, in a review by Jain et al[50] of 24 phase I oncology trials conducted in the MD Anderson Cancer Center between 2004 and 2008 with MTA, signs of efficacy were demonstrated at levels ≤25% of the MTD, which supports the necessity of optimal dose selection.[44,51]

Another advantage of HVs is the potential for shortening the timelines of the global clinical program as recruitment of HVs is easier, takes less time compared to patients and dose escalation can proceed more rapidly, and this expedited timeline could potentially reduce the overall cost.

Additionally, dose escalation generally for clinical trials in HVs proceeds more rapidly than for clinical trials in CPs. Dose escalation for oncology trials in CPs should not proceed before a review of the safety data from all patients of the cohort up to the completion of the last day of cycle 1 to determine whether a DLT was encountered, where one cycle could consist of 3 or 4 weeks. In contrast, for clinical trials in HVs, the minimum data required for a dose escalation review is determined based on the half-life of the compound, which can be relatively short for small molecules. For a SAD, it is common to include in the review data up to 2-7 days after the dose on day 1, whereas for a MAD, the safety committee would only meet once data up to 2-7 days post-last dose is available, where the total dosing duration for a MAD varies between 7 and 28 days. Although dose escalation in HVs may proceed more swiftly, it should be noted that it includes limited information after single doses compared to much more information after multiple doses.

An additional advantage is that intensive collection of PK blood samples in HVs is more acceptable than in CPs. This allows accurate calculation of the PK parameters of the investigational drug needed for the determination of the highest exposure/dose and dosing regimen. While it is acceptable and not problematic to collect a blood volume of up to 500 mL from HVs, such a volume may be seen as a burden for CPs with medical comorbidities such as anaemia, fatigue and who more often have damaged veins resulting in difficult blood draws.

It is noteworthy, however, that some endpoints of an oncology phase 1 program cannot be assessed in HVs and uncertainty in the translation of findings to CPs exist.

First, the pharmacokinetic profile of an IMP in HVs does not always mirror that of CPs, which can be explained by the difference in the expression level of the target in healthy and tumour tissue. It is a regulatory recommendation that target saturation should be taken into account when appropriate. This can be done in HVs if the target is present, but translation to target saturation in CPs is still unsure.[17] Second, evaluating PD effects/determining the effective dose can be difficult or impossible because of the difference in target expression. That is, the target in the tumour is not present in HVs and cannot be

TABLE 6 Advantages and disadvantages of including healthy volunteers in first-in-human trials for oncology therapeutics

Advantages	Disadvantages
Rapid subject accrual	Absence of the target in healthy tissue, which may render the model irrelevant to the patient
Limit unnecessary exposure of CPs to low, subtherapeutic doses[44,48–50]	Inacceptable tolerability in HVs
Rigorous evaluation of the safety profile of the investigational drug in the absence of comorbid conditions and concomitant medications	Risk of life-threatening unexpected serious adverse events
Thorough characterization of the pharmacokinetics parameters of the investigational drug	Uncertainty about translatability of pharmacokinetic findings in HVs to CPs
Integration of single-dose clinical pharmacology studies in the FIH study (food effect,[45] age effect, gender effect,[59] drug-drug interaction[46,47])	Limitations in evaluating PD effects
Accelerate timelines of clinical development program	

Abbreviations: CP, cancer patient; FIH, first-in-human; HV, healthy volunteer.

monitored. Hence, blood-based PD markers can be evaluated for some drugs, but may only provide a hint of the efficacy in CPs. Obviously, the advantage of including CPs is that tumour biopsies can be taken to monitor PD effects at the target site. Although important information may be provided by these biopsies, this is also a substantial burden and risk to patients, so biopsies sampling should be limited.[52]

Additionally, the difference in the PK profile of an IMP in CPs *vs* HVs (and eventually the PD responses, when this can be measured in HVs) could be a result of the altered hepatic metabolic function (e.g, cytochrome P450) due to liver malignancies in CPs. An important regulatory expectation is the conduct of a pharmacokinetic study in otherwise healthy subjects with impaired hepatic function when a drug is likely to be used in patients with altered hepatic function. Liver metabolism and/or biliary excretion of the drug and/or its active metabolites, and a dose adjustment may be needed for such patients, taking into account side effects and/or lack of efficacy (PK/PD relationship).[53,54]

Some issues in translatability between CPs and HVs are highlighted in this section but, naturally, the larger the difference between the studied population and the real-world population, the more uncertainties exist. This is an important consideration when translating the trial data to the real world. Collection of real-world data may help to identify the differences more accurately.[55]

Table 6 summarizes the advantages and disadvantages of including HVs in FIH trials for oncology therapeutics.

5 | CONCLUSION

Sponsors and investigators should be aware of the different requirements for starting drug development in HVs *vs* CPs, and should weigh carefully the benefit/risk of initial characterization of the safety and pharmacokinetics with an oncology IMP in FIH studies including HVs *vs* CPs. Although the nonclinical package and the mechanism of action are the key drivers to define the strategy, the potential to shorten the phase 1 study duration and ultimately the overall clinical timelines, avoid the exposure of subtherapeutic dose levels to CPs and the possible resulting cost reductions may also contribute to the decision.

Obviously, there is no "one size fits all" approach when it comes to the selection of the population of FIH clinical trials evaluating oncology therapeutics. The choice must be fully justified on a case-by-case basis, taking into consideration all the required elements in order to properly select the best scenario to advance the drug-development process in a responsible and efficient manner.

DISCLAIMER

The views expressed in this article are those of the authors and do not necessarily represent the views of, nor should be attributed to, the organizations or institutions for which they work.

COMPETING INTERESTS

N.S. provided consultation or attended advisory boards for AIMM Therapeutics, Boehringer Ingelheim, Ellipses Pharma. N.S. received research grants for the institute from AB Science, Abbvie, Actuate Therapeutics, Amgen, Array, AstraZeneca/MedImmune, Bayer, Blueprint Medicines, Boehringer Ingelheim, Bristol-Myers Squibb, Cantargia, CellCentric, Cytovation, Deciphera, Genentech/Roche, GlaxoSmithKline, Incyte, Lilly, Merck Sharp & Dohme, Merus, Molecular Partners, Novartis, Pfizer, Pierre Fabre, Roche, Sanofi, Taiho, Takeda (outside the submitted work). The other authors do not report any conflicts of interest.

CONTRIBUTORS

B.D.L.H., D.B.C. and L.R. conceptualized the manuscript and all authors provided significant inputs. B.D.L.H., D.B.C. and L.R. wrote the manuscript, and all authors reviewed, edited and approved the manuscript.

DATA AVAILABILITY STATEMENT

All data and references mentioned in this manuscript are from publicly available sources.

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How to cite this article: de las Heras B, Bouyoucef-Cherchalli D, Reeve L, et al. Healthy volunteers in first-in-human oncology drug development for small molecules. *Br J Clin Pharmacol*. 2022;88(4):1773-1784. doi: 10.1111/bcp.15092