

REVIEW

Pivotal Considerations for Optimal Deployment of Healthy Volunteers in Oncology Drug Development

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Oncology drug development is among the most challenging of any therapeutic area, with first-in-human trials expected to deliver information on both safety and activity. Until recently, therapeutic approaches in oncology focused on cytotoxic chemotherapy agents, ruling out even the possibility of enrolling normal healthy volunteers (NHVs) in clinical trials due to safety considerations. The emergence of noncytotoxic modalities, including molecularly targeted agents with more favorable safety profiles, however, has led to increasing numbers of clinical pharmacology studies of these agents being conducted in NHVs. Beyond rapid enrollment and cost savings, there are other advantages of conducting specific types of studies in NHVs with the goal of more appropriate dosing decisions in certain subsets of the intended patient populations, allowing for enrollment of such patients in therapeutic trials from which they might otherwise have been excluded. Nevertheless, the decision must be carefully weighed against potential disadvantages, and although the considerations surrounding conduct of clinical trials using NHVs are generally well-defined in most other therapeutic areas, they are less well-defined in oncology.

Clinical pharmacology studies (i.e., trials where the primary objectives are traditionally pharmacokinetic (PK)-related) focus on identifying and confirming appropriate dosing in various subsets of the intended patient populations. In most therapeutic areas, these trials are conducted in normal healthy volunteers (NHVs) and in special populations without the targeted disease (i.e., subjects who are renally or hepatically impaired but are otherwise healthy, and who, for the purposes of this paper, will be considered part of the NHV population). Results from these NHV PK studies are then used to expand the patient pool, including those with comorbidities or who are receiving concomitant medications, which might otherwise have resulted in them being excluded from enrollment in trials with therapeutic intent.

Until ~ 20 years ago, oncology drug development was almost exclusively focused on chemotherapeutics that were intentionally designed to be cytotoxic (and frequently genotoxic), limiting their development programs to patients with cancer. Given the terminal nature of most cancers and the generally short life expectancy following diagnosis, a higher level of toxicity than that observed in other marketed drugs has been considered acceptable for these agents. Poor tolerability is expected and mitigated, when possible, by supportive care measures as well as by frequent dose modifications and interruption. Given the poor long-term survival for patients with most types of cancer, the potential for development of long-term toxicities was considered less important in the overall risk-benefit assessment of the cytotoxic chemotherapeutic agent. Thus, safety considerations played a major role in exclusion of NHVs from oncology drug development.

Therapeutic approaches in oncology have shifted from the exclusive use of cytotoxic agents to the addition or substitution of immunomodulatory and molecularly targeted agents. The more favorable safety profiles of many of these agents and the lack of cytotoxicity have made it possible to include NHVs in their development programs, at least in limited-dose pharmacology studies (i.e., mass balance/ADME (absorption, distribution, metabolism, and elimination), BA/BE (bioavailability and/or bioequivalence), food effect, organ impairment effects, and drug-drug interaction (DDI) studies; **Table 1**) that are often helpful in developing the PK profile of the investigational agent. These clinical pharmacology studies are typically conducted using a single dose level and up to two doses of the investigational agent, and rarely require more than two doses. Additionally, first-in-human (FIH) studies enrolling NHVs can include placebo subjects, allowing for a more impartial assessment of safety in each dosing group.

Nevertheless, despite a more favorable safety profile, there are important practical considerations that may guide a decision to exclude NHV studies from a development program. Evaluating pharmacology of an investigational agent in FIH studies enrolling patients with cancer avoids delays in offering patients the opportunity to benefit from a potential cure. When patient selection may be informed by genetic screening, which is often the case for trials involving molecularly targeted agents, the patients most likely to respond can be identified with precision, allowing for early evidence of target validation and clinical response. FIH studies conducted in the indicated population can also offer a competitive advantage in the current regulatory environment in the United States by streamlining development. Recent regulatory updates from the US Food and Drug Administration (FDA) include a series of programs to address an unmet medical need in the

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Table 1 Clinical pharmacology trials that could be conducted in NHVs in support of oncology drug development

Type of clinical pharmacology study	Number of doses (if dosed to HVs)	Dose of investigational agent
Exploratory/microdosing/phase 0	1 dose	1/100 th * of the dose anticipated to elicit a therapeutic response *Note: may not be possible to determine for certain products.
ADME	1 dose	May be conducted at a dose lower than the clinical dose depending upon dose-linearity and potential for saturation of metabolic pathways
TQT	1 dose	Preferably @clinical dose, and if safety permits, supratherapeutic may be used
Relative BA/BE	2 doses	Preferably @clinical dose, depending on toxicity
Food effect	2 doses	Preferably @clinical dose, depending on toxicity
DDIs	2 doses ^{a,b}	@clinical dose. Lower dose may be considered depending upon dose linearity, expected exposure change & safety profile
Organ impairment	1 dose ^b	Lower dose may be considered
Ethnicity and other bridging	1 dose	Preferably @clinical dose, lower dose may be considered if appropriate

ADME, absorption, distribution, metabolism, and excretion; BA/BE, bioavailability/bioequivalence; DDIs, drug-drug interactions; HVs, healthy volunteers; NHVs, normal healthy volunteers; TQT, thorough QT.

^aFor drug as substrate. Two doses may be insufficient to test the drug as perpetrator.

^bAssuming linear PK.

treatment of a serious condition that allows for early consultation with the FDA during drug development to design more efficient trials.¹ Similar approaches have been adapted by the European Medicines Agency (EMA) in Europe.^{2,3}

Consequently, trial complexity has increased dramatically with numerous end points beyond traditional safety, efficacy, and PK, to include translational oncology assessments, such as receptor occupancy assessments and pharmacodynamic biomarkers. Given the costs associated with conduct of such complex clinical trials, early signals of activity are critical to the survival of many drug development programs.

Despite these advantages, there are also several challenges to direct-in-patients early phase oncology trials. Patients with advanced cancers often have additional comorbidities that may require management with prescription and nonprescription drugs; when there are no prior clinical evaluations of the investigational agent all the potential interaction liabilities must be based exclusively on preclinical *in vitro* data and associated risk assessment. However, severely restricting enrollment criteria may lead to unacceptably slow enrollment, long study timelines, and/or the potential for protocol deviations related to exclusion criteria, which may adversely impact the quality of efficacy and safety data. Orally administered drugs have the additional complexity of food interactions, which may alter PK, whereas fasting requirements may affect drug tolerability, administration convenience, and compliance.

Increasingly, drug developers in the oncology space are addressing some of these issues by including NHV studies in their development plans, particularly in the clinical pharmacology package, to leverage the advantages of faster timelines and better-quality data associated with studies conducted in NHVs, which tend to recruit faster and are associated with fewer potentially confounding intrinsic and extrinsic factors (i.e., fewer sites, better protocol compliance, healthy subjects with no major comorbidities, and not requiring concomitant medications). Additionally, studies conducted in NHVs can include more extensive confinement

than those conducted in patients, allowing for frequent PK assessments and closer safety monitoring, as well as drug-free washout period(s).

Nevertheless, the evidential burden on the proof of safety prior to the start of a trial is higher in studies involving NHVs compared with patients with cancer in terms of quantity and quality of data. In addition, there are difficulties that arise when extrapolating the results obtained in NHVs to patients with cancer, including how to integrate potential risk factors across preclinical toxicity data, previous clinical experience (if available), study design, dosing, and study conduct, or how to weigh the value of information obtained from NHVs when considering the development pathway, trial objectives, and potential differences in PK and/or safety profiles relative to those obtained in patients.

In this paper, we summarize information shared by presenters during the 2018 ASCPT symposium, entitled: “Healthy Volunteers Studies in Oncology Drug Development: Pivotal Considerations Toward Optimal Deployment,” which consolidated the issues and outlined a rational approach for guiding strategy, feasibility evaluation, and logistics for inclusion of normal healthy volunteer (NHV) trials within an oncology drug development program. The presentations included an overview of the challenges that clinicians face in enrollment and retention of patients in early phase oncology trials (presented by Eric Roeland, MD), examples of clinical trials of oncology drug candidates where NHV studies were particularly beneficial to the program (presented by Chirag Patel, PhD), including one FIH single ascending dose (SAD) study example (presented by Weiwei Tan, PhD), and regulatory considerations when evaluating the appropriateness of inclusion of NHV studies in an oncology drug development program (presented by Nicole Drezner, MD).

THROUGH THE LENS OF THE PATIENT

The first presentation illustrated some of the challenges facing clinicians when enrolling patients into an oncology

clinical trial. The majority of FIH studies in oncology are conducted in patients with incurable and/or refractory cancers who are highly symptomatic, have progressed on multiple lines of treatment, are often cachectic and weak, and struggle with fatigue. These patients are on multiple medications with potential for DDIs and have compromised or rapidly evolving functional renal or hepatic impairment. Not surprisingly, the greatest challenges for clinicians to patient enrollment and retention have been associated with inclusion/exclusion criteria dealing with comorbidities and concomitant medications.

Other challenges are subtle. Compassionate clinicians who run out of treatment options for their patients may inadvertently become subjective in their assessments of the patient's eligibility for the trial. Well-informed patients who want to be enrolled in anticipation of the possible therapeutic benefit can experience heightened anxiety, especially in blinded studies, when trying to determine if they are receiving the experimental treatment vs. the standard of care or placebo, or if the dosing cohort they have been assigned to will be sufficient for therapeutic benefit. Those patients are also more likely to under-report adverse events (AEs), motivated by the fear of dose reductions or being removed from the trial.

A discussion of challenges surrounding informed consent and decisional capacity in chronically ill and rapidly declining patients, particularly those who are less informed of their condition, raised the opposite issue. In extreme cases, the patient may not understand his or her own condition and may be further shielded by caregivers motivated by cultural or familial customs surrounding a cancer diagnosis.

The presentation also discussed geographic issues of access to care and the associated burden on patients and their caregivers by the need for numerous appointments. In particular the early-phase and clinical pharmacology-focused studies tend to include frequent returns for study assessments, such as PK blood draws and biopsies. Sample and tumor evaluation schedule optimization and consolidation across all study visits could help with patient retention.

The presenter noted that while study subjects' well-being is always the priority regardless if the study is conducted in patients or NHVs, nursing staff at oncology Clinical Research Units (CRUs) are likely to have a different focus and standards when assessing subject's well-being, than those conducting a study in NHVs at a phase I CRU.

OPPORTUNITIES FOR HEALTHY VOLUNTEER CLINICAL PHARMACOLOGY STUDIES IN ONCOLOGY DRUG DEVELOPMENT: TARGETED AGENTS, IMMUNOMODULATORY AGENTS, AND BEYOND

The second presentation provided an overview of the general advantages of conducting clinical pharmacology studies in NHVs (**Table 2**) with the goal of improved equipoise through exposure of fewer end-of-life patients to agents of undetermined efficacy. Examples of several targeted oncology agents were provided where up to two doses of the investigational agent were administered to NHVs, usually at the marketed approved doses.^{4–28} The most common AEs were headache, nausea, vomiting, and diarrhea, with only one study reporting serious AEs (SAEs) at the approved dose.⁹ Furthermore, four examples of immunomodulators (small molecule lenalidomide and pomalidomide and biologics mifamurtide and recombinant interferon- α) were also presented, which, although not free of potentially SAEs, have been successfully evaluated in NHVs with no SAEs following implementation of appropriate inclusion/exclusion criteria and risk mitigation strategies.^{29–37} An overview of how and when to optimally supplement oncology drug development with studies in NHVs was presented (**Figure 1**) with a short discussion on the utilization of NHV study data and how they can accelerate development timelines by helping make timely, well-informed, quality decisions.³⁸

Evaluation by a pharmaceutical company of the feasibility of conducting clinical pharmacology studies in NHVs instead of patients with cancer requires cross-functional collaboration (**Figure 2**). An example of such a systematic evaluation was illustrated via an overview of considerations evaluated by

Table 2 Practical advantages and disadvantages of conducting clinical pharmacology trials in NHVs vs. patients with cancer

	NHVs	Patients with cancer
Advantage	<ul style="list-style-type: none"> • Less expensive trials with lower cost per subject • Rapid subject accrual • Lower dropout rates • Homogenous study population (i.e., results not confounded by comorbidities and/or concomitant medications) • Allow for longer washout and “inconvenient” sampling • Rich PK data throughout the day • Require fewer sites and more consistent clinical operations • Better compliance resulting in fewer protocol deviations • Better quality data help make quicker decisions • Reduced burden on drug supplies 	<ul style="list-style-type: none"> • PK is relevant • PD can be measured and can detect early signals of efficacy (allow determination of receptor occupancy, collection of surrogate tissues and biopsies, imaging translational oncology) • Potential for benefit at therapeutic doses
Disadvantage	<ul style="list-style-type: none"> • Benefit-risk assessment imposes great minimization of risk (no potential benefit but safety risks) • The PK properties of the drug may differ between healthy volunteers and patients • PD measurements may be of limited or no use • Target related safety may be different in patients 	<ul style="list-style-type: none"> • Trial time is longer and may involve multicenter sites, thus increasing the clinical trial operational complications • PK data can be confounded by comorbidities and comedications and, thus more variable • Trial attrition rates, greater potential for noncompliance, and missing or erroneously collected data can confound safety and efficacy readouts

NHVs, normal healthy volunteers; PD, pharmacodynamic; PK, pharmacokinetic.

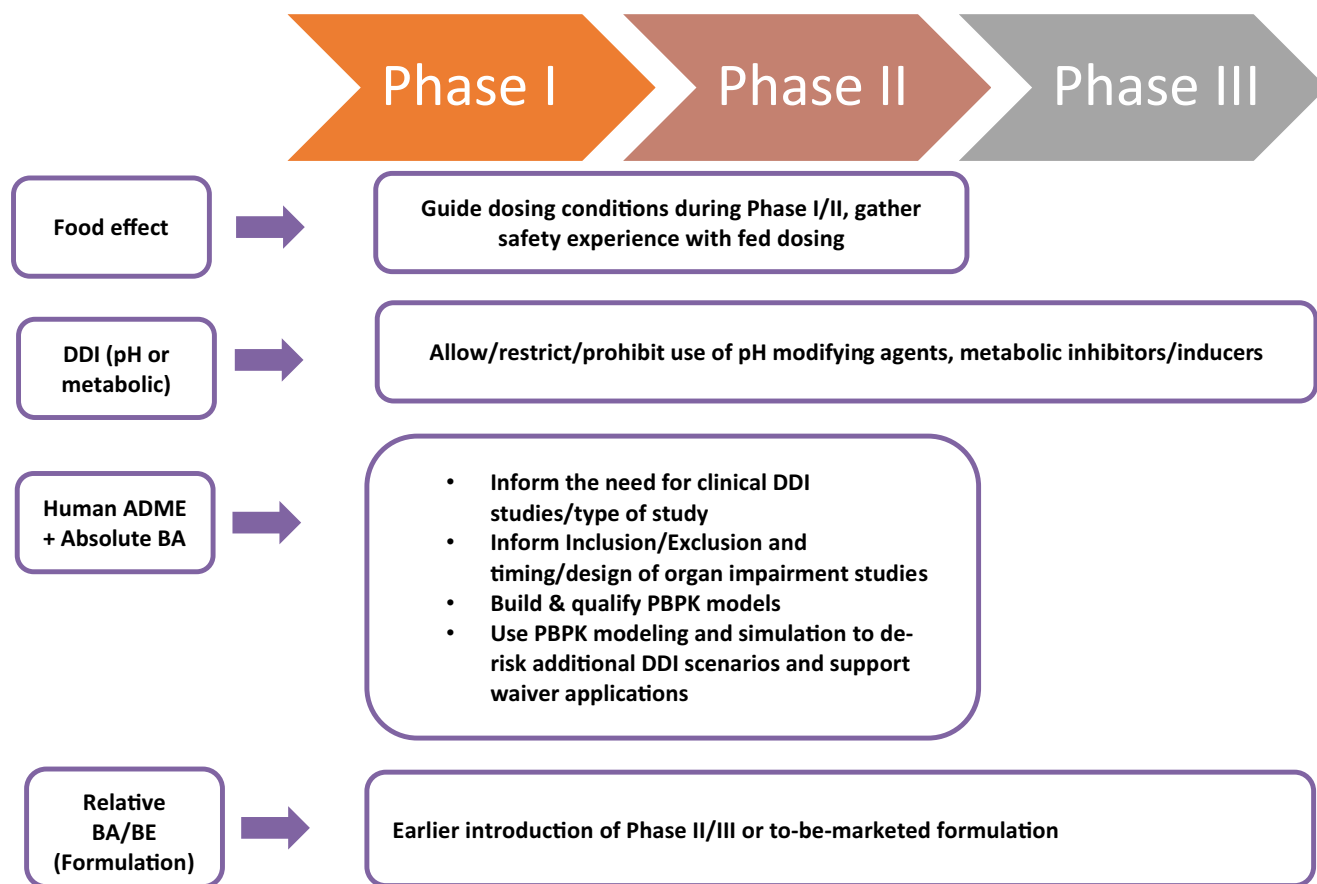


Figure 1 Potential deployment timeline and benefits of utilizing normal healthy volunteer (NHV) study data in oncology drug development. Note: NHV food effect and human absorption, distribution, metabolism, and excretion (ADME) studies are typically conducted prior to phase III studies. NHV drug-drug-interaction (DDI) and relative bioavailability/bioequivalence (BA/BE) assessments may be conducted throughout the drug development program. PBPK, physiologically-based pharmacokinetic.

Millennium Pharmaceuticals, Cambridge, MA, a wholly owned subsidiary of Takeda Pharmaceutical Company Limited, surrounding the decision to conduct clinical pharmacology studies of TAK-117, a small molecule, potent and selective oral PI3K α isoform inhibitor, in NHVs, in order to characterize the sources of high PK variability observed in an FIH study in patients with cancer (ClinicalTrials.gov: NCT01449370).³⁹

The FIH dose-escalation study was conducted in 71 patients with advanced solid tumors. Its objectives were to evaluate the safety, maximum tolerated dose (MTD), PK, pharmacodynamic, and preliminary antitumor activity of TAK-117 using the conventional 3 + 3 design.³⁹ Several once-daily and intermittent dosing regimens were evaluated in 21-day cycles until disease progression or unacceptable toxicities. Although TAK-117 plasma exposures were found to be generally dose-proportional over the 100–1,200 mg dose range evaluated, intersubject variability was high (area under the curve to infinity (AUC_{inf}) percentage of coefficient of variation of 39–85%). The MTD was 150 mg in the once-daily dosing cohorts and 900 mg in the intermittent dosing cohorts. This study also provided the basis for the TAK-117 recommended phase II dose (RP2D) of 900 mg monday, wednesday, friday (MWF) or monday, tuesday, wednesday (MTuW) in combination with docetaxel (ClinicalTrials.gov: NCT02393209).

TAK-117 is considered a Biopharmaceutics Classification System class 2 drug (i.e., high permeability and low solubility). TAK-117 exhibits a low and pH-dependent aqueous solubility profile, with a solubility of 4.5 mg/mL at pH 1 and 0.002 mg/mL at pH 5. These poor biopharmaceutical properties may help to explain the observed clinical PK variability of TAK-117 in patients with cancer. Near the end of this phase I study, a new tablet formulation was developed for introduction in future clinical studies. The tablets were developed to reduce the number of unit dosages that patients needed to take to achieve a dose of 900 mg TAK-117, and to enhance the solubility, thus reducing interpatient variability. A formulation bridging relative bioavailability study was, therefore, needed to bridge the capsule formulation to the tablet formulation of TAK-117. In addition, it was important to understand whether administration of TAK-117 in fed state would help reduce interpatient variability and whether co-administration with pH modifying agent can help explain the PK variability observed in the FIH study of TAK-117.

Thus, a single clinical study was planned to evaluate the relative bioavailability (formulation bridging), food effect, and impact of gastric acid modulators on TAK-117 PK. Given the scope of the assessments, such a study was not deemed feasible in oncology patients due to design considerations

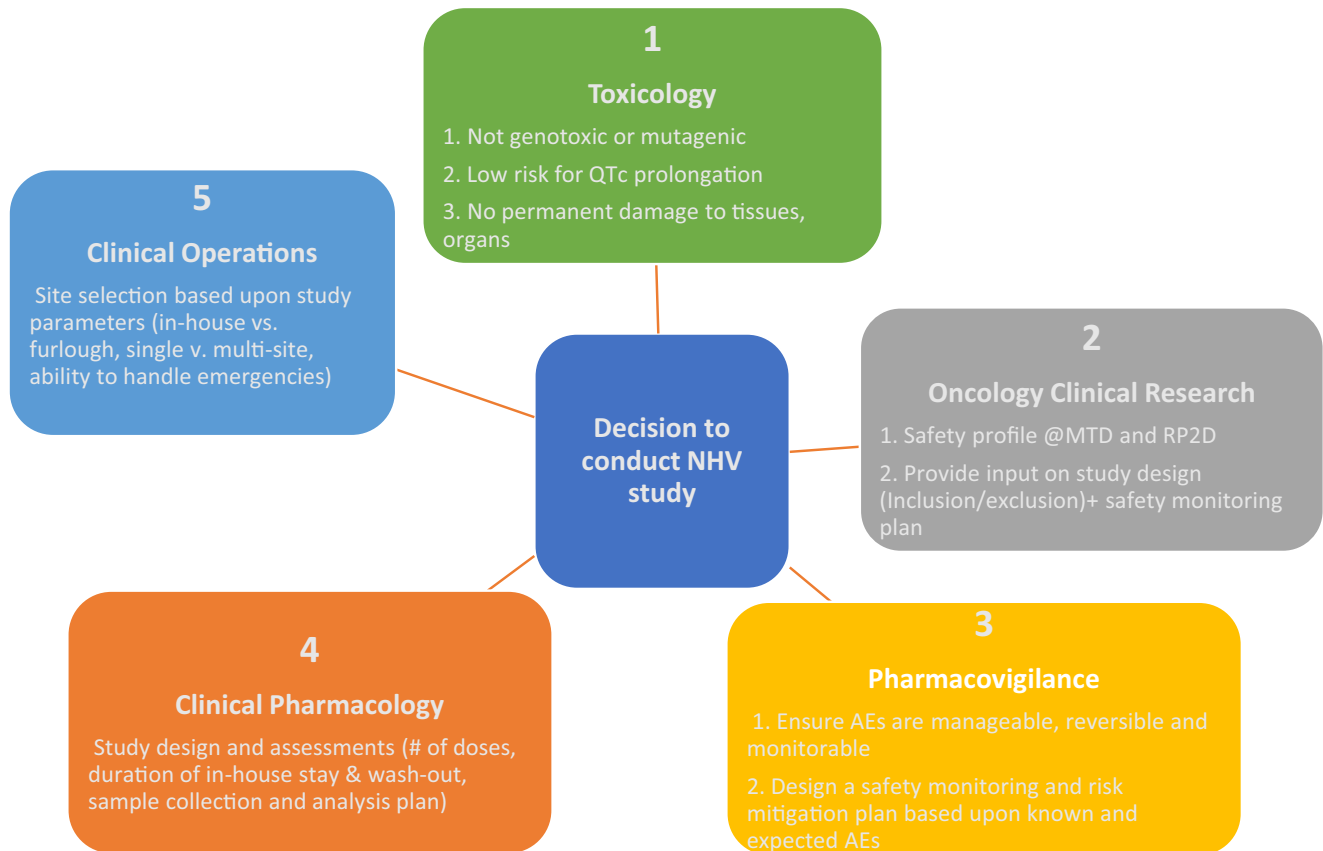


Figure 2 Systemic multidisciplinary assessment of feasibility of inclusion of normal healthy volunteers (NHVs). Note: The decision to include NHVs in oncology development spans different disciplines. The final decision is based on assessment of all available nonclinical (box 1) and clinical data (box 2) at the time of proposing the trial in NHVs, the nature of adverse events (AEs) available from clinical data (box 3), clinical study design (i.e., inclusion/exclusion criteria, dosing regimen, duration of the study, analysis plan, and safety monitoring plan; box 2 and box 4), and feasibility of the study in NHVs vs. patients (box 5). MTD, maximum tolerated dose; QTc, corrected QT; RP2D, recommended phase II dose.

and the projected timelines to complete the study (estimated at 2–3 years.) Thus, the feasibility of conducting this study in NHVs was evaluated through a holistic consideration of the clinical safety profile of TAK-117 and the nonclinical toxicology information.

TAK-117 was nonmutagenic and nongenotoxic. Although a single-dose safety profile was not available, safety profiles at both the MTD and RP2D were known, with all AEs manageable, reversible, and monitorable. TAK-117 did not cause hemolysis and was considered low risk for QT prolongation based on the results from a hERG assay and telemetry data. This systematic evaluation of the clinical safety profile of TAK-117 in the context of nonclinical toxicology supported conducting this second phase I study of TAK-117 in NHVs (ClinicalTrials.gov: NCT02625259).⁴⁰

The study consisted of three parts, which were conducted sequentially. Part 1 evaluated the PK and relative bioavailability of a new tablet formulation (3 × 300 mg) of TAK-117 as compared with current capsule formulation (9 × 100 mg). Following completion of part 1, parts 2 and 3 were conducted to assess, respectively, the interaction of TAK-117 tablets with food and when co-administered with a gastric pH modifying agent (lansoprazole 30 mg for 6 days).

Participants were confined to the clinic anywhere from 4–10 days, depending on study part, with one follow-up visit at 30–33 days after their last dose. No SAEs were observed. Most AEs were mild (grade 1) and resolved within a few days.⁴⁰

Results of this trial supported switching from the capsule to the new tablet formulation with an appropriate dose modification and also provided valuable information that would support the potential administration of TAK-117 with food (pending further characterization of food effect with alternate meal options, such as low fat/low calorie) to enhance oral absorption and improve the clinical tolerability profile. In addition, the data from the study confirmed the suspicion of a strong DDI of TAK-117 with proton pump inhibitors, providing valuable insight into this suspected source of PK variability in patients with cancer who rely on these and other types of gastric pH modifying agents for treatment of comorbid gastrointestinal conditions, and supporting the exclusion of such gastric pH modifying agents from being co-administered with TAK-117.

Collectively, this single study in NHVs provided substantial clinical pharmacology data in a single and concise clinical experiment to rapidly inform and implement an appropriate

dosing strategy for TAK-117 in downstream clinical studies. Most importantly, these results were available to the clinical team within 4.5 months from the first subject dosed in this NHV study.⁴⁰

APPLICATION OF HEALTHY VOLUNTEERS IN THE FIH STUDY FOR ONCOLOGY DRUG DEVELOPMENT

FIH dose-escalation studies with investigational oncology drugs are typically conducted in patients with advanced cancer who have not responded to available treatments. This presentation illustrated the application of an FIH SAD study that assessed the safety, tolerability, and PK of PF-04217903, a potential oncology drug candidate, in healthy adult subjects.⁴¹

PF-04217903 is a novel, small-molecule, selective, adenosine 5'-triphosphate-competitive inhibitor of the mesenchymal-epithelial transition factor receptor/hepatocyte growth factor receptor, which has been developed for targeted therapy in oncology.⁴² PF-04217903 showed marked antitumor activity in tumor mice models harboring mesenchymal-epithelial transition gene amplification and demonstrated clinical antitumor activity in a patient with mesenchymal-epithelial transition-mutated papillary renal cell carcinoma.

The FIH study aimed to evaluate the safety and tolerability of escalating single doses of PF-04217903, as well as the PK of both PF-04217903 and its metabolite PF-04328029, in healthy adult subjects under fed and fasted conditions. This study was a randomized, placebo-controlled, double-blind, single dose escalation study with a parallel-group design in 70 healthy subjects. Administered doses were 1, 4, 8, 15, 30, 60, 120, and 240 mg. The proposed starting dose of 1 mg was not expected to be associated with any pharmacological effect. Subjects within a dose cohort were randomly assigned to receive either PF-04217903 ($n = 6$) or placebo ($n = 2$) in the fasted state. In an additional cohort ($n = 6$), a single dose of 60 mg was administered in the fed state to estimate the effect of food. Single PF-04217903 doses up to 120 mg were safe and well-tolerated. Dose escalation was stopped at 240 mg due to elevations in alanine aminotransferase/aspartate aminotransferase in 2 of 6 subjects.

PK and safety data from this NHV study were used by the sponsor to recommend the starting dose for a dose-escalation, multiple-dose study of PF-04217903 in patients with advanced solid tumors (ClinicalTrials.gov identifier: NCT00706355). A dose of 50 mg b.i.d. was chosen as the starting dose of PF-04217903 in patients with cancer based on the following: (i) this dose was expected to result in plasma levels exceeding the predicted efficacious drug concentration for at least 50% of the dosing interval; and (ii) the predicted steady-state area under the curve (AUC) and peak plasma concentration (C_{max}) of PF-04217903 at 50 mg b.i.d. were expected to be below the lowest observed AUC and C_{max} at which dose-limiting AEs were observed in the NHV study. Notably, this selected starting dose of 50 mg b.i.d. for patients with advanced cancer was lower than the dose calculated by using the algorithm as described by DeGeorge et al.,⁴³ which was one-sixth of the highest dose that did

not cause severe, irreversible toxicity in non-rodents from a 1-month toxicity study. The 50 mg b.i.d. dose proved adequate and was only one dose level below the 100 mg b.i.d. dose identified as the MTD on this study in patients with cancer.

The presented FIH SAD study represents a unique example of the potential utility of a phase I clinical study conducted in NHVs to the development plan of an oncology drug candidate. Although a conservative starting dose was chosen for the NHV study, accrual of this population is generally very rapid and, safety permitting, a wider range of doses can be explored with a reasonably short trial conduct timeframe and may help inform a more appropriate starting dose in an FIH trial.

Nevertheless, in discussions following this conference, the FDA had some concerns about the FIH SAD example. The presented study shows that it is possible to justify including NHVs for an FIH study of an oncology product beginning at low doses and, depending on the available nonclinical data at the time of study initiation, extending to doses in the pharmacologically relevant range. The FDA oncology group does not, however, often actively encourage these designs at early stages of development because of concerns that single-dose data are unlikely to be sufficient to support continuous dosing in patients without sufficient nonclinical data that also support the proposed dose. In addition, whereas, in this example, the sponsor included a justification based on the NHV clinical pharmacology data to support the proposed 50 mg b.i.d. starting dose in patients, in many cases, using the animal data available at the time of original investigational new drug (IND) submission may result in a very similar patient starting dose as that suggested by the NHV exposure data. Given the differences in both the nonclinical expectations and safety margins used to support an FIH dose, as well as the flexibility in some clinical trial designs for drugs intended for the treatment of patients with cancer compared with those with less immediately life-threatening conditions, the utility of FIH NHV PK data may be less impactful in oncology than in other therapeutic areas. Therefore, a careful consideration of the utility of including NHV at very low dose levels for FIH trials of these drugs is warranted.

REGULATORY CHALLENGES IN THE USE OF HEALTHY VOLUNTEERS

The last presentation focused on regulatory considerations for mitigating the risk to NHV that support oncology drug development.

Regulatory guidance documents discussing considerations for initiation of clinical trials for investigational drugs in the oncology space include the International Conference on Harmonization (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use S9 guidance: Nonclinical Evaluation of Anticancer Pharmaceuticals,⁴⁴ the Committee for Medicinal Products for Human Use anticancer guidance from the EMA,⁴⁵ and the FDA Guidance for Industry for Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adults Healthy Volunteers.⁴⁶ The first two documents provide guidance on

early stage clinical drug development and a description of the type and timing of nonclinical studies in relation to the development of anticancer pharmaceuticals. The third describes a standardized process by which the maximum recommended starting dose may be selected for FIH trials of investigational agents enrolling NHVs, and, with the exception of the toxicological basis for determining the dose and the actual safety factor applied, this guidance is also relevant for selecting the dose for FIH trials in patients with cancer. International standards for the safe conduct of human clinical trials, including the supportive nonclinical and clinical pharmacology safety requirements, are summarized in the ICH M3, S7A, and S7B guidelines.^{47–49}

In the setting of oncology drug development today, the use of single-dose or limited-dose studies for collection of supportive clinical pharmacology is not uncommon, especially in the development of nonclastogenic targeted small molecules. The FDA is extremely cautious regarding the use of NHV in FIH clinical studies of investigational oncology agents for two major reasons: concerns about the usefulness of these studies in supporting continuous dosing in the intended patient population, and that even noncytotoxic anticancer agents generally have significant side effects at effective doses. Given that clinical studies are generally not conducted in NHVs, the ICH S9 guidance provides advice regarding a streamlined set of nonclinical studies expected to support both IND and marketing applications for drugs intended for the treatment of patients with cancer. The guidance includes advice that allows for higher starting doses and greater toxicity than for drugs in other therapeutic areas to expedite the process of determining an effective dose and limit the number of patients treated at subtherapeutic levels.

Sponsors using the ICH S9 guidance to plan the nonclinical program needed to support clinical development may, therefore, have to conduct additional studies or include additional end points in such studies provided in their nonclinical packages, to support exposure of NHVs early in clinical anticancer drug development. Clinical trials enrolling NHVs use a more conservative algorithm for determining the FIH starting dose than trials intended for the treatment of patients with cancer. For example, in clinical trials of small molecule drugs and some biologic drugs conducted in patients with advanced cancer, one-tenth of the severely toxic dose in 10% rodents or one-sixth of the highest nonseverely toxic dose in non-rodents is considered an appropriate starting dose⁴⁴; however, when considering starting doses in NHVs, one-tenth of the human equivalent dose calculated from a “no observed adverse effect level” (NOAEL) or a “no observed effect level” in the most sensitive species is used.⁴⁶ Therefore, in contrast to the advice in ICH S9 that identification of the NOAEL or no observed effect level is not essential in the 28-day repeat-dose toxicology studies, determination of an NOAEL is important when trying to support FIH dosing in NHVs. In addition, in the absence of clinical experience in the intended patient population, the maximum studied dose in NHVs should not exceed the NOAEL, based on exposure at doses evaluated in the preclinical studies.

Per the ICH S9 guidance, use of the minimally anticipated biological effect level may be warranted to determine a

reasonably safe starting dose for products, such as immune modulating products, in which nonclinical models may not accurately reflect toxicity in humans. This approach should be considered if risk factors are derived from knowledge of (i) the mode of action, (ii) the nature of the target, and/or (iii) the relevance of animal or *in vitro* models.⁵⁰ Such an approach may apply to FIH trials in patients with cancer as well as NHVs.

The core battery of safety pharmacology studies, including assessment of cardiovascular, central nervous, and respiratory systems, should be conducted in accordance with the ICH S7A and S7B guidelines prior to exposure in NHVs, although the *in vivo* end points can be included in general toxicology studies, consistent with advice in ICH S9 guidelines.^{44,47,49} In addition, at minimum, the results of *in vitro* genotoxicity studies are required prior to dosing in NHVs regardless of whether they are FIH studies or later in clinical development to investigate PK end points. These studies are typically not required until submission of a marketing application when sponsors only include patients with cancer in clinical trials.

The clinical study design must ensure that NHVs have only limited exposure to an anticancer drug (a maximum of 1 or 2 doses), given the potential for toxicity. Moreover, a plan for careful observation of effects on major organ systems, early identification of safety signals that were detected in the preclinical studies, and early detection of AEs, which may not have been observed or predictable using the standard battery of tests (e.g., antibody formation) should be included in the protocol.

For NHV studies of anticancer drugs for which there is prior human experience, inclusion criteria should be carefully evaluated and adjusted as necessary based on emerging safety information from studies in patients with cancer or NHVs. For FIH studies, additional risk mitigation strategies should be considered for predicted risks and cessation of exposure at the first evidence of toxicity in NHVs.^{51,52} One-dose to two-dose studies investigating specific clinical pharmacology end points may rely on the known toxicity profile of the drug following continuous dosing in patients to help support the safety of the proposed dose. Investigators may, however, be directed to lower the dose of an oncology drug in a limited duration NHV study compared with the RP2D or MTD in patients with cancer.

In an FDA review of phase I trials of anticancer drugs to be conducted in NHVs submitted to IND applications between 2003 and 2004, eight NHV studies were identified for the following types of products: signaling agents ($n = 2$); receptor modulators ($n = 3$); growth factors ($n = 2$); and a chemoprevention agent ($n = 1$). In all eight of the proposed studies, the genotoxicity battery results were negative in all studies or in the *in vitro* studies. The starting dose was less than or equal to one-tenth the rodent NOAEL in three of the studies and was based on previous clinical data in the remaining five studies. Six were single-dose studies, one was a two-dose study, and one study evaluated five daily doses.⁵²

Immune checkpoint inhibitors and other immunomodulators, which are emerging as treatment options for multiple tumor types across all lines of therapy, either remove

blockades on a patient's immune system to recognize tumor or attempt to directly stimulate or enhance the patient's immune response to cancer. Because of their unique mechanisms of action, these agents present new development and regulatory challenges.⁵³ These challenges are exemplified by the 2006 TeGenero tragedy, in which a double-blind, randomized, placebo-controlled phase I study of the CD28 super-agonist theralizumab (TGN1412) in NHVs was conducted in the United Kingdom. Within a few hours of infusion, all six NHVs developed life-threatening severe inflammatory reactions resulting from rapid release of cytokines by activated T cells.^{54,55} These SAEs were not anticipated by the investigators despite preclinical studies in peripheral blood mononuclear cell culture and cynomolgus macaques. The 2007 EMA guidelines⁵⁶ were published in part as a response to this event, and put an increased emphasis on the relevance of animal models, a revision of strategies to determine the starting dose (including the concept of minimally anticipated biological effect level), and an adaptation of safety measures for FIH studies (e.g., "sentinel" cohort and intensive care access). Despite these updated safety regulations, the risks of immunomodulators are unlikely to support early development in NHVs without a compelling reason for why the same study cannot be conducted in patients with advanced cancers.

DISCUSSION

According to ClinicalTrials.gov, as of June 2018, there were > 5,000 ongoing trials in oncology in the United States alone, requiring the participation of hundreds of thousands of patients.⁵⁷ Other sources estimate that only 1 in 20 adult patients with cancer enroll in a clinical trial for their cancer therapy.^{58,59} By identifying and mitigating the barriers to trial participation for patients with cancer, the pharmaceutical industry could enable more patients to have the opportunity to enroll in a clinical study.

Unger *et al.*⁶⁰ have characterized the nature of the barriers to enrollment in cancer trials and have classified them into structural (i.e., access to a cancer clinic and availability of clinical trial), attitudinal (i.e., physician preferences in treating their patients and patient's preference/choice), and clinical barriers (i.e., narrow patient eligibility and exclusion of patients with comorbid conditions). Structural barriers can be geographic and logistical, including the need to travel to and from a cancer clinic, as clinical trials often require frequent monitoring and assessments; these barriers are outside the scope of clinical pharmacology. Attitudinal barriers can be a consequence of trial design, where patients may choose not to participate in a clinical trial due to the anxiety associated with receiving an investigational treatment (i.e., randomization uncertainty), fear that the treatment may be less effective than the standard of care, fear of potential toxicities that may further lower their quality of life, and/or fear of receiving a subtherapeutic dose that will be of no benefit. Attitudinal barriers associated with fear of receiving subtherapeutic doses are amplified in FIH trials, even though FIH trials in patients with cancer typically use higher doses than would be supported in trials for less life-threatening indications and/or use more aggressive dose escalation strategies. Clinical

pharmacology data may, however, play a role in helping to overcome these types of attitudinal barriers for enrollment in other phase I, II, and III trials, as well as in alleviating concerns regarding loss of activity in patients following changes in formulation or manufacturing. Helping to mitigate some of the clinical barriers regarding eligibility of patients with comorbidities and on concomitant medications is also within the realm of clinical pharmacology.

Clinical pharmacology can aid in expanding access to trials for all patients, including traditionally excluded patient populations by: (i) mitigating and evaluating risks from extrinsic and intrinsic factors (i.e., DDIs, organ impairment, and comorbidities); (ii) leading patient-centric trial designs by minimizing assessment burden in patients while maximizing potential for benefit; and (iii) throughout drug development, continuously evaluating and concisely presenting evidence to patients and investigators that patients will potentially benefit from a particular agent, at the tested dose, with minimal risk to their safety. Emergence of novel noncytotoxic treatment modalities in oncology, such as immunomodulators and molecularly targeted agents, has opened up opportunities to conduct certain types of clinical pharmacology studies in NHVs to more quickly inform studies in patients.³⁸ The practical advantages and disadvantages of conducting an oncology drug trial in NHVs are summarized in **Table 2**.

Advantages of conducting a study in NHVs

Trials conducted in NHVs recruit more quickly than those conducted in patients due to a much larger normal healthy population base, and tend to have better protocol compliance. NHVs are generally in good health with no major comorbidities and can be controlled for intrinsic (i.e., age, ethnicity, and renal and hepatic functions) and extrinsic factors (i.e., concomitant medications and smoking status), thereby limiting and controlling sources of potential PK variability and allowing for more impartial safety assessments. Studies conducted in NHVs can often be completed at a single center, eliminating site-to-site variations in procedures.

Typically, early studies in NHVs comprise confinement to the CRU until discharge.⁶¹ Confinement allows for rich PK sampling schemes, including at "inconvenient" times, and allows for closer safety monitoring and management of safety events. Clinical pharmacology studies requiring crossover design and prolong washout can be very challenging in patients but are standard in NHVs. These considerations lead to faster availability of better-quality data, allowing for quicker and more accurate strategic decisions.

Disadvantages of conducting a study in NHVs

Because NHVs participating in clinical trials gain no personal benefit, any risk must be minimized compared with the risks considered acceptable in patients who may receive a benefit from the therapy being evaluated. Therefore, there is a higher burden on the quantity, quality, the level of data interpretation, and risk tolerance reflected in the differences in regulatory requirements for preclinical toxicological investigation and determination of an appropriate starting dose for clinical investigation in patients with cancer⁴⁴ vs. NHVs.^{48,56}

Furthermore, drug candidate trials in NHVs offer no opportunity for any efficacy assessments, as the target pathways are generally expressed on or in the cancer cell.^{62,63} In addition, a pathway that is expressed to a lesser extent in NHVs than in patients may be saturated in NHVs more quickly than in patients, potentially resulting in significant toxicities at concentrations that may not elicit an effect in patients. In those cases, a trial conducted in NHVs may hinder rather than aid a drug development program.

There are also interpretational considerations if the PK properties of the drug differ greatly between NHVs and patients with the target disease. This is often the case when PK depends on the amount of target ligand present. Target-mediated disposition is not unique to oncology, as it can occur with any drug that binds with sufficiently high affinity to its pharmacological target site to affect its PK characteristics.⁶⁴ NHVs may express such a target ligand or receptor to a lesser degree than patients or may not express it at all. Thus, for agents exhibiting target-mediated disposition, a trial in NHVs may yield PK information that is unhelpful because it is not predictive of what will be observed in patients with the targeted disease. Nevertheless, with advances in understanding of cancer biology and evolving disease progression models, modeling and simulation approaches, such as physiologically-based pharmacokinetic (PBPK) modeling approaches, can aid in bridging results from NHVs to patients. PBPK combine anatomic and physiological data from the given patient population with the drug-specific parameters that describe the absorption, distribution, metabolism, and excretion of the drug.^{65–67} However, verification of the PBPK prediction is necessary and without this verification drugs cannot be tested using the virtual cancer population. Verification could be accomplished by successful prediction of observed PK data of a drug or group of drugs in patients with cancer. Work is still ongoing for evaluation of the ability of PBPK model to accurately predict outcomes in patients with cancer.

CONCLUSIONS

Emergence of novel noncytotoxic treatment modalities in oncology has created opportunities to consider conducting clinical pharmacology studies in NHVs to inform studies in patient populations. Conducting trials in NHVs may be beneficial for drug developers with respect to study timelines, costs, and data quality; however, these studies must be supported with more rigorous preclinical toxicologic assessments relative to those required for studies conducted in patients. The drug candidate's PK characteristics may differ in NHVs vs. patients, or its mechanism of action may contraindicate conducting studies in NHVs entirely. Therefore, decisions regarding the inclusion of NHVs in oncology trials should be made following a systemic multidisciplinary feasibility assessment focused on risk minimization to subjects, including an accurate prediction of immediate and delayed toxicities as well as the implementation of potential mitigation strategies.

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