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# Leveraging Healthy Volunteers for Anticancer Drug Clinical Pharmacology Studies: A Review Article Featuring Futibatinib as an Example

Aernout D. van Haarst[1] | Sabina Paglialunga[1] | Ziv Machnes[1] | Ikuo Yamamiya[2] | Nanae Hangai[2] | Aram Oganesian[2]

[1]Celerion Inc., Lincoln, Nebraska, USA | [2]Taiho Oncology Inc., Pleasanton, California, USA

**Correspondence:** Aram Oganesian (aoganesian@taihooncology.com)

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## ABSTRACT

Early clinical development of anticancer drugs traditionally focused on exploring candidate treatments in patients. For instance, due to their cytotoxic action, administration of chemotherapies to healthy volunteers (HVs) for evaluation of their pharmacokinetic profiles was not considered feasible nor ethical from a safety and tolerability perspective. With the introduction of more targeted anticancer agents, such as the tyrosine kinase inhibitors (TKIs), enrolment of HVs in clinical pharmacology trials has become an advantageous alternative to early, non-therapeutic testing in cancer patients. Futibatinib (Lytgobi) is a TKI acting upon the fibroblast growth factor receptor (FGFR) 1–4 and is approved for the treatment of patients with locally advanced or metastatic intrahepatic cholangiocarcinoma harboring FGFR2 gene fusions or other rearrangement. During its clinical development, a series of studies were conducted enrolling HVs, for example, to evaluate pharmacokinetic properties (ADME), drug–drug interaction (DDI) potential and QT liability. In this review article, we will discuss when and why enrolment of HVs can be considered for small molecule anticancer drug trials and touch upon the risks and limitations as well as the advantages of administering this type of drugs to HVs. The case of futibatinib provides an illustrative example of the opportunities and challenges for exploring an anticancer small molecule in HVs.

## 1 | Introduction

Targeted oncology therapies represent a promising tool in the treatment "toolbox" to inhibit tumor cell growth and proliferation. Specifically, receptor kinase inhibitors have substantially changed the landscape of cancer treatment, providing safe and effective oral medication for patients across a wide range of cancers [1]. Tyrosine, serine, and threonine kinases and their receptors tend to be overexpressed in tumor cells [2], where they are involved in regulating cell proliferation, migration, and angiogenesis; thus, these are ideal targets for drug developers. This targeted approach to cancer treatment is a major improvement over traditional chemotherapy that can damage both tumor and healthy cell DNA resulting in cytotoxic effects. Although kinase inhibitors may still hold risks of adverse reactions, they are considered non-genotoxic agents that are relatively well tolerated.

There are currently more than 20 tyrosine receptor kinase inhibitors approved for various cancers [3]. Since receptor kinase inhibitors generally display a good safety profile and do not interfere with DNA, many regulatory agencies permit drug developers to engage healthy volunteers (HVs) for clinical pharmacology studies to support the drug label. Indeed, HVs have successfully been enrolled in clinical trials administering investigative anticancer drugs to expedite drug development since 2001. Imatinib was the first tyrosine kinase inhibitor (TKI) approved for chronic myelogenous leukemia. Its development program also leveraged HVs for clinical pharmacology studies [4]. Futibatinib, a novel

small molecule drug that is a highly selective inhibitor of fibroblast growth factor receptor (FGFR) 1–4, is another example of a TKI for which clinical pharmacology studies heavily relied on enrolment of HVs. To shorten its development timelines, operational and design efficiencies were gained by enrolling HVs for all clinical pharmacology trials.

There are several benefits of considering HVs for anticancer drug development, especially for single-dose clinical pharmacology assessments. These include rapid participant enrolment, extensive and complete pharmacokinetic (PK) characterization in the absence of comorbidities or concomitant medications, and conduct at a well-controlled clinical research unit, which contributes to the statistical rigor of the trial (Table 1). Moreover, the number of sites needed for subject recruitment as well as the mean time to study completion is dramatically reduced, for example, 1–2 months for DDI studies for futibatinib and other TKI DDI studies listed on www.clinicaltrials.gov enrolling HVs versus 7–60 months for patient DDI studies (see Figure 1 and Table S1). This approach is an advantageous alternative to early, non-therapeutic testing in cancer patients, where patients may be hesitant to participate in a trial if there is no potential benefit.

To illustrate how the clinical development of an anticancer drug can benefit from enrolment of HVs, this article will feature the development of futibatinib and may serve as a roadmap for drug developers who are considering HV trials for receptor kinase inhibitors. Futibatinib was granted accelerated approval by the FDA in September 2022 for adult patients with locally advanced or metastatic intrahepatic cholangiocarcinoma harboring FGFR2 gene fusions or other rearrangement [8]. The FDA's Accelerated Approval Program allows for an earlier approval of a drug if it is aiming to address a serious, unmet medical need. As previously expressed by Gandhy et al. [9] the FDA based their decision on the durable overall response rate and safety profile observed in the TAS-120-101 (FOENIX-CCA2; NCT02052778)

**TABLE 1** | Potential advantages & limitations of enrolling healthy volunteers for Phase 1 anticancer trials.

| Factors | Advantages | Limitations |
|---|---|---|
| *Operational and study design* | • Single center study | • Often only a single dose administration is acceptable for HVs |
| | • Fast recruitment | |
| | • Potential for faster dose escalation in SAD study compared to 3 + 3 scheme in patients | |
| | • Integrate additional study aspects, for example, food effect or drug interactions | |
| | • Reduced costs (associated with faster enrollment and single site approach) | |
| | • Can plan for longer washout period, and obtain "inconvenient" sampling as needed | |
| *Data quality and outcomes* | • Opportunity to collect extensive data for PK characterization | • Limited feasibility of pharmacodynamic (PD) or target engagement assessments |
| | • High quality data can facilitate rapid decision making | • Potential PK data does not appropriately translate from HVs to cancer patients |
| *Participant safety and experience* | • Safety profile not confounded by disease state or progression | • Risk of suspected unexpected serious adverse reaction (SUSAR) and unacceptable tolerability for HVs |
| | • Avoids variability caused by comorbidities and/or concomitant medication | • Safety assessments/targets in HVs may differ in patients |
| | • HVs are accustomed to participating in clinical pharmacology studies in which there is no clinical benefit | |
| | • Lower dropout rates | |
| | • Can tolerate multiple and frequent observations | |
| | • Better participant compliance and often fewer protocol deviations | |
| | • Monetary compensation for compliance and study completion | |

*Note:* Adapted from Refs. [5–7].
Abbreviations: HV, healthy volunteer; PK, pharmacokinetic; SAD, single ascending dose.

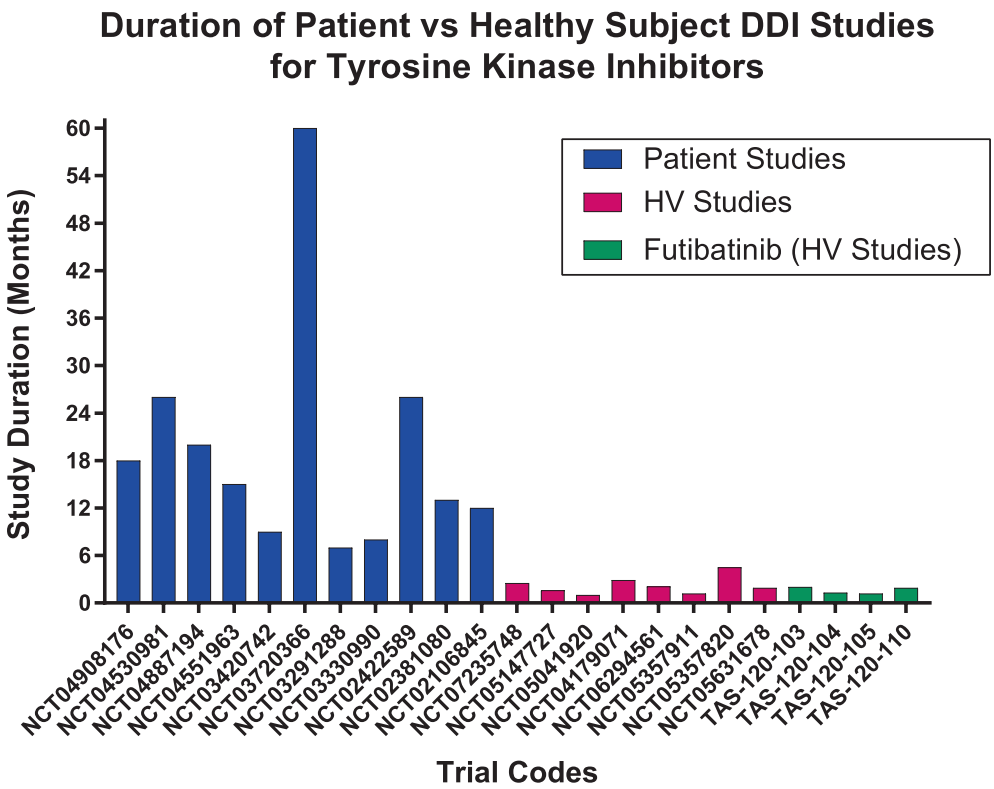


**FIGURE 1** | Duration of patient and healthy volunteer DDI studies for tyrosine kinase inhibitors, including futibatinib. Duration in months of DDI studies for TKI trials enrolling patients (blue) or HVs (pink). HV DDI studies for futibatinib are shown in green. See Table S1 for full list of study drugs, interacting precipitants, and substrates.

trial. The accelerated approval path of futibatinib, including the timing of clinical pharmacology studies, is presented in Figure 2.

## 2 | First-in-Human Studies: Patient Versus HV Participants

Traditional chemotherapy drugs are prohibited to administer to HV participants due to their genotoxic properties. Newer, more specific cancer treatments like TKIs have a favorable safety profile as they are not genotoxic agents. Consequently, a single (and in some cases multiple) administration(s) is considered ethically feasible for an HV study with a kinase receptor inhibitor. For that reason, studies focusing on PK collection are ideal for this approach (Table 2). Both small molecules [5–7] and immunetherapies [23] can benefit from enrolling HVs for early stage and labeling studies. Here we outline three pathways available for anticancer drug development (Figure 3). Compared to the traditional path in which all studies enroll cancer patients, efficiencies can be gained in clinical pharmacology studies by leveraging HVs in either a "hybrid" or "HV first" approach. In contrast to the "traditional" pathway, in which safety data as per ICH S9 nonclinical guidance support clinical development in cancer patients (only), a hybrid approach would start with dose escalation studies in patients and only thereafter proceed with HV studies, supported by negative genotoxicity findings (ICH S2B) and utilizing a narrow range of doses, to form the basis for the clinical pharmacology program. A somewhat more ambitious approach is the "HV first pathway," where nonclinical studies are conducted according to ICH M3(R2) to allow FIH studies in HVs before entering patient efficacy trials, while also leveraging HVs for clinical pharmacology trials (Figure 3). In the case of futibatinib, the hybrid scenario was followed and HV trials expedited drug development timelines and ultimately supported drug approval (Figure 2). The findings obtained during these Phase 1 studies were applied to inform the drug label.

## 3 | Defining Acceptable Risks When Considering HV Trials for Anticancer Drug Development

For all drugs in development, a comprehensive series of nonclinical data are needed before considering entering into clinical phase trials. The required study types are outlined in various ICH guidance documents detailing safety pharmacology, toxicokinetic, general toxicology and genetic toxicology for nonclinical development. Table 3 describes the nonclinical studies typically required to initiate a first-in-human (FIH) study following two main regulatory paradigms: ICH M3(R2) [24] for small molecules in general or ICH S9 [25] for anticancer pharmaceutics.

The timing of nonclinical studies for futibatinib relative to key regulatory milestones (e.g., investigational new drug [IND] application or new drug application [NDA] submissions) and commencement of HV trials is outlined in Table 3. Safety pharmacology studies conducted in rats and dogs revealed that futibatinib had no effects on central nervous or respiratory systems [10]. Cardiovascular pharmacology studies conducted in vitro indicated that futibatinib has the potential to inhibit the human

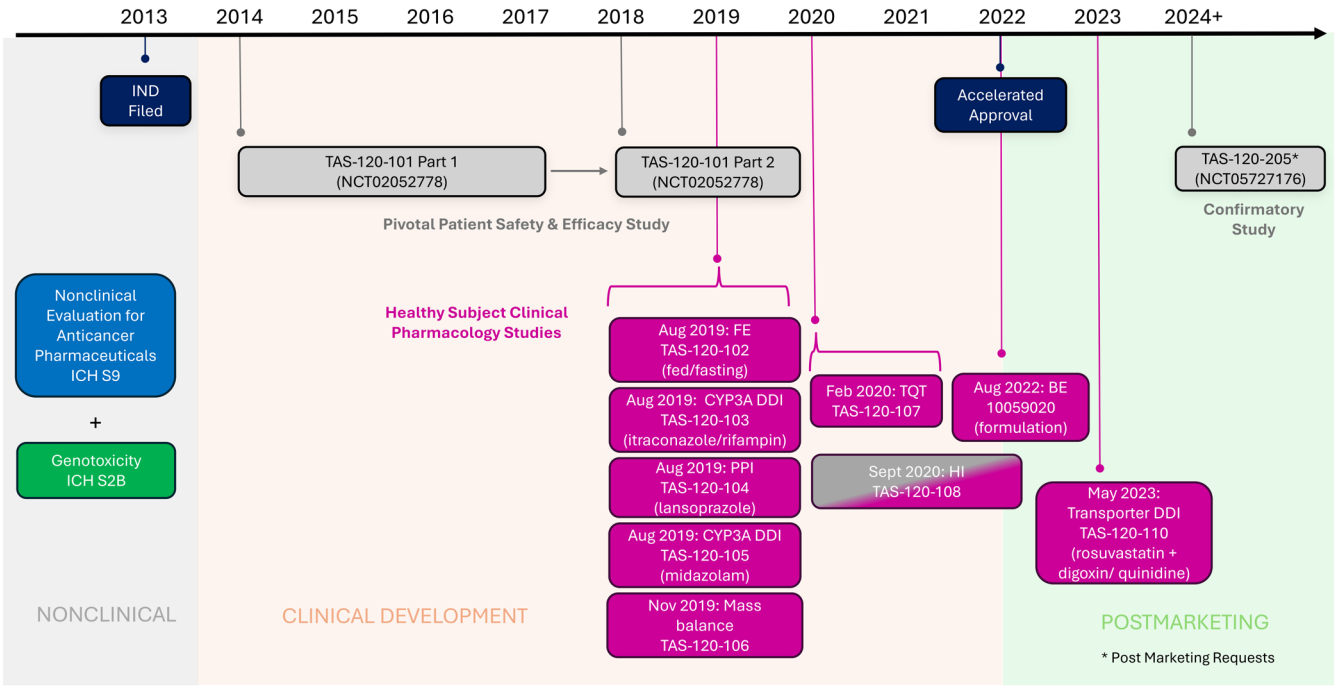


**FIGURE 2** | Accelerated approval pathway of futibatinib and timeline of clinical pharmacology trials in healthy volunteer. Timeline and overview of clinical trials conducted to support accelerated approval of futibatinib for the treatment of adult patients with previously treated, unresectable, locally advanced or metastatic intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 (FGFR2) gene fusions or other rearrangements. Clinical pharmacology studies such as DDI, FE, and BE trials enrolled HVs to help expedite timelines. The confirmatory trial TAS-120-205 is ongoing and expected to conclude in 2027. Key regulatory milestones are shown in navy, patient studies in gray, and clinical pharmacology studies in HVs in pink. Hepatic impairment PK study is displayed as gray and pink two-tone, as it enrolled patients with liver disease and healthy matched controls. See text for study details. Protocol numbers as listed in futibatinib NDA multi-discipline review dossier under Summary of Clinical Pharmacology Assessment [10]. BE, bioequivalence; CYP3A, cytochrome P450 3A; DDI, drug–drug interaction; FE, food effect; HI, hepatic impairment; IND, investigational new drug (application); MDZ, midazolam; PPI, proton pump inhibitor; TQT, thorough QT.

ether-à-go-go-related gene (hERG) current, however, the half-maximal inhibitory concentration (IC50 value: 3105 ng/mL) was much higher than the maximum concentration ($C_{max}$) of 531 ng/mL observed at a severely toxic dose in dogs and the peak exposure in humans at the recommended clinical dose of futibatinib, that is, 20 mg once daily (QD) [10]. Based on these nonclinical results, futibatinib was considered to be safe for human testing.

Next, the data obtained from nonclinical studies must be scrutinized to determine whether an anticancer therapy would satisfy a safety threshold to allow its administration in HVs. There are several considerations to this assessment; however, three key aspects subsequently discussed include (i) the lack of genotoxicity of the investigational drug, (ii) determining a safe dose (for a FIH study), and (iii) understanding and monitoring for known drug class effects.

### 3.1 | Assessing Genotoxicity Potential

Genetic toxicity is the potential of an investigational product to induce genetic damage (genotoxicity) and/or mutations to DNA (mutagenicity) and is evaluated in a battery of in vitro assessments. Drug developers have two options to evaluate these endpoints, using bacterial and mammalian cell models [27]. In the first instance, an Ames test using bacteria (*Salmonella typhimurium* or *Escherichia coli*) to detect reverse mutations is complemented with mammalian liver S9 fraction (rat or mouse) evaluation for the induction of cell mutations, chromosomal aberrations, or micronucleus changes. The alternative approach is to evaluate the Ames test in combination with an in vivo genotoxicity assay such as a rodent combined COMET and micronucleus test. The COMET assay is a sensitive single-cell gel electrophoresis method to detect DNA damage [28]. In either scenario, a negative finding supports a "nongenotoxic" determination, while further evaluation is highly recommended for any positive results. It is interesting to note that a positive genotoxic finding does not automatically preclude HV studies. A review of market authorization applications for small molecule anticancer drugs submitted to the European Medicines Agency (EMA) between 2010 and 2019 revealed that 12 out of 48 investigational drugs examined in HVs had an initial positive genotoxic finding [7]. Additional nonclinical studies were able to determine that these anticancer drugs were aneugenic at doses higher than human exposure doses or supplemental data supported a no or weak clastogenic effect, and, thus, the totality of evidence was used to form the basis of safety assessment to proceed with HV studies.

In the case of futibatinib, a battery of genotoxicity studies was completed in order to conduct a series of clinical pharmacology studies in HVs. Genotoxicity assessment was found to be negative in an Ames assay and, thus, futibatinib was considered

**TABLE 2** | Examples of clinical studies enrolling healthy participants.

| Study types | Number of HVs | Protocol No.[a] [reference] |
|---|---|---|
| *Futibatinib trials* | | |
| DDI: CYP3A precipitants (Part 1: itraconazole; Part 2: rifampin) | 40 (20 each part) | TAS-120-103 [11] |
| DDI: PPI (lansoprazole) | 20 | TAS-120-104 [12] |
| DDI: CYP3A substrate (midazolam) | 24 | TAS-120-105 [11] |
| DDI: Transporter substrates (Part 1: rosuvastatin + digoxin)/inhibitor (Part 2: quinidine) | 20 (Part 1)/24 (Part 2) | TAS-120-110 [13] |
| Food effect | 17 | TAS-120-102 [12] |
| Mass balance | 6 | TAS-120-106 [14] |
| Thorough QT (TQT) | 48 | TAS-120-107 [15] |
| Hepatic impairment | 16 healthy matched controls | TAS 120–108 [16] |
| Bioequivalence | 24 | 10059020 |
| *Examples of additional trial types* | | |
| Single ascending dose (SAD) | ~8 per cohort | [17, 18] |
| Multiple ascending dose (MAD)[b] | ~8 per cohort | [17, 18] |
| Pharmacodynamic (e.g., target engagement/receptor occupancy) | ~8 per cohort for exploratory purposes | [19] |
| Bioavailability (incl. FE, formulation change) | ~12–16 if not powered | [12, 20] |
| Renal impairment | ~6–8 matched controls | [21, 22] |

*Note:* Clinical pharmacology studies contributing to the futibatinib development program are listed, as well as additional study types in which other TKI clinical pharmacology studies were conducted in healthy participants.
Abbreviations: BE, bioequivalence; CYP3A, cytochrome P450 3A; DDI, drug–drug interaction; FE, food effect; HV, healthy volunteer; NDA, new drug application; PPI, proton pump inhibitor.
[a]Protocol number listed in futibatinib NDA multi-discipline review dossier under Summary of Clinical Pharmacology Assessment [10].
[b]Good safety profile required for multiple doses up to 14 days in HV participants.

not mutagenic. Although there were clastogenic findings in the in vitro chromosomal aberration assay after 6 h of treatment, there was no induced clastogenicity with continuous treatment. In addition, both rat bone marrow micronucleus and rat DNA damage (COMET) assays were negative across doses of 0, 30, 100, 300 mg/kg [10]. Altogether, when considering the totality of genotoxicity evidence, the negative in vivo studies and mutagenicity assays support a non-genotoxic determination for futibatinib.

### 3.2 | Dose Selection

Depending on the nonclinical safety profile, drug class, development timelines and company strategy, anticancer drug developers may opt for their FIH study to be conducted in either HV or patients (Figure 2), supported by nonclinical guidance documents ICH M3(R3) [24] or ICH S9 [25], respectively.

For many FIH studies planning to enroll HVs, the no observed adverse effect level (NOAEL) is determined based on the most sensitive species, then is converted to a human equivalent dose (HED) with a 10-fold safety margin, as outlined in the FDA guidance, "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers" [29]. In addition to dose selection, important safety factors in early stage trials in HVs include sentinel dosing, limiting exposure of an investigational drug (small cohort size), and rigorous safety data review prior to dose escalation.

When the FIH study is to be conducted in patients, per ICH S9 "Nonclinical Evaluation for Anticancer Pharmaceuticals," toxicology studies to determine the NOAEL are not considered essential to support clinical use of an anticancer pharmaceutical (in cancer patients) [25]. A common approach for many small molecules is to set a starting dose at 1/10 the severely toxic dose in 10% of the animals (STD10) in rodents.

Following the ICH S9 pathway, general toxicity studies for futibatinib included both rat and dog studies to evaluate administration over 4 and 13 weeks with either every day (QD) or every-other day (QOD) regimens. Drug-related findings in both animal models included elevated plasma phosphate and calcium, ectopic mineralization in multiple tissues, and lesions in both bone and cartilage [10]. As noted below, these findings are mechanistically related to FGFR inhibition on mineral homeostasis and were confirmed as reversible except for ectopic mineralization. Overall, in rats a STD10 of 10 mg/kg was established in the QOD regimen and no STD10 was observed for 3 mg/kg QD dosing. The STD10 of 10 mg/kg for futibatinib was converted to a HED, and

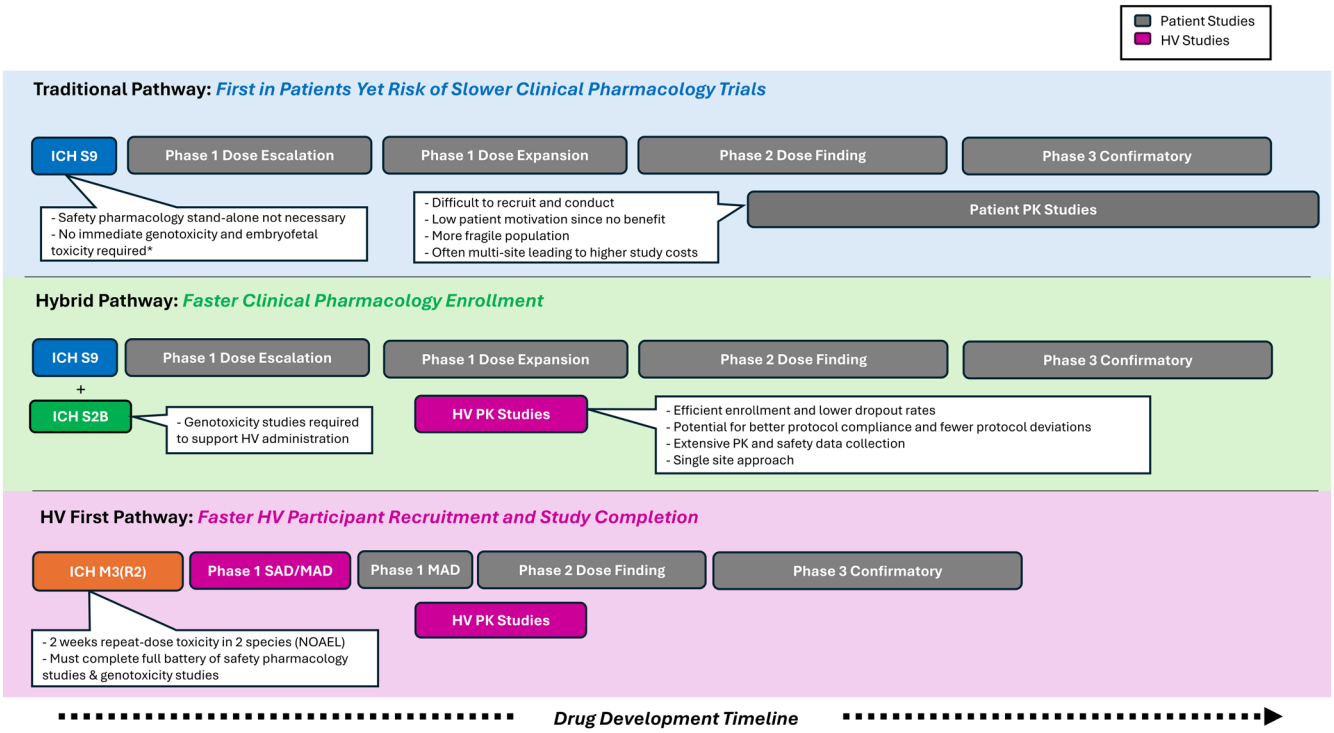


**FIGURE 3** | Traditional vs. healthy volunteer pharmacology drug development pathways. Schematic illustrating three potential drug development pathways for anticancer agents, highlighting key considerations. The *traditional pathway* (top panel) involves patient recruitment for safety, tolerability, efficacy, and clinical pharmacology trials. The ICH S9 nonclinical guidance supports this approach, which has the advantage of requiring fewer nonclinical studies required for an IND. The *hybrid pathway* (middle panel) combines initial exploration of a drug in patients with clinical pharmacology studies conducted in HVs supported by negative genotoxicity findings (ICH S2B). This is the approach applied to support futibatinib drug approval. In the *HV first pathway* (bottom panel), nonclinical studies are conducted according to ICH M(R2). Safety, tolerability, and PK are assessed in healthy subjects in a SAD and MAD study, before shifting to patient cohorts for dose finding and efficacy trials. A MAD cohort in patients enables dosing the anticancer agent at higher exposure levels before initiating dose finding studies. All clinical pharmacology studies are conducted in HVs. Overall, this approach can expedite development timelines to a maximum compared to the traditional pathway. The *hybrid pathway* (middle panel) combines elements of both approaches, with clinical pharmacology studies conducted in HVs supported by negative genotoxicity findings (ICH S2B). This is the approach applied to support futibatinib drug approval. HV, healthy volunteer; ICH, International Council for Harmonization; IND, Investigational New Drug (application); MAD, multiple ascending dose; NOAEL, No-Observed-Adverse-Effect Level; PK, pharmacokinetics; SAD, single ascending dose.

applying a safety factor, the maximum recommended starting dose was determined as a fixed dose of 9.7 mg futibatinib.

Previously, dose escalation was driven by the dose-limiting toxicities (DLTs) in patient studies, but to better balance efficacy versus safety and tolerability the FDA initiated Project Optimus [30] and issued final guidance on optimizing the dose for anticancer drugs in 2024 [31]. Rather than a rule-based, non-randomized approach to determine the DLTs, the reformed guidance recommends randomized, longitudinal, dose-ranging studies to evaluate chronic and late-onset effects [31, 32]. Because the FIH study for futibatinib in patients was completed prior to the initiation of Project Optimus, it was still designed to establish the maximum tolerated dose (MTD) in addition to the recommended Phase 2 dose (RP2D) [33]. The futibatinib dosing regimen that was considered safe for evaluation in HVs will be discussed in Sections 4.1 and 4.3.

### 3.3 | Monitoring for Class Adverse Effects

Another component of the risk assessment is to understand known drug class adverse effects as well as incorporating mitigation strategies tailored to the drug under study, thus taking into account the latest nonclinical and clinical safety findings available for that drug and the drug class. For instance, FGFR inhibitors are associated with on-target adverse effects such as hyperphosphatemia [34]. In a 2023 literature review of AEs associated with marketed FGFR inhibitors, including futibatinib, it was estimated that approximately 60%–80% of patients administered the anticancer treatments had an AE of hyperphosphatemia [34]. This is not surprising as FGFRs play an integral role in phosphate homeostasis via regulation of FGF23, klotho and vitamin D [34]. In the event of hyperphosphatemia, depending on the specific FGFR inhibitor, it may be recommended to reduce the dose [35], or withhold the dose, instruct the patient to consume a low-phosphate diet, or in some circumstances phosphate-lowering therapy may be recommended [34]. However, in HV studies, where participants may receive only a single dose of the FGFR inhibitor, severe hyperphosphatemia AEs are not readily anticipated, though phosphate levels should nonetheless be monitored closely. Other common class AEs include cardiac effects such as hypertension, cardiomyopathy, QT prolongation, as well as dermatologic and gastrointestinal toxicities (reviewed in Shyam Sunder et al. [36]). For HV studies, risk mitigation steps

**TABLE 3** | Key nonclinical studies to support a small molecule IND/NDA under ICH M3(R2) or ICH S9.

| | | All other pharmaceuticals ICH M3(R2) (For HV FIH) | | Anticancer pharmaceuticals ICH S9 (for patient FIH) | | Example: futibatinib |
|---|---|---|---|---|---|---|
| **Nonclinical study** | **GLP study?** | **ICH guidance** | **Recommended to support IND (or other phases)** | **ICH guidance** | **Recommended to support IND (or other phases)** | **Data available prior to** |
| Pharmacodynamic (e.g., mode of action, effect on desired therapeutic target) or pharmacology (e.g., anti-tumor activity) | No | S7A | Yes | S9 | Yes | Prior to IND |
| In vitro metabolic profile & plasma binding or conjugated products | Yes | S3A | Yes | S9 | Yes | Prior to IND |
| Systemic exposure or PK | Yes | S3A | Yes | S9 | Yes | Prior to IND |
| Comparative in vivo animal & human metabolism (i.e., ADME) | Yes | S3A | Generally required prior to Phase 3 | S9 | Generated in parallel with clinical development | Animal ADME prior to IND; Human ADME prior to NDA |
| Safety pharmacology<br>• CV (e.g., hERG inhibition, ECG evaluation)<br>• Respiratory (e.g., respiratory rate, tidal volume)<br>• CNS (e.g., Irwin, functional observational battery) | Yes | S7A & S7B | Yes | Can be included as general toxicology studies | Yes | Prior to IND |
| General toxicology<br>• Dose range finding<br>• Acute and/or Repeat dosing in 2 species (rodent & non-rodent) | • No<br>• Yes | M3(R2) | • Yes<br>• Yes | S9 | Proposed clinical dosing schedule will guide nonclinical treatment schedule | Prior to IND |
| Genotoxicology[a]<br>• In vitro mutagenicity<br>• In vitro & in vivo chromosomal aberrations<br>• In vivo micronucleus | Yes | S2B | • Sufficient for single dose<br>• Sufficient for multiple doses<br>• Prior to Phase 2 | S2 | Prior to market application (or to support HV studies) | Prior to HV studies |
| Reproductive toxicology | Yes | M3(R3) & S5(2) | Recommended prior to Phase 3 | S5(R2) | Prior to market application | Prior to NDA |

(Continues)

**TABLE 3** | (Continued)

| Nonclinical study | GLP study? | All other pharmaceuticals ICH M3(R2) (For HV FIH) | | Anticancer pharmaceuticals ICH S9 (for patient FIH) | | Example: futibatinib |
|---|---|---|---|---|---|---|
| | | ICH guidance | Recommended to support IND (or other phases) | ICH guidance | Recommended to support IND (or other phases) | Data available prior to |
| Carcinogenicity | Yes | S1A | For chronic drugs, prior to NDA<br>Not typically recommended for oncology indications | S1A | Not warranted to support marketing for therapeutics intended to treat patients with advanced cancer | NA |
| Local tolerance | Yes | M3(R2) | Product specific, generally prior to Phase 3 | NA | NA | NA |
| Special toxicity testing (ex. photosafety, immunotoxicity, abuse liability) | Yes | M3(R2) | Product specific or as needed, generally prior to Phase 3/NDA | Photosafety: M3(R2) | Product specific<br>Immunotoxicity is often incorporated in general toxicity studies | In vitro photosafety: prior to NDA |

*Note:* Adapted from: ICH M3(R2) [24] and ICH S9 [25]; FDA CDER webinar "Overview and Difference in Nonclinical Safety Assessments for Small Molecules and Biologic Drug Development" [26].
Abbreviations: ADME, absorption, distribution, metabolism, excretion; CNS, central nervous system; CV, cardiovascular; ECG, electrocardiogram; GLP, good laboratory practice; hERG, human ether-à-go-go-related gene; IND, investigational new drug; NA, not applicable; NDA, new drug application.
[a]A complete battery of tests for genotoxicity should be completed prior to Phase 2, however mutagenicity and chromosomal damage in a mammalian systems testing are sufficient to support single and multiple doses in clinical development, respectively. See text for further details on futibatinib nonclinical studies.

such as additional safety laboratory assessments, vitals and ECG measurements to monitor both potential on- and off-target AEs are regularly incorporated into the schedule of events. Key safety assessments and de-risking strategies implemented in futibatinib studies will be described in the next section.

## 4 | Summary of Early Phase Futibatinib Clinical Trials

The encouraging safety profile and PK data obtained from nonclinical studies supported clinical development of futibatinib. Following the hybrid scenario, clinical evaluation of futibatinib was initiated in patients and subsequently in clinical pharmacology studies in HVs to support the drug label, as will be discussed hereafter.

### 4.1 | First-in-Human Study in Patients With Advanced Cancer and Bridging to HVs

To gather initial data on futibatinib's safety profile in humans, a FIH study was conducted at escalating dose levels of futibatinib in patients with advanced solid tumors refractory to standard therapies. In this FIH study, the safety, PK and pharmacodynamics of dose regimens of 8–200 mg futibatinib three times a week (TIW) or 4–24 mg QD were evaluated [33]. In addition, this study aimed to explore the drug's antitumor activity against the diversity of cancer types presented across the enrolled patients with histologically/cytologically confirmed advanced metastatic solid tumors with any number of prior therapies. Enrollment was restricted to patients with FGF/*FGFR* aberrations from dose Level 5 and up and was later amended to include an intermediate 20 mg QD cohort. A total of 86 patients were enrolled in this study, with 42 patients across 9 TIW and 44 patients across 5 QD dosing cohorts. Patients primarily had cholangiocarcinoma, breast cancer, colorectal cancer, brain tumors and urothelial cancer, while in total 71 patients presented with tumors with a positive FGF/FGFR aberration status.

Futibatinib exposure parameters increased dose-proportionally in all QD dosing groups, whereas plateauing of exposure was observed with doses beyond 80 mg TIW. Because dose-limiting liver function test toxicities were observed in the 24 mg QD cohort, the MTD and RP2D were determined to be 20 mg QD. As anticipated, the most frequent treatment-emergent AE (TEAE) was hyperphosphatemia, an expected on-target effect of FGFR1 inhibition [34], in which 12% of patients experienced a Grade 3 TEAE. Dosing interruptions (15 patients, 17%) and dose reductions (5 patients, 6%) were applied to manage the TEAE [33].

Across all futibatinib dosing cohorts, in which the majority of patients had FGF/FGFR aberrations, antitumor activity was evaluated as patients experiencing a partial response or stable disease. The QD dosing regimen, however, exhibited a stronger exposure–response relationship; hence, the 20 mg QD dose was selected as the dosing regimen to be evaluated in efficacy studies as well as HV trials. Although futibatinib was found to be nongenotoxic, nonclinical dose range finding studies were positive for female reproductive toxicity, which was supported by embryo-fetal developmental toxicity findings demonstrating

that futibatinib has teratogenic effects on the rat embryo-fetus at clinically relevant exposures [10]. Therefore, only males (with appropriate contraceptive measures) and women of nonchild-bearing potential were considered for the HV trials.

### 4.2 | Clinical Mass Balance Characteristics

In nonclinical studies, the majority of futibatinib was excreted in feces in rats and dogs and via bile in bile-cannulated rats, suggesting hepatic metabolism [10]. To confirm the mass balance results from animal models, a mass balance study was conducted in healthy men to characterize the clinical PK, elimination routes and metabolic profile of futibatinib in humans. In this mass balance study, a single oral dose of 20 mg $^{14}$C-radiolabeled futibatinib (≈100 μCi) was administered to 6 healthy males [14]. Approximately 70% of the total administered radioactivity was recovered over 14 days, with fecal recovery accounting for a total of 64% of radioactivity [14]. No significant levels of futibatinib parent drug were detected in urine and feces. However, several metabolites were identified in feces, but not in urine.

Since hepatic elimination proved to be the major route of excretion, a hepatic impairment study was indicated to evaluate the impact of reduced liver function on the PK of futibatinib (see Section 4.7). Because of the prominent role of hepatic elimination and as futibatinib undergoes significant metabolism, DDI studies for hepatic liver enzymes and transporters were also initiated (see Section 4.4), in line with the ICH M12 guidance on DDI studies [37]. Since renal excretion was only a minor elimination pathway [14], no renal impairment study was warranted for futibatinib.

### 4.3 | Evaluation of Potential DDIs for Futibatinib in HVs

In in vitro assays, it was noted that CYP3A is a major enzyme implicated in futibatinib hepatic metabolism, with only minor involvement of CYP2C9 and CYP2D6 in futibatinib metabolism. In vitro studies also concluded that futibatinib is a substrate and inhibitor of transporter molecules P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) [10].

To evaluate the potential impact of DDIs through CYP3A and P-gp for futibatinib in a clinical setting, two Phase 1 DDI studies were conducted prior to NDA and one post-marketing. All DDI studies enrolled HVs, including males and women of nonchild-bearing potential [11, 13].

Based on nonclinical data, clinical findings in patients, and physiologically based pharmacokinetic (PBPK) modeling, the dose of 20 mg futibatinib was considered safe for administration in a DDI study in HVs. PBPK modeling was, for instance, applied to predict the fold increase in futibatinib exposure resulting from multiple doses of 200 mg itraconazole and when assuming a worst-case scenario with 2-fold larger fractional contributions of CYP3A than estimated in vitro (unpublished data).

Itraconazole, a dual P-gp and strong CYP3A inhibitor, and rifampin, a dual P-gp and strong CYP3A inducer, were each co-administered with a single 20 mg dose of futibatinib to evaluate the CYP3A inhibition and induction effects on futibatinib, respectively. In addition, the effect of 7 days of 20 mg futibatinib administration on the PK of midazolam, a sensitive clinical index substrate of CYP3A, was evaluated [11].

As shown in (Figure 4), itraconazole increased the relative mean total and peak exposure of futibatinib, whereas rifampin reduced relative mean total and peak exposures of futibatinib. These results indicate that strong CYP3A inhibitors and inducers should be avoided with futibatinib co-administration. On the other hand, the findings demonstrate that futibatinib is not a CYP3A inhibitor nor inducer in itself; coadministration of futibatinib did not affect the PK of midazolam, as relative exposure was within the bioequivalence limits of 80%–125% (Figure 4).

Throughout drug development, PBPK modeling and simulation were applied to gather insight into potential futibatinib drug interactions in both HVs and cancer patients. PBPK models of itraconazole, clarithromycin, fluconazole, fluvoxamine, cimetidine, rifampicin, carbamazepine, efavirenz, digoxin, and rosuvastatin were analyzed for DDI prediction [10]. The analysis predicted that coadministration of strong, moderate, and weak inhibitors of CYP3A potentially increases the AUC of futibatinib over the dosing interval ($AUC_{tau}$) by around 50%, 25%–40%, and 10%, respectively, whereas carbamazepine (strong CYP3A inducer), rifampicin (strong CYP3A inducer), and efavirenz (moderate CYP3A inducer) were predicted to decrease $AUC_{tau}$ of futibatinib 20 mg QD by approximately 35%, 60%, and 50%, respectively. The model did not account for the involvement of P-gp in the absorption of futibatinib and, thus, was not adequate to inform the drug label in that regard. Therefore, a clinical trial with a P-gp substrate (digoxin) and inhibitor (quinidine) was conducted post-marketing to definitively ascertain the contribution of P-gp to futibatinib metabolism.

To that end, coadministration of quinidine (P-gp inhibitor) with futibatinib generated minor increases in futibatinib total (+17%) and peak exposures (+8%), these changes were considered not clinically relevant. In the same study, the potential effects of 7 days administration of 20 mg futibatinib QD on the PK of digoxin, a substrate of P-gp, and rosuvastatin, a substrate of BCRP, were evaluated in a cocktail design [13]. However, coadministration of futibatinib did not impact the PK of transporter substrates digoxin and rosuvastatin (Figure 4).

Overall, futibatinib was well tolerated in HVs and these DDI studies informed the drug label that coadministration of futibatinib with dual P-gp and strong CYP3A inhibitors or inducers should be avoided [35]. As the contribution of P-gp to futibatinib exposure is limited, there is no concern for other concomitantly administered drugs with a potential to inhibit P-gp without strongly affecting CYP3A activity.

### 4.4 | The Effects of Food and Acid-Reducing Agents on the Absorption of Futibatinib in HVs

Futibatinib is a weak-base drug that is poorly soluble. Because futibatinib is orally administered, it is conceivable that food intake or concomitant administration of acid-reducing agents

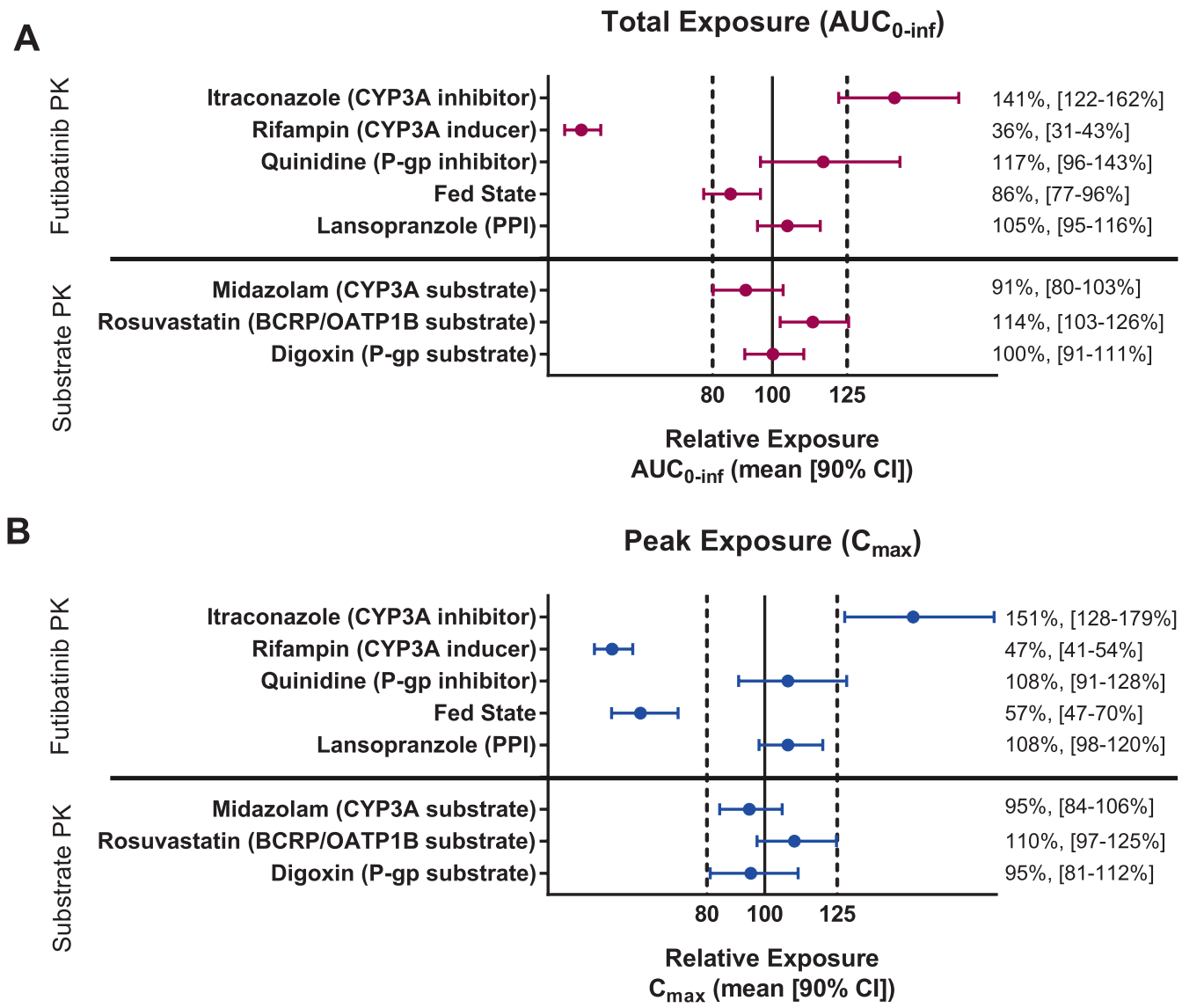


**FIGURE 4** | Relative exposures from DDI, PPI and food effect studies. Mean relative total (A) and peak exposure (B) for 20 mg futibatinib when co-administered with precipitant and substrate drugs. Data are presented as GMR estimates and 90% CI. Bioequivalence limits noted as vertical dashed lines. See text for study details. Adapted from [11–13]. $AUC_{0\text{-inf}}$, area under the curve from time is 0 to infinity; BCRP, breast cancer resistance protein; CI, confidence interval; $C_{max}$, maximum concentration; CYP3A, cytochrome P450 3A; OATP1B, organic anion transporting polypeptide 1B; P-gp, P-glycoprotein; PPI, proton pump inhibitor.

(ARAs) may interfere with its absorption. To better understand the potential impact of food intake and concomitant use of ARAs on the bioavailability of futibatinib, a food effect study and an ARA DDI study were conducted [12]. In the food effect study, the effects of a high-fat, high-calorie meal on futibatinib PK were assessed in HVs and compared to the PK of futibatinib under fasted conditions. Under fed conditions, mean relative total and peak futibatinib exposure were decreased as compared to the exposures under fasting conditions (see Figure 4). Despite a pronounced effect on $C_{max}$, the overall reduced exposure was not found to impact drug efficacy; therefore, the drug label states the tablet can be taken with or without food [35].

In the ARA study, the effect of concomitant administration of the proton-pump inhibitor (PPI) lansoprazole on the absorption of futibatinib was evaluated in HVs under fasting conditions. Coadministration with lansoprazole did not significantly change total and peak futibatinib exposures compared to futibatinib alone, with relative exposure ratios well within bioequivalence limits of 80%–125% (shown in Figure 4), therefore, there is no concern if patients take an ARA along with futibatinib.

### 4.5 | Cardiovascular Risk Assessment in HVs

A positive signal from the nonclinical studies prompted assessment of a proarrhythmic risk in a clinical setting. A standalone TQT study is one of three options to clinically assess a drug's cardiac liability via QT prolongation as reviewed in Lester et al. [38], and is typically conducted at therapeutic and supratherapeutic dose levels, where the latter should establish at least a $C_{max}$ approximately 2-fold greater than the $C_{max}$ attained at steady state with the (projected) clinical dose [38, 39]. This TQT approach has previously been followed for other TKIs [40–42]

and a TQT study was also conducted for futibatinib. In line with ICH E14 2005 recommendations, the 4-period crossover, single dose futibatinib TQT study included a positive control (moxifloxacin) and a placebo treatment arm [43].

The FIH study in oncology patients showed that futibatinib exposure increased approximately dose-proportional for doses of 8 mg up to 80 mg [33], with no apparent accumulation (see Section 4.1). In the TQT study, therapeutic (20 mg) and supratherapeutic (80 mg) dose levels were evaluated, neither of which prolonged the QT interval and hence, it was concluded that futibatinib had no effect on cardiac repolarization [15]. In addition, both futibatinib dose levels were well tolerated in HVs.

### 4.6 | PK of Futibatinib in Patients With Hepatic Impairment

Although not a HV study per se, an organ impairment PK study does include healthy-matched controls. As a key clinical pharmacology study, this trial is designed to assess drug PK and does not provide any clinical benefit to the patient. For hepatic elimination being the main contributor to futibatinib clearance (see Section 4.2), a study was conducted to evaluate the PK, safety and tolerability of futibatinib in patients with hepatic impairment. In this study, the PK of a single oral dose of 20 mg futibatinib was assessed in patients with mild, moderate or severe hepatic impairment and compared to the PK in matched healthy controls. In comparison to the control group, the $AUC_{0\text{-inf}}$ increased by 21%, 20% and 18% in subjects with mild, moderate and severe hepatic impairment, respectively, whereas $C_{max}$ increased by 43%, 15% and 10%, respectively [16]. Based on these results, no dose adjustment would be required for patients with hepatic impairment when administered futibatinib 20 mg QD.

### 4.7 | Integrated Safety Profile of Futibatinib in HVs

Overall, futibatinib was well tolerated in HVs. The most common TEAEs across all HV studies included headache, diarrhea, and blurred vision [11–16]. Following administration of multiple doses of futibatinib over 7 days in the midazolam and digoxin/rosuvastatin DDI studies, several participants experienced transient and asymptomatic increases in serum phosphate, which did not require any phosphate-lowering therapy. These AEs were classified as mild or moderate in nature and were considered to result from the pharmacological effect of FGFR inhibitors [11, 13].

## 5 | Discussion

Although the feasibility of enrolling HVs in clinical trials primarily depends on the (nonclinical) safety profile of a candidate oncology drug, particularly the absence of genotoxicity signals and good understanding of potential AEs, conduct of clinical pharmacology studies in HVs has the important advantage of speeding up clinical conduct as compared to studies in patients, which may help shorten the drug development process. Enrolment of patients in non-therapeutic studies can be time-consuming, for example, due to a lack of appropriate incentives for participants and strict entry criteria. Although clinical conduct of such studies requires engagement of multiple sites and additional resources, whereas in-house confinement can be challenging, which may all contribute to increased study timelines.

The data obtained from Phase 1 studies in HVs, conducted within a matter of weeks, can readily inform key aspects of the subsequent efficacy trials, including inclusion and exclusion criteria, dose level recommendation, dosing regimen, and safety risks. Moreover, in this approach, conduct of several studies can occur in parallel or be combined with multiple assessments (e.g., a cocktail of substrate drugs, incorporation of a food effect arm) in a single study, which can further reduce the overall timeline and costs.

With over 2 decades of TKI experience since the initial approval of imatinib, the paradigm of enrolling HVs in studies during clinical development of anticancer drugs has now been well established. A clinicaltrials.gov search (conducted on 04/25/25) revealed that since 2001, nearly 290 studies enrolled HVs as part of a clinical trial for anticancer drugs in development. When considering a FIH study with HVs, an extensive nonclinical dataset is required under ICH M3(R2) prior to drug administration if the investigational product will be dosed to HVs rather than patients with the targeted (cancer) indication (see Figure 3 and Table 3). However, a hybrid approach can also be considered; for example, a common trend for anticancer drug developers is to conduct nonclinical studies following ICH S9 for an efficient first-to-patient approach, and in addition run a full battery of genotoxicity studies to support conducting pharmacology studies in HVs. Subsequently, after early safety and efficacy is achieved in their Phase 1 patient studies, clinical pharmacology studies can be conducted in HVs as outlined in the futibatinib case study (Figure 2).

Like many TKIs, futibatinib showed no genotoxicity signals and had a favorable safety profile (in nonclinical and patient studies), thus paving the way for administration to HVs in product labelling studies, and its clinical development path is a prime example illustrating how studies in HVs have the potential to yield valuable information about the clinical PK and safety of a drug and may thus contribute to an efficient drug development process. Of note, key futibatinib labelling studies enrolled nearly 200 HVs, were initiated within a period of 6 months (Table 2; Table S1 and Figure 2) and were conducted at a single site; had these studies been performed in patients with advanced cancer, enrolment of eligible patients would readily have taken an estimated nine-fold amount of time and required multiple sites (Figure 1 and Table S1). As a consequence, the time required for completion of clinical conduct of the futibatinib labelling studies in HVs saved a substantial amount of time, accumulating to an estimated total of 2 years. Implicitly, the reduction in development time also translated into substantial financial savings. Moreover, the data obtained from the HV clinical pharmacology studies, especially from the DDI and FE studies, helped inform the concomitant medications allowed and fasting requirements during the TAS-120-101 trial (FOENIX-CCA2; NCT02052778) [44] and the ongoing confirmatory trial (TAS-120-205; NCT05727176). For instance, the list of potential concomitant

medications allowed for participants in the patient studies was widened based on the findings from the transporter DDI study which demonstrated that there was no risk of interaction with drugs that are transporter substrates.

Some drug sponsors may be reluctant to administer an anticancer drug to HVs due to safety concerns. To address this, safety profiling and pharmacovigilance in human trials will largely depend on findings from nonclinical models as well as any AEs observed in patient studies, especially for a novel drug class. It is paramount that potential AEs of interest are manageable, reversible, and monitorable before considering administering an anticancer drug to HV clinical pharmacology trials [5]. However, when there are known drug class effects, these AEs should be closely monitored in HV studies to assess the safety profile.

In addition to safety concerns, changes in exposure may affect the safety profile of a novel investigational product. In the case of futibatinib, nonclinical and patient exposure data as well as PBPK modeling data were therefore carefully reviewed prior to initiating studies in HVs. Based on the nonclinical general toxicity data, the maximal recommended starting dose of futibatinib was a fixed dose of 9.7 mg. Therefore, the initial first-in-patient study starting dose was set at 8 mg TIW. As discussed above, in this study the MTD and the RP2D were determined to be 20 mg QD [33], and a single dose of 20 mg was selected for the majority of HV Phase 1 trials. Furthermore, both single dose and steady-state exposures of 20 mg in HVs were similar to that observed in patients with cancer at the same dose level [11, 33, 45]. Neither extrinsic factors like food intake or a PPI, nor intrinsic factors such as hepatic impairment drastically increased exposure. However, itraconazole coadministration significantly increased futibatinib exposure, but less than 2-fold. Therefore, the 80 mg supratherapeutic dose in the TQT study, which reflects a nearly 4-fold increase in exposure compared to the clinical dose, sufficiently bracketed the upper end of high clinical exposure and showed no QTc prolonging effect.

In general, single dose administration of TKIs to HVs may pose minimal risk; however, common (known) AEs experienced by patients can also arise in HVs with multiple doses, which requires close monitoring. In such cases, additional risk mitigation measures may need to be taken. For instance, premedication such as granisetron may be considered when administering the candidate drug to prevent nausea AEs. To the extent feasible, dose reductions can also be considered in case of unexpected intolerabilities during the conduct of a study in HVs. However, it is important to note that TKIs have been safely administered to HVs in multiple ascending dose studies for up to 14 days [17, 18].

There are currently two other FGFR inhibitors approved by the FDA. Erdafitinib [46] and pemigatinib [47], while infigratinib has been withdrawn from the US market due to business decisions [48]. Like for futibatinib, HV studies were incorporated in their development program, yet the extent and approach varied. For example, review of the drug approval dossiers reveals that during erdafitinib and pemigatinib development, several HV trials were conducted to evaluate the drug's clinical pharmacology [46]. Clinical development of erdafitinib encompassed 6 HV studies (ADME, food effect, a DDI, and 3 bioavailability studies) [46]. For pemigatinib, only 3 HV studies (ADME, itraconazole and rifampin multi-part DDI, and a PPI) were conducted [47]. On the other hand, 10 HV studies were performed to support the infigratinib application [49].

Although there are clear advantages of conducting clinical pharmacology studies in HVs, it is important to highlight several differences between HVs and cancer patients that may be relevant to the interpretation of study results (Table 1). For example, it is recognized that CYP3A metabolism can be downregulated by inflammation in cancer patients [50], which could limit the relevance of PK findings in HVs for the drug under study to the target patient population. However, the effects observed in HVs may reflect a worst-case scenario that may help guide optimal treatment of patients, considering that CYP3A activity will be highly variable among patients, due to factors such as disease stage, inflammation, liver function, age and sex [51, 52]. Likewise, overexpression of the drug target (e.g., tumor FGF receptors in the case of futibatinib) in cancer patients may increase target-mediated drug disposition and, hence, lead to lower systemic drug exposure in patients. Again, assessment of PK and safety (including TQT studies) in HVs could therefore be slightly exaggerated and not be representative for patients, nonetheless could still provide guidance to help limit drug toxicity in patients. However, in terms of target engagement and implications for drug efficacy, data from HV studies may be limited due to low or no expression of the drug target in HVs. Yet, pharmacodynamics of anticancer drugs can occasionally be studied adequately in HVs, as has been described for acalabrutinib, for which the level of Bruton tyrosine kinase target engagement was similar in HVs and patients with hematological malignancies [53].

In conclusion, early phase clinical pharmacology studies are needed not only to inform the drug label aiding clinicians in appropriate use of an anticancer agent, but also to guide Phase 2 and 3 efficacy study designs. Gaining information on how specific conditions may impact the safety or efficacy of the investigational drug early in development is important to set appropriate inclusion and exclusion criteria and allowable concomitant medications for patient trials, as well as to ensure patient safety and the integrity of the study. For many TKI drugs, HVs can be enrolled safely into labelling studies, which may help reduce timelines and cost for study conduct. As illustrated with the case of futibatinib, HV studies can yield robust clinical pharmacological data and substantially expedite the drug development program.


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## Disclosure

A.D.H., S.P. and Z.M. are employed by Celerion. I.Y. is an employee of Taiho Pharmaceutica Corp.; N.H. and A.O. are employees of Taiho Oncology Inc. (TOI).

## Conflicts of Interest

The authors declare no conflicts of interest.

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## Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Duration of patient versus healthy subject DDI studies for tyrosine kinase inhibitors.