Quotient Sciences

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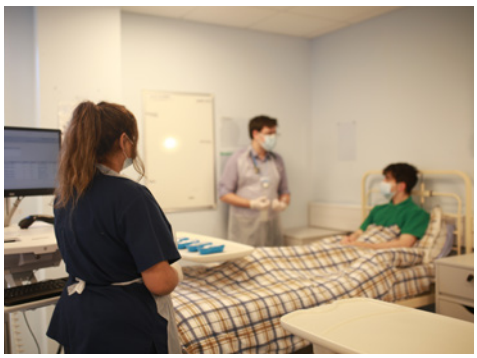
Information sheet

Drug-Drug Interaction (DDI) Studies

Assessing how your drug interacts with other drugs in vivo is a critical step in the drug development process and is essential in ensuring safe and efficacious drug delivery. This assessment is known as a drug-drug interaction (DDI) study and is a regulatory requirement for submissions of investigational new drugs (INDs). With patients frequently taking multiple prescriptions, or even over-the-counter drugs, there has been a rise in serious adverse events caused by two or more drugs interacting with each other. Drug interactions can also reduce the effectiveness of a drug, thus making data collected from these studies even more important to developers when understanding the likelihood of downstream clinical and commercial success.

Our expertise

At Quotient Sciences, we have over 30 years of experience in the design of clinical pharmacology studies, and have conducted more than 200 DDI studies in our US and UK clinical units. Our medical and scientific teams are experts at designing DDI study protocols in line with regulatory guidance from the US Food and Drug Administration (FDA) and European Medicines Agency (EMA). With our integrated, in-house data sciences team, we can also provide full-service data management, statistics, and medical writing support.



Our DDI study experience includes:

- Exploratory investigations and registration studies
- Enzyme induction and inhibition
- Oral contraceptives
- Interactions with specific concomitant medications, e.g. proton pump inhibitors (PPIs)
- Probe cocktail studies

We have also performed studies in which we have genotyped subjects to allow assessment or selection of certain phenotypes, e.g. poor and extensive metabolizers for CYP2D6.

What is a DDI assessment?

DDI studies assess the interaction between two or more drugs in a healthy volunteer or patient. The drug that is affected by the interaction is called the **victim** or **substrate**. The interaction can be mediated via an enzyme, a transporter, or a physiological process. The drug that causes the effect is called the **perpetrator**. The perpetrator could be an **inhibitor**, which is a compound that stops or limits the functionality of an enzyme or transporter, or an **inducer**, which is a compound that increases the rate of de-novo synthesis or upregulation of an enzyme or transporter.

Pharmacokinetics (PK) can be used to understand this effect and the impact. For example, an increase in the maximum plasma concentration (C_{max}) or total exposure of the drug in plasma (AUC) as a result of inhibition of a clearance mechanism (e.g. enzymatic or efflux transporter) could result in toxicity or off-target effects, while a decrease in C_{max} or AUC due to enzyme or transporter induction could mean reduced efficacy.

When can a DDI occur?

DDIs can occur during absorption, distribution, metabolism, or excretion (ADME) of drugs.

Absorption
Some drugs rely on the acidity in the stomach to dissolve. One of the most common types of over-the-counter medications are PPIs, which ease symptoms of acid reflux by increasing stomach pH. Drugs with pH-dependent solubility may have a DDI when administered with a PPI.

Distribution
Most drugs rely on active transport to move the drug in and out of cells. Interfering with these drug transporters can affect the way the drug is distributed throughout the body. Concomitant medications that are substrates or inhibitors of the active transport systems can result in a DDI.

Metabolism
The body has two systems of enzymes, Phase I and Phase II. Often working in succession, the aim is to make the drug more soluble so that it can be excreted in urine or feces. The cytochrome P450 (CYP450) enzyme family are responsible for the vast majority of drug-related metabolism. Co-medications that are substrates or inhibitors of the Phase I or II enzyme systems can result in a DDI.

Excretion
Similar to distribution, drugs often rely on transporters to eliminate the drug into urine or feces. Co-medications that are substrates or inhibitors of the active transport systems in the kidney can result in a DDI.

Types of DDI studies

At Quotient Sciences, we offer a variety of DDI studies, tailored to your individual program needs.

Pivotal, regulatory study
This study type is used for the label claim. It is usually comprised of two periods, including assessment of the victim alone followed by the perpetrator at steady state, dosed concomitantly with a single dose of the victim. Known sensitive victims and perpetrators are used, as defined by the regulatory agencies. The study needs to be statistically powered, so a large population could be required depending on the variability of the victim.

Probe cocktail study
This is an exploratory study to assess multiple DDIs in one study. Multiple victim drugs are dosed in period 1, followed by the perpetrator at steady state, dosed concomitantly with a single dose of the victims in period 2. Data from this study will then be used to inform future DDI studies.

Combined oral contraceptive (COC) study
This study assesses the liability of the drug to interact with COC drugs. Depending on the COC, it can be a straightforward DDI design, or it could be a multiple-month menstrual cycle-based interaction study. Consideration needs to be given to sex hormone-binding globulin (SHBG), and how it affects the exposure of the COC.

Concomitant interaction study
Instead of using known sensitive victims and perpetrators, likely concomitant medications taken during Phase II/III will be assessed to ensure any potential interactions are understood.

Case study

Probe cocktail DDI study

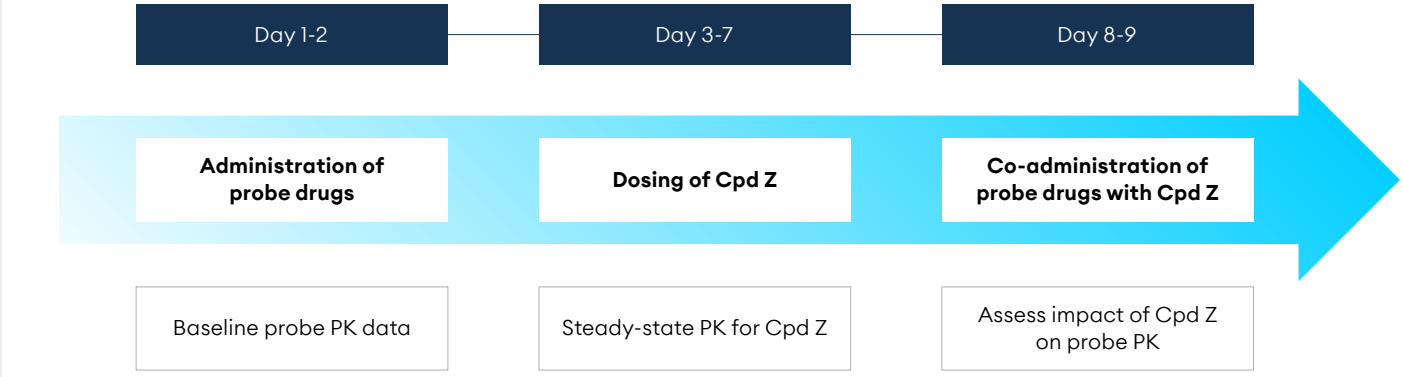
In this example, a probe cocktail DDI study was conducted to assess the impact of Compound Z on CYP450 enzymes.[1] If the probe cocktail DDI study showed no effect, it would be possible to justify not performing a pivotal DDI study.

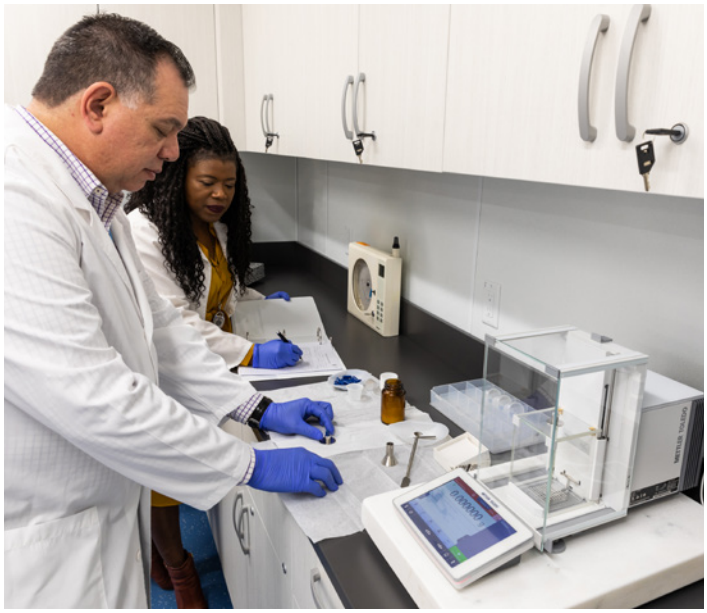
Subjects were genotyped to exclude poor metabolizers for CYP2D6 and CYP2C19. On Day 1 and 8, a probe cocktail of oral caffeine, tolbutamide, omeprazole, and dextromethorphan, and intravenous (IV) midazolam, was administered. On Day 2 and 9, oral midazolam was administered. Dosing IV and oral midazolam allowed the difference between gastric and systemic CYP3A4 to be evaluated.

Compound Z showed an interaction with all the probe drugs to some extent, which allowed classification of the probes as weak, moderate, or strong inhibitors. The interaction was described as two categories:

- **Category 1:** AUC increased and half-life ($T_{1/2}$) remained the same, indicative of a first-pass effect
- **Category 2:** AUC increased and prolonged $T_{1/2}$, indicative of the effect occurring post first-pass metabolism

A greater increase in exposure for oral midazolam compared to IV was found, and this was considered to be a result of a greater effect on gut CYP3A4 compared to hepatic inhibition.



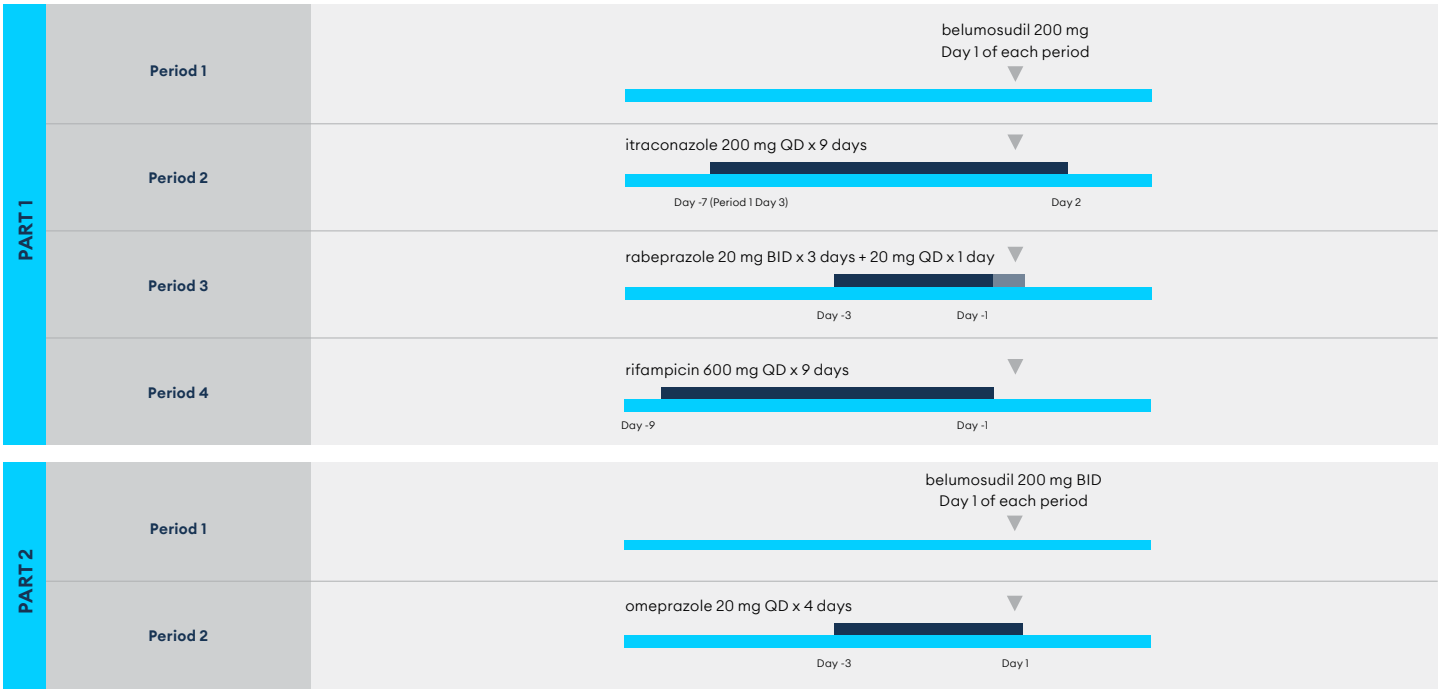


CYP3A4 inhibition, induction, and PPI effect

Kadmon have recently had belumosudil approved by the FDA for chronic graft versus host disease. In-vitro studies have shown that belumosudil is primarily metabolized by CYP450 enzymes and that the solubility is pH dependent.

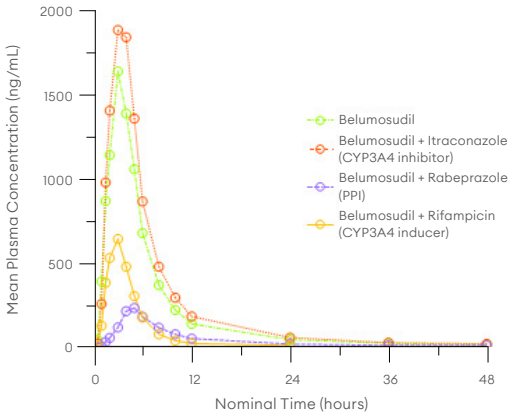
A two-part clinical study was conducted to assess the impact of a strong CYP3A4 inhibitor (itraconazole), a strong CYP3A4 inducer (rifampicin), and two PPIs (rabeprazole and omeprazole) on belumosudil exposure.[2] Part 1 dosed 35 subjects in four sequential periods, and Part 2 dosed 38 subjects in two sequential periods with appropriate washout between dosing periods.

Belumosudil exposure did not have a clinically significantly change when dosed with itraconazole. However, exposure of KD025m2 (the main metabolite) was decreased. The CYP3A4 inducer rifampicin significantly decreased exposure of belumosudil and KD025m2, and increased KD025m1 exposure. When belumosudil was co-administered with both rabeprazole and omeprazole in their respective assessments, parent and metabolite exposures were largely reduced, suggesting that belumosudil dosage should be increased when given with PPIs. Label information therefore advises to increase the dose of belumosudil to 200 mg twice daily when administered with strong CYP3A4 inducers and PPIs.

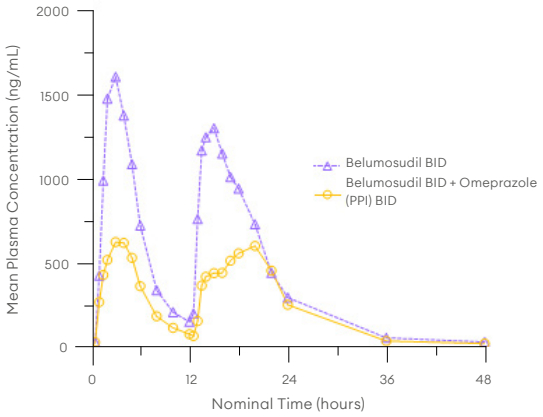


Abbreviations: BID = twice per day, QD = once per day

Graph 1: Mean belumosudil pharmacokinetic profiles following administration of 200 mg belumosudil single dose alone, with itraconazole, with rabeprazole and with rifampicin



Graph 2: Mean belumosudil pharmacokinetic profiles following administration of 200-mg belumosudil BID alone and with omeprazole.



Integrated development and clinical strategies

DDI studies can be conducted as standalone clinical studies, or they can also be integrated with other clinical studies, such as being included as an additional part in a first-in-human study, as well as in formulation optimization studies. Once a suitable formulation or dosing regimen is identified for your drug, this can then be assessed in a DDI study in a new cohort of subjects. Additionally, at Quotient Sciences, we have the unique ability to fully integrate DDI studies as part of an integrated drug development program using our Translational Pharmaceutics® platform to accelerate development timelines and improve the likelihood of downstream success.

References

1. Shaw et al., 2017, P48 ISSX, Cologne
2. Schueller et al., 2022, *Clinical Pharmacology in Drug Development*, 1-12

Who is Quotient Sciences?

Quotient Sciences is a drug development and manufacturing accelerator providing integrated programs and tailored services across the entire development pathway. Cutting through silos across a range of drug development capabilities, we save precious time and money in getting drugs to patients. Everything we do for our customers is driven by an unswerving belief that ideas need to become solutions, molecules need to become cures, fast. Because humanity needs solutions, fast.

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