Absolute bioavailability trial of oral imatinib (Glivec®) using a stable isotope labeled intravenous imatinib microdose.

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To determine the absolute bioavailability of imatinib (Glivec®) at steady state after concomitant administration of a single 100 µg microdose of imatinib-d8

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON46280

Source
ToetsingOnline

Brief title
Absolute bioavailability oral imatinib (Glivec®)

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: AVL

Intervention

Keyword: bioavailability, imatinib, isotope, microdose

Outcome measures

Primary outcome

To determine the absolute bioavailability of imatinib (Glivec®) at steady state

after concomitant administration of a single 100 µg microdose of imatinib-d8

Secondary outcome

N/A

Study description

Background summary

Absolute bioavailability (ABA) is a measurement of the rate and extent to which the active ingredient or active moiety of a drug is absorbed, reaches the systemic circulation and becomes available at the site of action. ABA assessment is an important component of new drug development. ABA data in humans is increasingly requested by the EMA and FDA for new chemical entities.

Small molecular tyrosine kinase inhibitors (smTKIs) are generally characterized by a poor oral, and thus variable, bioavailability. This results in significant variation in plasma levels and exposure. For many smTKIs, the human oral bioavailability is unknown or inaccessible in the public domain due to several reasons and if published, values are generally low and the exposure is variable. Imatinib (Glivec®, Novartis) is an exception to this case with almost complete bioavailability in humans after oral dosing.

Glivec® bioavailability was tested in twelve healthy volunteers using a traditional three-period randomized crossover trial approach, where patients were assigned to 100 mg of imatinib as a 60-minute IV infusion, 400 mg of imatinib as a capsule, or 400 mg of imatinib as an oral solution in different sequences. The absolute bioavailability of oral imatinib either as a solution or in capsule form was found to be higher than 97%. (1)

Absolute oral bioavailability is ideally studied using a microtracer approach. This can be done by administering a therapeutic dose of the drug via the non-IV route, after which a microtracer (either radiolabelled drug or stable isotope

labeled (SIL) drug is given via the IV route at 1/100th of therapeutic dose or less than 100 µg at the expected Tmax. This approach has several advantages over the traditional crossover study design.

First, since the dose of the microtracer is very low, supportive IV toxicology studies are not required. Second, formulation development work is also limited. Even very insoluble compounds can be easily formulated with physiological concentrations of saline, glucose, or co-solvent at such a low dose. Third, the IV microtracer is administered at the peak concentration of the non-IV route at steady state, at which time the body is already behaving in the therapeutic dosing range, therefore, the possibility of non-equivalent kinetics that might otherwise occur between separate dosing occasions is virtually limited. And fourth, a microtracer study with a single dosing period shortens the study duration and eliminates interoccasion variability present in the crossover study design.

With the recent advancement of ultrasensitive liquid chromatography with tandem mass spectrometry (LC-MS/MS) technologies, it is now possible to accurately measure drug concentrations in plasma following an IV administration of a stable isotope labeled microtracer using LC-MS/MS. Therefore, it is no longer required to use a radiolabeled drug (often 14C) as the microtracer. This can save time and money, as accelerator mass spectrometry (AMS), which is the analysing technique for 14C-labeled microdoses, is labour- and time-intensive and more costly than LC-MS/MS.

The aim of this proof of concept study is to determine the ABA of imatinib using a SIL-microtracer trial design. Imatinib is chosen as a model compound because ABA trial results using a cross-over trial design are already available. (1) The results obtained from this new proof of concept study can be compared to the results obtained using the traditional cross-over trial design. When the results are comparable, this study provides proof that microtracer ABA trials are feasible in our institute, making it possible to reduce patient burden and saving costs and time in future trials where the ABA of oral anticancer agents needs to be investigated.

Study objective

To determine the absolute bioavailability of imatinib (Glivec®) at steady state after concomitant administration of a single 100 µg microdose of imatinib-d8

Study design

This is a single center, open-label, single dose, absolute bioavailability study in which the absolute bioavailability of imatinib (Glivec®) will be determined at steady state by concomitant administration of an IV microdose of stable isotope labeled imatinib-d8. Patients will be hospitalized during 24

hours. After intake of Glivec® (at around 08:30 a.m.) blood samples will be sequentially collected for bioanalysis for the period of 24 hours. On the first day they will receive one intravenous dose of 100 µg imatinib-d8 at approximately 11.00 a.m. An additional 48 hour post-dose sample will be collected in an outpatient setting.

Intervention

Injection of a 100 microgram imatinib-d8 microdose

Study burden and risks

Burden:
• Placement of a Venflon catheter;
• Administration of the IV microdose imatinib-d8;
• 12 x 4 mL blood sample collections;
• Hospital visit lasting at least 24 hours;
• 1 follow-up visit;

As microdosages are considered non-therapeutic and non-toxic, no risk is expected to be associated with administration of the imatinib-d8 microdose.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Locally advanced or metastatic cancer;
2. On imatinib treatment at a stable dose of 400 mg once daily in the morning for at least 7 days (steady state plasma concentration)
3. Age >= 18 years;
4. Able and willing to give written informed consent;
5. WHO performance status of 0, 1 or 2;
6. Able and willing to undergo blood sampling for PK analysis;

Exclusion criteria

1. Any treatment with investigational drugs within 30 days or 5 half-lives prior to receiving the investigational treatment;
2. Any treatment with inhibitors of CYP3A4 (e.g. boceprevir, claritromycine, erytromycine, indinavir, itraconazol, ketoconazol, ritonavir and voriconazol), inhibitors of Pgp (e.g. ciclosporine, kinidine and verapamil), inhibitors of BCRP (e.g. lapatinib), inductors of CYP3A4, Pgp or BCRP;
3. Woman who are pregnant or breast feeding;
4. Patients suffering from any known disease or dysfunction that might influence the dissolution and/or absorption of imatinib (e.g. inflammatory bowel disease).

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-03-2019
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	19-11-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	21-12-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	04-04-2019
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-003997-28-NL
CCMO	NL67660.031.18

Study results

Date completed:	05-09-2019
Actual enrolment:	7