In vitro Screening of drug candidates against cancer and autoimmune diseases for effects on human blood cells

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Primary Objective: Test the capacity of drug candidates to specifically inhibit the signalling pathways they target in human blood cells in vitro in the setting of human whole blood.Secondary Objective(s): Test whether drug candidates exert...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Plasma cell neoplasms
Study type	Observational invasive

Summary

ID

NL-OMON47365

Source
ToetsingOnline

Brief title
In vitro screening of new drug candidates

Condition

- Plasma cell neoplasms
- Autoimmune disorders
- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
auto-immune diseases, Cancer

Research involving
Human

Sponsors and support

Primary sponsor: Farmacologie

Source(s) of monetary or material Support: Acerta Pharma

Intervention

Keyword: Human blood cells, In vitro efficacy, Kinase inhibitors

Outcome measures

Primary outcome

Whole blood or purified PBMC will be stimulated in vitro in absence or presence

of the drug candidates.

The % inhibition of stimulation and frequency of dead cells will be measured.

Potent and selective inhibitors will be chosen for further profiling in animal

models and ultimately in clinical development.

Secondary outcome

Not applicable

Study description

Background summary

Acerta Pharma develops covalently binding kinase inhibitors for treatment of human diseases including cancer and autoimmune diseases. We target signalling pathways in disease-relevant immune cells. Optimising target specificity, selectivity and reactivity is crucial for successful drug development (Barf T et al. 2012)

The ideal in vitro method to aid selection for further development is testing of drug candidate effects on human blood cells in the context of whole blood (Covey TM et al. 2010). It is important to perform tests in whole blood because blood components such as plasma proteins might non-specifically bind drug candidates. Non-specific binding can dramatically reduce potency and efficacy. In addition, with all cells present in the circulation cell-cell mediated interactions affected by the drug substance tested will be part of the overall study outcome. In order to dissect the effect of whole blood components on efficacy, white blood cells will be purified and tested in parallel.

We have already successfully applied this method in preclinical studies testing a Bruton*s tyrosine kinase (Btk) inhibitor. Our colleagues in San Carlos (California) demonstrated that our drug candidate ACP-196 was less susceptible to potency loss in whole blood testing compared to competitors (Covey TM et al. 2015). Avoiding potency loss through non-specific binding to whole blood components translates into a lower drug dose required to achieve clinical effects which reduces the risk of side effects due to off target effects of the drug. The use of the whole blood assay has been an important selection tool, significantly lowering the need for in vivo studies. Therefore, we want to continue optimising the potency of our new drug candidates and implement this method in Acerta Pharma*s location in Oss, the Netherlands.

The study population used for blood donation will be healthy volunteers because we aim to test drug candidates under normal conditions of blood composition and blood cell function.

References:

Barf T and Kaptein A: Irreversible Protein Kinase Inhibitors: Balancing the Benefits and Risks. 2012 J Med Chem 55:6243-6262.

Covey TM, Putta S, Cesano A: Single cell network profiling (SCNP): mapping drug and target interactions. 2010 Assay Drug Dev Technol 8(3):321-343

Covey TM, Barf T, Gulrajani M, Krantz F, van Lith B, Bibikova E, van de Kar B, de Zwart E, Hamdy A, Izumi R, Kaptein A: ACP-196: a novel covalent Bruton*s tyrosine kinase (Btk) inhibitor with imporved selectivity and in vivo target coverage in chronic lymphocytic leukemia (CLL) patients. 20 April 2015, Annual Meeting American Association for Cancer Research (AACR), Abstract 2596

Study objective

Primary Objective: Test the capacity of drug candidates to specifically inhibit the signalling pathways they target in human blood cells in vitro in the setting of human whole blood.

Secondary Objective(s): Test whether drug candidates exert undesired off-target effects on human blood cells in vitro in the setting of human whole blood.

Study design

Up to 50 ml of peripheral blood will be drawn from healthy volunteers. No further intervention is required. The blood will be transferred to the laboratory of Acerta Pharma in Oss, the Netherlands and used for in vitro

assays to address the objectives mentioned above.

The frequency with which freshly drawn human whole blood is required will depend on the number of drug candidates that require testing. Only compounds that fulfill pre-selection criteria such as binding capacity in biochemical assays and in relevant cell lines will be tested using these human whole blood samples. It is anticipated that 10-20 drug candidates per year will be profiled in human whole blood assays. Therefore, we expect testing, and thus blood draws, will be required once a month or less frequently.

Compounds will be initially tested in whole blood and purified PBMC from 1 donor. Potent and selective inhibitors that present potential clinical candidates will be tested up to 4 independent donors in total.

Study burden and risks

This study is solely carried out in vitro. The only risk for the participants is the standard risk associated with drawing peripheral blood, which is minimal.

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

Healthy
aged 18-65 years

Exclusion criteria

Not healthy
Use of prescription drugs up to 1 week before blood draw

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-09-2015
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	16-07-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	24-10-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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
CCMO	NL53607.028.15