A Phase Ib, open-label, dose-finding study of the JAK inhibitor INC424 tablets administered orally to patients with Primary Myelofibrosis (PMF), Post-Polycythemia Vera-Myelofibrosis (PPV-MF) or Post-Essential Thrombocythemia-Myelofibrosis (PET-MF) and baseline platelet counts * 50 x109/L and <100 x109/L (CINC424A2201)

Published: 13-04-2012
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Primary objective: To establish the MSSD of INC424 in patients with MF and baseline PLT count < 100 x 109/L and * 75 x 109/L (first stratum) and PLT count < 75 x 109/L and * 50 x 109/L (second stratum).Secondary objective: safety, PK, PK/PD,...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39946

Source
ToetsingOnline

Brief title
CINC424A2201

Condition

- Other condition

Synonym
myelofibrosis

Health condition

myelofibrose

Research involving
Human

Sponsors and support

Primary sponsor: Novartis Pharma BV
Source(s) of monetary or material Support: Novartis Pharma BV

Intervention

Keyword: INC424, JAK inbibition, myelofibrosis, thrombocytopenia

Outcome measures

Primary outcome

DLT

Secondary outcome

Safety parameters, PK, platelets, cytokines, spleen length, proportion of

patients achieving *50% reduction in palpable spleen length at Week 24, Change

in spleen length as measured by palpation from Study Day 1 to Week 24.

Study description

Background summary

For a significant population of thrombocytopenic MF patients there are limited data about the safety of INC424 (a JAK inhibitor) or what might be an appropriate dose, since in all studies conducted to date with INC424, baseline

PLT count of * 100 x109/L has been an inclusion criterion. However, thrombocytopenia is a frequent event in MF. A previous phase I/II study, has established thrombocytopenia as the DLT of INC424 in MF patients with a MTD of both 25 mg b.i.d. and 100 mg qd. The incidence of grade * 3 thrombocytopenia in this trial was 20% at 10 mg b.i.d., 2.9% at 15 mg b.i.d. and 36% at 25 mg b.i.d. The higher incidence of grade * 3 thrombocytopenia in the 10 mg b.i.d. dose group compared to 15 mg b.i.d. can be partially explained by the more frequent presence of patients with low baseline PLT counts in the former dose group compared to the latter one. Thrombocytopenia occurred rapidly and resolved with drug interruptions or dose decreases. Some patients continued to receive INC424 while their platelet count ranged between 50 and 100 x109/L, but no patients with platelet counts below 100 x109/L have initiated INC424 therapy, and therefore the MTD for patients with low platelets needs to be directly established.
The purpose of this phase Ib clinical trial is to directly evaluate the safety of INC424 in the low-PLT MF population and to establish the Maximum Safe Starting Dose.

Study objective

Primary objective: To establish the MSSD of INC424 in patients with MF and baseline PLT count < 100 x 109/L and * 75 x 109/L (first stratum) and PLT count < 75 x 109/L and * 50 x 109/L (second stratum).
Secondary objective: safety, PK, PK/PD, estimate of efficacy.

Study design

Open-label, dose finding phase Ib study. For each patient, the study consists of 2 parts: Core phase and Extension phase.
1. Core period (1st 168 days). Patient is enrolled in a or b (only difference between both groups is the dose of INC424)
o Dose-escalation: Subsequent cohorts (3-6 pats). Increasing doses of INC424 until MSSD has be dreached. Approx. 62 patients.
o Safety expansion phase. 20 patients in total (10 patients from each stratum), additional to those treated at the MSSD during dose escalation, will be treated at the respective MSSD for their stratum.
2. Extension period (after day 168): Patient will visit hospital once in 12 weeks. In addition, blood is drawn for safety labs every 12 weeks (6 weeks after each hospital visit).
Study is terminated with an EOT visit.
See also protocol page 33.

Intervention

Treatment with INC424.

Study burden and risks

Risk: Adverse events of study medication.
Burden:
Study visits with an interval of 1, 2, 4 and eventually 6 weeks.
Blood draws 15-30 ml/visit; every visit.
Regular pregnancy testing.
Physical examination every 2-4, later on 12weeks.
ECG every 4-8 weeks (until day 168)
Questionnaire (quality of life) every 4-8 weeks (until day 168).
Diary (daily) about symptoms (1st 6 months only) and use of study medication.

Contacts

Public
Novartis Pharma BV

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Scientific
Novartis Pharma BV

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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

* 18 years of age or older
* Diagnosed with Primary Myelofibrosis (MF), Post-Polycythemia Vera-Myelofibrosis or Post-Essential Thrombocythemia-Myelofibrosis irrespective of JAK2 mutation status, guided by the criteria outlined in the 2008 WHO criteria for PMF.
* MF requiring therapy must be classified at least as intermediate risk level 1, as defined by the International Working Group (see protocol page 42 for details).
* Palpable spleen of at least 5 cm.
* Active symptoms of MF (see protocol page 42 for details).
* Baseline PLT count < 100 x 109/L and * 75 x 109/L (first stratum) and PLT count < 75 x 109/L and * 50 x 109/L (second stratum).
* INR and PTT < 1.5 x ULN.
* ECOG performance status 0, 1, 2.

Exclusion criteria

* Pregnant or nursing women.
* Patients of childbearing potential who are unwilling to take appropriate contraceptive measures.
* Treatment with hematopoietic growth factor receptor agonists for at least 30 days prior to receiving the first dose of study drug.
* Any history of PLT counts <45 x 109/L within 30 days prior to Screening. See protocol page 43 for exceptions.
* Any history or predisposition to clinically significant bleeding, platelet dysfunction and/or bleeding diathesis.
* Treated concurrently with a potent systemic inhibitor or a potent systemic inducer of CYP3A4.
* Life expectancy of less than 6 months.

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):	23-10-2012
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	INC424
Generic name:	INC424

Ethics review

Approved WMO Date:	13-04-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-07-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	23-05-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-07-2013

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-07-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-10-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-01-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-02-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-02-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	20-01-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-02-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	20-02-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-03-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	06-04-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	08-07-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	15-08-2017
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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
Other	clinicaltrials.gov; registratienummer n.n.b.
EudraCT	EUCTR2010-023055-29-NL
CCMO	NL40146.078.12