A single ascending dose study to assess the safety, tolerability and pharmacokinetics of RO5428029 in healthy male subjects

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To evaluate the safety, tolerability and pharmacokinetics of RO5428029 in healthy male subjects.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON34361

Source
ToetsingOnline

Brief title
PP25327

Condition

- Viral infectious disorders

Synonym
HCV, Hepatitis C Virus infection, infection of the liver

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: F. Hoffmann-La Roche Ltd.

Intervention

Keyword: HCV, pharmacokinetics, safety, tolerability

Outcome measures

Primary outcome

The primary study variables of single doses of RO1080713, Part A and B, are

-the safety and tolerability variables:

-the primary pharmacokinetic study parameters: AUC and Cmax of RO1080713

Secondary outcome

-other pharmacokinetic parameters

-all pharmacodynamic parameters of RO1080713 and/or other metabolites as needed

for all treated subjects

Study description

Background summary

Hepatitis C virus (HCV) is responsible for a large proportion of chronic liver disease cases worldwide and accounts for 70% of cases of chronic hepatitis in industrialized countries. The global prevalence of chronic hepatitis C is estimated to average 3% (ranging from 0.1% to 5%); with an estimated 170 million chronic carriers worldwide. (2.7 million in the USA and 5 million in Western Europe).

The current recommended standard of care (SOC) for patients with chronic hepatitis C is treatment with Pegylated Interferon (PEG-IFN) in combination with Ribavirin (RBV) over 48 weeks for viral genotype 1 patients and 24 weeks or more for patients infected with viral genotypes other than genotype 1. Patients who are chronically infected with HCV genotype 1 represent the majority of the HCV-infected population; however, the response to PEG-IFN treatment within this population are suboptimal, with sustained viral response (SVR) rates between 42%-52%. Consequently, there is a substantial need to improve therapeutic options for patients infected with HCV genotype 1 population.

When added to SOC, potent small molecule inhibitors of HCV can improve SVR rates in genotype 1 HCV infected patients with shorter durations of total therapy, as has been demonstrated with the protease inhibitors (eg, telapravir and boceprevir). While protease inhibitors are promising agents, they have potential limitations, including rapid selection of protease inhibitor resistant mutants, pharmacokinetics (PK) that likely requires multiple daily dosing, and adverse events (AEs) (e.g., rash, anemia). Evaluation of other small molecules, particularly those that inhibit different HCV targets, is therefore essential.

RO5428029 is a novel, tripropionate ester prodrug of the uridine nucleoside analog RO1080713. RO5428029 targets the HCV polymerase enzyme NS5B, an essential RNA-dependent RNA polymerase that plays a crucial role in HCV protein translation and synthesis, leading to viral replication for HCV replication and is a target for effective antiviral therapy.

Study objective

To evaluate the safety, tolerability and pharmacokinetics of RO5428029 in healthy male subjects.

Study design

This is a randomized, double-blind, placebo controlled, parallel group, single ascending dose study in healthy male subjects conducted in Europe for Part A, and China for Part B. 8 study subjects will receive study medication, 2 study subjects will receive placebo.

The proposed dose levels and assignment of doses and placebo for the planned dose groups are as follows:
• Cohort 1: A single oral dose of 50 mg RO5428029 or matching placebo under fasting conditions.
• Cohort 2: A single oral dose of 200 mg RO5428029 or matching placebo under fasting conditions.
• Cohort 3: A single oral dose of 400 mg RO5428029 or matching placebo under fasting conditions.
• Cohort 4: A single oral dose of 800 mg RO5428029 or matching placebo under fasting conditions.
• Cohort 5: A single oral dose of 1600 mg RO5428029 or matching placebo under fasting conditions.
• Cohort 6: A single oral dose of 3200 mg RO5428029 or matching placebo under fasting conditions.

The total duration of the study for each subject will be up to 31 days divided as follows:
• Screening: Up to 21 days;

• In Clinic period: Days -2 to 2;
• Safety Follow-up: 7 to 10 days after last dose.

Subjects will be admitted to the clinical research unit on Day -2 and will be discharged approximately 48 hours after study drug administration.

Intervention

Screening:
The following assessments will be performed to evaluate eligibility:
• Signed, written informed consent
• Inclusion/exclusion criteria
• Previous medical/surgical history
• Complete physical examination
• Height
• Weight)
• Vital Signs (including temperature, respiratory rate, single measurement of BP and PR)
• Triplicate 12-lead ECG
• Safety lab assessments (hematology, fasting blood chemistry and urinalysis))
• Urine drug screen
• Alcohol breath test
• Serology

Inclusion:
Subjects will be admitted to the clinic on Day -2 and reside in the unit until the morning of Day 2. The following assessments will be performed at inclusion:

Day -2
• Admission to Clinical Unit
• Urine drug screen
• Alcohol breath test

Day -1
Subjects will reside at the unit overnight. The following assessments will be performed on Day 1:
• In clinic meals
• Review of inclusion/exclusion criteria
• Complete physical examination
• Weight
• Triplicate BP/PR
• Triplicate 12-lead ECG
• ECG Holter Monitoring
• Safety lab assessments (hematology, fasting blood chemistry and urinalysis)

Day 1
Subjects will reside at the unit overnight. The following assessments will be

performed on Day 1:
• Randomization (before study drug administration)
• Administration of RO5428029 or placebo, under fasting conditions
• In clinic meals
• Temperature and respiratory rate (one hour before study drug administration)
• Triplicate BP/PR
• Triplicate 12-lead ECG
• ECG Holter Monitoring
• Pre-dose blood PK sample (one hour before study drug administration)
• Pre-dose urine PK sample (one hour before study drug administration)
• Blood PK
• Urine PK

Day 2
Subjects will reside at the unit overnight. The following assessments will be performed on Day 2:
• Abbreviated physical examination
• Temperature and respiratory rate
• Triplicate BP/PR (before meals)
• Triplicate 12-lead ECG (before meals)
• ECG Holter Monitoring
• Safety lab assessments (hematology, fasting blood chemistry and urinalysis [before meal])
• Blood PK sampling
• Urine PK sampling
• In clinic meals

Day 3 and 4
The following assessments will be performed on Days 3 and 4:

Day 3
• Abbreviated physical examination
• Temperature and respiratory rate (before meals)
• Triplicate BP/PR (before meals)
• Triplicate 12-lead ECG (before meals)
• Safety lab assessments (hematology, fasting blood chemistry and urinalysis [before meal])
• 48 hr post dose blood PK sampling (before meal)
• Urine PK sampling
• In clinic meal
• Discharge

Subjects will be discharged from the unit once all Day 3 study assessments have been completed and will return to the unit for an outpatient visit on Day 4.
Day 4
• Temperature and respiratory rate
• Triplicate BP/PR

• Triplicate 12-lead ECG
• 72 hr post dose blood PK sampling

Follow up
Subjects will return to the unit for a follow up examination 7 to 10 days after the last dose of study drug. The following assessments will be performed at the follow up visit:
• Full physical examination
• Weight
• Temperature and respiratory rate)
• Triplicate BP/PR at time points
• Triplicate 12-lead ECG
• Safety lab assessments (hematology, fasting blood chemistry and urinalysis)

Study burden and risks

As this study is with a new drug, not all of the side effects may be known. It is possible that unexpected side effects occur during the study, such as allergic reactions. This drug has not been tested in humans before. Studies in animals did not show findings that caused concern to evaluate this drug in humans. Participation in this study can be accompanied by headache, often due to a period of fasting and abstinence from coffee. To ease blood drawing, a cannula will be inserted in a vein of the arm. This can be painful and sometimes lead to a bruise.

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. Healthy male subjects, 18 to 45 years of age, inclusive. Healthy status is defined by absence of evidence of
any active or chronic disease following a detailed medical and surgical history, a complete physical examination
including vital signs, 12-lead ECG, hematology, blood chemistry, and urinalysis.
2. Body mass index (BMI) between 18 and 30 kg/mE2, inclusive (Part A) and between 18 and 26 kg/mE2,
inclusive (Part B), and with a minimum weight of 50 kg.
3. Subjects and their partners of childbearing potential must use 2 methods of contraception, one of which must
be a barrier method for the duration of the study and for 70 days after the last dose.
4. Able to participate and willing to give written informed consent and to comply with the study restrictions.

Exclusion criteria

1. Positive test for drugs of abuse at screening or Day -2.
2. History (within 3 months of screening) of alcohol consumption exceeding 2 standard drinks per day on average
(1 standard drink = 10 grams of alcohol). Alcohol consumption will be prohibited during study confinement and
at least 48 hours before screening, before dosing, and before each scheduled visit.
3. History or symptoms of any significant disease including (but not limited to), neurological, psychiatric,
endocrine, cardiovascular, respiratory, gastrointestinal, hepatic, or renal disorder.
4. History of active malignancy within the last 5 years, with the exception of localized or in situ carcinoma (e.g.,
skin basal or squamous cell carcinoma).
5. Positive Hepatitis B surface antigen (HBsAg), Hepatitis C antibody (HCV Ab) or human immunodeficiency
virus antibody (HIV Ab) at screening.

6. Confirmed (based on the average of 3 semi-supine, resting blood pressure measurements, properly measured
with well-maintained equipment, at each of > 2 visits to the office or clinic) systolic blood pressure (SBP) greater
than 140 or less than 90 mm Hg, and diastolic blood pressure (DBP) greater than 90 or less than 50 mm Hg.
7. Use of any medications (prescription or over-the-counter [OTC]), vitamin, mineral, herbal, and dietary
supplements within 21 days of study drug administration, or less than 5 half-lives (whichever is longer).
Exceptions are paracetamol (up to 4 g/day) and ibuprofen (up to 1g/day). Other exceptions will only be
made if the rationale is discussed and clearly documented between the Investigator and the Roche*s Clinical
Pharmacologist.
8. Clinically significant abnormalities in laboratory test results (including hepatic and renal panels, complete
blood count, chemistry panel and urinalysis). In the case of uncertain or questionable results, tests performed
during screening may be repeated before randomization to confirm eligibility or judged to be clinically irrelevant
for healthy subjects.
9. Participation in an investigational drug or device study within 3 months prior to screening.
10. Donation of blood over 500 mL within three months prior to screening.
11. Concomitant disease or condition that could interfere with, or for which the treatment of might interfere with,
the conduct of the study, or that would, in the opinion of the Investigator, pose an unacceptable risk to the subject
in this study.
12. Smoker of more than 10 cigarettes per day prior to Screening or who use tobacco products equivalent to more
than 10 cigarettes per day.
13. Any of the following findings in the resting ECG.
a) QTcF> 450 or < 300 msec at screening or baseline visit;
b) Notable resting bradycardia (HR < 45 bpm) or tachycardia (HR > 100 bpm) at screening or baseline visit;
c) Personal or family history of congenital long QT syndrome or sudden death;
d) Screening or baseline ECG with QRS and/or T wave judged to be unfavorable for a consistently accurate QT
measurement (e.g., neuromuscular artifact that cannot be readily eliminated, arrhythmias, indistinct QRS onset,
low amplitude T wave, merged T- and U-waves, prominent U waves);
e) Evidence of atrial fibrillation, atrial flutter, complete branch block, Wolf-Parkinson-White Syndrome, or
cardiac pacemaker at screening or baseline visit.
14. Any confirmed significant allergic reactions (urticaria or anaphylaxis) against any drug, or multiple drug

allergies (non-active hay fever is acceptable).
15. Unwillingness or inability to comply with the study protocol for any other reason.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-09-2010
Enrollment:	60
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	RO5428029
Generic name:	RO5428029

Ethics review

Approved WMO Date:	05-08-2010
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	23-08-2010

Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	01-10-2010
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-11-2010
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2010-019946-17-NL
CCMO	NL33259.058.10