A PHASE I, SPONSOR-OPEN, INVESTIGATORBLINDED,SUBJECT-BLINDED, MULTI-CENTER, PLACEBO-CONTROLLED STUDY TO EVALUATE SAFETY, TOLERABILITY, PHARMACOKINETICS AND PHARMACODYNAMICS OF ORAL ADMINISTRATION OF RO7020531: (1). SINGLE AND MULTIPLE ASCENDING DOSES IN HEALTHY MALE AND FEMALE SUBJECTS; (2). 6-WEEK TREATMENT OF VIROLOGICALLY SUPPRESSED PATIENTS WITH CHRONIC HEPATITIS B VIRUS INFECTION

Published: 19-09-2017
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OBJECTIVESPrimary ObjectivesThe primary objective is:* To assess the safety and tolerability of 6 weeks of treatment with RO7020531 administered orally to virologically suppressed chronic hepatitis B (CHB) patients.Secondary ObjectivesThe secondary…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON55546

Source
ToetsingOnline

Brief title
RO7020531

Condition

- Hepatic and hepatobiliary disorders
- Viral infectious disorders

Synonym
Chronic Hepatitis B virus infection

Research involving
Human

Sponsors and support

Primary sponsor: Covance
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: Chronic, Hepatitis-B, RO7020531

Outcome measures

Primary outcome

SAFETY OUTCOME MEASURES

* Incidence and severity of adverse events (AE).

* Incidence of laboratory abnormalities based on hematology, clinical

chemistry (including liver function tests), coagulation and urinalysis test

results.

* Incidence of vital signs (blood pressure, pulse rate, respiratory rate and body temperature) or ECG (PR [PQ], QRS, QT, QTcF) abnormalities.

A detailed medical history and physical examination will be performed at the time-points indicated in the SoA. Height will only be recorded at screening.

AEs and concomitant medications will be monitored throughout the entire study (screening through follow-up) as defined by International Conference on Harmonization (ICH) guidelines.

Monitoring for liver flares will be conducted for the duration of the CHB patient study (Part 2).

PHARMACOKINETIC OUTCOME MEASURES

* Summary descriptive statistics of plasma PK parameters for RO7020531, the main active metabolite RO7011785, and additional metabolites, including RO7018822 and RO7033805, will be computed. These parameters include Cmax, Tmax, AUCinf, AUClast and t1/2 and will be presented by dose cohorts including mean, standard deviation (SD), coefficient of variation (CV), medians and ranges.

* The total amount of RO7020531, the main active metabolite RO7011785 and additional metabolites, including RO7018822 and RO7033805, in urine over a 24 hour period will be computed and provided in tables and listings.

* In Part 2, sparse sampling for tenofovir (including tenofovir alafenamide,

if approved for

HBV and applicable), entecavir, adefovir and telbivudine will be made. As

appropriate,

tables and listings of these concentrations will be provided.

PHARMACODYNAMIC OUTCOME MEASURES

Part 1: SAD and MAD in Healthy Volunteers

* Blood samples will be collected to evaluate a number of PD outcome measures

including, but not

limited to, the protein and metabolite markers (neopterin, IFN-*, IP-10, TNF-*,

IL-6, IL-10,

IL-12p40), and markers of transcriptional responses (ISG15, OAS-1, MX1 and

TLR7).

Part 2: Chronic Hepatitis B Patients

* Blood samples will be collected to evaluate a number of PD outcome measures

including, but not

limited to, the protein and metabolite markers (neopterin, IFN-*, IP-10, TNF-*,

IL-6, IL-10,

IL-12p40), markers of transcriptional responses (ISG15, OAS-1, MX1 and TLR7),

and

immunophenotyping. Immunophenotyping will be performed by flow cytometry and

include the

determination of the number and percentage of TBNK (T-cells, B-cells and NK

cells)

and of myeloid and plasmacytoid dendritic cells (pDCs).

* Additional PD assessments (proteins and mRNA) may be added to those listed above as needed.

EXPLORATORY OUTCOME MEASURES

HBV Antiviral Measures

The antiviral outcome measures for this study are the following:

* Quantitative HBV DNA

* HBsAg (qualitative)

* HBsAg (quantitative)

* Hepatitis B envelope antigen (HBeAg) (qualitative)

* Anti-HBe and anti-HBs antibody status.

* Additional exploratory biomarkers such as HBsAg/anti-HBsAg complex levels, HBeAg levels (semi-quantitative assessment based on signals in the HBeAg assay), HBcAg, anti- HBc antibody and total nucleic acids (TNA) may be assessed at the time-points specified in the SoA as an evaluation of potentially predictive markers of therapeutic response, in conjunction with the viral parameters listed above.

Outcomes of antiviral response will include quantitative HBeAg decline, loss of HBeAg, development of anti-HBe, HBeAg seroconversion (loss of HBeAg and presence of anti-HBe), quantitative HBsAg decline, loss of HBsAg, development

of anti-HBs, HBsAg seroconversion (loss of HBsAg and presence of anti-HBs), and maintenance of HBV DNA levels less than 90IU/mL (at the end of the treatment period and at the end of the follow-up period).

Monitoring of viral resistance will be performed in any patient who experiences virological Monitoring of breakthrough.

Secondary outcome

Other Exploratory Measures

Other exploratory outcome measures for Part 2 of this study include, but are not limited to, the following:

* Ex vivo stimulation of whole blood samples may be performed on Day -1. Samples may be analyzed for cytokine/chemokine production using the Truculture method.
* Global gene expression analysis may be performed for selected whole blood RNA samples collected at the time-points specified in the SoA to identify markers or signatures potentially predictive of antiviral responses.
* Changes in T-, B-, NK, pDC- and mDC cells may be explored for their potentially predictive value for treatment with RO7020531.

Study description

Background summary

1.1 BACKGROUND ON DISEASE

Chronic hepatitis B (CHB) and its sequelae are major global healthcare problems. Despite the implementation of effective vaccination in many countries, hepatitis B is one of the most common infectious diseases in the world. It is estimated that more than
2 billion people or one third of the world*s population have been infected with the hepatitis B virus (HBV) at some time in their lives and an estimated 240 million are now chronically infected (WHO 2002, WHO 2016). Nearly 25% of all chronic HBV carriers develop serious liver diseases such as chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma. More than 686 000 people die every year due to the consequences of hepatitis B (WHO 2016).

The endemicity of HBV varies substantially by region, with East Asia and sub-Saharan Africa having prevalence rates of CHB above 8% (Ott et al 2012). In these highly endemic areas, the most common means of transmission is by perinatal infection, and up to 90% of the population has serological evidence of prior infection (Alter et al 2003). Although prevalence levels in developed countries are relatively low, immigration from
highly endemic regions has had a significant influence on the local need for therapy, and even countries with low endemicity are currently experiencing the burden of CHB (Wasley et al 2010).

HBV belongs to the Hepadnaviridae family. It is a partly double-stranded DNA virus with approximately 3200 base pairs. The transcriptional template of HBV is the covalently closed circular DNA (cccDNA), which resides inside the hepatocyte nucleus as a minichromosome (Locarnini et al 2010). Several HBV subtypes have been identified. Most CHB patients are infected with the wild-type strain of HBV, which produces large amounts of the hepatitis B envelope antigen (HBeAg) resulting in the HBeAg-positive form of CHB. However, in a significant proportion of patients, variant forms of the virus predominate later in the course of the disease, which have diminished ability to produce HBeAg. Another serological marker, hepatitis B surface antigen (HBsAg), is a hallmark of the infection and remains persistently positive in CHB patients. There is a correlation between the presence of HBsAg and patients* outcome with HBsAg level being predictive of fibrosis severity, development of hepatocellular carcinoma and survival rates (Fattovich et al 1998, Tseng et al 2012, Martinot-Peignoux et al 2013).

HBV is not cytopathic: both liver damage and viral control are immunomediated (Trepo et al 2014). The clinical outcome of infection is dependent on the complex interplay between HBV replication and both the innate and adaptive immune responses. The dominant cause of the long-term viral persistence and pathogenesis of HBV liver disease is the development of an inefficient

antiviral response to the viral antigens (Bertoletti et al 2012).

Currently available treatments for CHB include interferon (IFN), pegylated-interferon (PEG-IFN), and nucleos(t)ide analogues (NUC): lamivudine, adefovir, entecavir, tenofovir and telbivudine (Papatheodoridis et al 2012; Sarin et al 2016; Terrault et al 2016). Although these therapies achieve long-term effects in lowering HBV DNA levels, chronic HBV infection cannot be completely eradicated with currently approved therapeutics due to the persistence of cccDNA in the nucleus of infected hepatocytes (Lucifora et al 2014). With these treatments, rates of HBsAg clearance and seroconversion, which are associated with reduced or reversed cirrhosis and prevention of HCC development, are low (<15% HBsAg seroconversion after 1 to 5 years follow-up) (Chang et al 2010,Marcellin et al 2013). In addition, the notable deficiencies of current HBV treatments include indefinite duration of NUCs and risk of viral resistance with some NUC treatments, while PEG-IFN therapy is poorly tolerated and a significant portion of patients do not have a virological response (Papatheodoridis et al 2008).

Due to the therapeutic limitations of the currently available agents for the management of HBV infection, there is a need for new treatments of CHB that can provide clinical cure (HBsAg loss) and sustained suppression of HBV replication (Wang and Chen 2014).

Toll-like receptors (TLRs) are a family of pathogen-recognition receptors that activate the innate immune response. Stimulation of TLRs leads to the release of multiple cytokines, including type I and type II IFNs, to the induction of pathways and enzymes that destroy intracellular pathogens, and to the maturation of professional antigen-presenting cells, resulting in the activation of the adaptive immune response (Iwasaki and Medzhitov 2004). To date, 11 functional TLRs have been identified in humans. Most TLRs are located in the plasma membrane, except TLR3, TLR7, TLR8 and TLR9, which are intracellularly expressed, particularly in endosomes. TLR7 receptors are able to recognize viral components and induce IFN production and downstream responses (Lester and Li 2014).

A number of small molecule agonists for TLR7 have been identified (Horscroft et al 2012). The stimulation of TLR7 mediates an endogenous type I IFN response, which is critical in development of a broad, effective and protective immunity against hepatitis viruses (Horscroft et al 2012, Funk et al 2014). Compared to PEG-IFN therapy, treatment with a TLR7 agonist induces broader immuno-modulatory effects that are likely to lead to more effective control and functional cure of chronic HBV infection (Strader et al 2004, Isogawa et al 2005). TLR7 agonists induce the production of multiple isotypes of IFN from plasmacytoid dendritic cells (pDCs) which have

been shown in vitro to possess additive or synergistic antiviral effects compared to exogenous PEG-IFN.

1.2 BACKGROUND ON RO7020531

RO7020531, an oral double prodrug of the TLR7-specific agonist, RO7011785, is being developed for the treatment of CHB patients. A prodrug approach was chosen for oral delivery of the TLR7 agonist RO7011785 in order to improve bioavailability and limit TLR7 activation in the gastrointestinal (GI) tract, which may be associated with GI

intolerability. Non-clinical studies with RO7020531 suggest that it is rapidly converted to the active metabolite RO7011785. Data from in vivo studies with RO7020531 and in vitro studies with RO7011785 support immune activation as the mechanism of action.

See the RO7020531 Investigator Brochure (IB) for details on non-clinical studies.

Study objective

OBJECTIVES
Primary Objectives

The primary objective is:
* To assess the safety and tolerability of 6 weeks of treatment with RO7020531 administered
orally to virologically suppressed chronic hepatitis B (CHB) patients.

Secondary Objectives

The secondary objectives are:
* To investigate the plasma PK of RO7020531, the main active metabolite RO7011785, and
additional metabolites, including RO7018822 and RO7033805, in CHB patients.
* To investigate the PD markers of TLR7 activation, including cytokines and interferon-
stimulated genes (ISGs), following administration of RO7020531 to patients with CHB.
Exploratory Objectives
The exploratory objective for Part 2 (CHB patients) is:
* To investigate the antiviral effect of 6 weeks of treatment with RO7020531 in virologically
suppressed CHB patients.

Study design

Part 2 will commence after completion of the HV MAD portion of Part 1. It will be a multiple-
center, randomized, Sponsor-open, Investigator-blinded, patient-blinded, placebo-controlled study
to investigate the safety, tolerability, PK and PD of treatment with RO7020531 for 6 weeks
in virologically suppressed CHB patients.

Intervention

NA

Study burden and risks

NA

Contacts

Public
Covance

Avenue Marcel Thiry 77
Bruxelles 1200
NL
Scientific
Covance

Avenue Marcel Thiry 77
Bruxelles 1200
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

Patients must meet the following criteria for study entry:
1. Adult male and female patients, 18 to 65 years of age, inclusive.
2. Informed of, and willing and able to comply with, all of the protocol requirements and the
investigational nature of the study, and have signed an informed consent form (ICF) in accordance
with institutional and regulatory requirements.
3. A BMI between 21 to 32 kg/m2, inclusive. Males must be above 55 kg and females above 45 kg body weight.
4. Chronic hepatitis B infection (positive test for hepatitis B surface antigen (HBsAg) for more
than 6 months prior to randomization).
5. HBsAg detectable at screening.
6. On treatment with tenofovir, entecavir, adefovir, or telbivudine, either as single agents or
in combination, for at least 6 months. For Cohort 4: HBV treatment naïve or not on any anti-HBV treatment for the past 6 monts.
7. HBV DNA < 90 IU/mL for at least 6 months prior to randomization; HBV DNA < 90
IU/mL at screening by Roche Cobas assay. For Cohort 4: HBV DNA at screening *2 x 104 IU/mL for HBeAg positive and * 2 x 103 IU/mL for HBeAg negative patients.
8. Alanine amino transferase (ALT) * 1.5 × upper limit of normal (ULN) during the 6 months prior
to randomization confirmed by two measurements separated by at least 14 days (one of the ALT measurements can be done at screening); ALT at screening * 1.5 × ULN. For Cohort 4: ALT and aspartate aminotransferase (AST) at screening and Day -1 visit: *5 x ULN.
9. Screening laboratory values (including hematology, chemistry, urinalysis) obtained up
to 28 days prior to first study treatment within acceptable range or judged to be not clinically
significant by the Principal Investigator (PI) and Medical Monitor.
10. Aspartate aminotransferase (AST), Gamma glutamyl transpeptidase (GGT), alkaline phosphatase
(ALP), albumin, total and direct bilirubin within normal range or judged to be not clinically
significant by the Investigator and Medical Monitor at screening.
11. Negative ANA test, or positive with dilutions not greater than 1:40 and with no associated
history or symptoms of potential connective tissue disease or other immune-mediated diseases.

12. Liver biopsy, fibroscan* or equivalent elastography test obtained within 6 months prior to
randomization demonstrating liver disease consistent with chronic HBV infection with absence of
cirrhosis and absence of extensive bridging fibrosis (cirrhosis or extensive bridging fibrosis are
defined as * Metavir 3, recommended cutoff for fibroscan 8.5 kPa).
13. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual
intercourse) or use two approved contraceptive methods, of which one must be a barrier method and
the other should be an established non-barrier form of contraception with a failure rate of < 1%
per year, during the treatment period and for at least one month after the last dose of study drug.
a. A woman is considered to be of childbearing potential if she is post-menarcheal, has not
reached a post-menopausal state (* 12 continuous months of amenorrhea with no identified cause
other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or
uterus).
b. Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal
occ lusion, male sterilization, established proper use of hormonal contraceptives that inhibit
ovulation, hormone-releasing IUDs, and copper IUDs.
c. The reliability of sexual abstinence should be evaluated in relation to the duration of the
clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g.,
calendar, ovulation, symptothermal, or post-ovulation methods) and withdrawal are not acceptable
methods of contraception.
14. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use
contraceptive measures, and agreement to refrain from donating sperm, as defined below:
a. With female partners of childbearing potential or pregnant female partners, men must remain
abstinent or be willing to use two methods of contraception with their partners, one of which must
be a condom and the other should be an established form of contraception, during the treatment
period and for at least one month after the last dose of study drug to avoid exposing the embryo.
Other acceptable forms of contraception include vasectomy, bilateral tubal

occlusion, IUD or proper
use of hormonal contraceptives (e.g. contraceptive pills). Men must refrain from donating sperm
during this same period.
b. The reliability of sexual abstinence should be evaluated in relation to the duration of the
clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence and
withdrawal are not acceptable methods of contraception.
15. Negative pregnancy test on Day -1 for female patients.

Exclusion criteria

Patients who meet any of the following criteria will be excluded from study entry:
1. Pregnant (positive pregnancy test) or lactating women and male partners of women who are
pregnant or lactating.
2. History of liver cirrhosis.
3. History or other evidence of bleeding from esophageal varices.
4. Decompensated liver disease (e.g., Child-Pugh Class B or C clinical classification or clinical
evidence such as ascites or varices).
5. History or other evidence of a medical condition associated with chronic liver disease other
than HBV infection (e.g., hemochromatosis, autoimmune hepatitis, alcoholic liver disease, toxin
exposure, thalassemia, nonalcoholic steato-hepatitis, etc.).
6. Documented history or other evidence of metabolic liver disease within one year of
randomization.
7. Positive test for Hepatitis A virus (IgM anti-HAV), Hepatitis C (HVC), Hepatitis D virus, Hepatitis E virus (HEV), or human immunodeficiency virus (HIV).
8. Expected to need systemic antiviral therapy other than that provided by the study at any time
during their participation in the study, with the exception of oral therapy for Herpes simplex
virus type I (HSV I) or HSV II.
9. History of or suspicion of hepatocellular carcinoma or alpha fetoprotein * 13 ng/mL at
screening.
10. History of immunologically mediated disease (e.g., inflammatory bowel disease,
idiopathic thrombocytopenic purpura, lupus erythematosus, autoimmune hemolytic

anemia, scleroderma,
severe psoriasis, rheumatoid arthritis, multiple sclerosis, or any other autoimmune disease).
11. History of clinically significant cardiovascular, endocrine, renal, ocular, pulmonary or
neurological disease (as per Investigator*s judgment).
12. History of clinically significant GI disease including inflammatory bowel disease, peptic ulcer
disease, GI hemorrhage.
13. History of clinically significant psychiatric disease, especially major depression (significant
psychiatric disease is defined as treatment with an antidepressant medication or a major
tranquilizer at therapeutic doses for major depression or psychosis, respectively, or any history
of the following: a suicide attempt, hospitalization for psychiatric disease, or a period of
disability due to a psychiatric disease).
14. Evidence of an active or suspected cancer or a history of malignancy, where in the
Investigator*s opinion, there is a risk of recurrence
15. History of having received or currently receiving any systemic anti-neoplastic (including
radiation) or immune-modulatory treatment (including systemic oral or inhaled corticosteroids, IFN
or PEG-IFN) within the 8 weeks prior to the first dose of study drug or the expectation that such
treatment will be needed at any time during the study. Eye drop-containing and infrequent inhaled
corticosteroids are permissible up to 4 weeks prior to the first dose of study drug.
16. History of organ transplantation.
17. Clinically significant thyroid disease; also, patients with clinically significant elevated
TSH concentrations at screening.
18. Any confirmed clinically significant allergic reactions (anaphylaxis) against any drug, or
multiple drug allergies (non-active hay fever is acceptable).
19. Clinically significant acute infection (e.g., influenza, local infection) or any other
clinically significant illness within 2 weeks of randomization.
20. Clinically relevant ECG abnormalities on screening ECG.21. Any of the following laboratory parameters at screening:
a. WBC < 3,000 cells/mm3
b. Neutrophil count < 1500 cells/mm3 c. Platelet count < 140,000 cells/mm3
d. aPTT > 40
seconds, INR > 1.2

e. Hb < 12 g/dL in females or 13 g/dL in males
22. Abnormal renal function including serum creatinine > ULN or calculated CrCl < 60 mL/min (using
the Cockcroft Gault formula).
23. Positive results for AMA, ASMA or thyroid peroxidase antibody.
24. Participation in an investigational drug or device study within 30 days prior to randomization.
25. Donation or loss of blood over 500 mL, or administration of any blood product, within 90 days
prior to starting study medication.
26. History of alcohol abuse (consumption of more than 2 standard drinks per day on average; 1
standard drink = 10 grams of alcohol) and/or drug abuse within one year of randomization.
27. Positive test for drugs of abuse or positive alcohol test at screening or Day -1. For positive
cannabinoids test, the eligibility is at the Investigator*s discretion.
28. Patients under judicial supervision, guardianship or curatorship.
29. Any medical or social condition which may interfere with the patient*s ability to comply with
the study visit schedule or the study assessments.
N8Æ²d

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	17-04-2018
Enrollment:	4

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Baraclude
Generic name:	Entacavir

Ethics review

Approved WMO Date:	19-09-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-03-2018
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2019

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-09-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-11-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-12-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-03-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-06-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2016-003723-38-NL
ClinicalTrials.gov	NCT02956850
CCMO	NL62205.018.17

Study results

Results posted: 21-02-2022

First publication
29-01-2022