Een fase 1 dubbel-blind, gerandomiseerde, placebo-gecontrolleerde studie in gezonde vrijwilligers om de veiligheid, verdraagbaarheid en farmacokinetiek van opklimmende orale doseringen van TMC435350 te onderzoeken na enkelvoudige en meervoudige doseringen, gevolgd door een herhaalde open label dosering in 6 HCV-genotype-1 geinfecteerde patienten, niet placebo gecontroleerd.

Gepubliceerd: 08-01-2007 Laatst bijgewerkt: 14-05-2024

The purpose of this study is to investigate how safe the study drug (TMC435350) is and how well it is tolerated. The study will also investigate how quickly and to what extent the study drug is absorbed and eliminated from the body either after a...

Ethische beoordeling	Goedgekeurd WMO
Status	Werving gestopt
Type aandoening	Virale infectieziekten
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON30518

Bron
ToetsingOnline

Verkorte titel

TMC435350, SRD en MRD-studie (FIH)

Aandoening

- Virale infectieziekten

Synoniemen aandoening
hepatitic-C infectie

Betreft onderzoek met
Mensen

Ondersteuning

Primaire sponsor: Janssen-Cilag
Overige ondersteuning: Tibotec Pharmaceuticals Ltd;Little Island;Co Cork;Ierland

Onderzoeksproduct en/of interventie

Trefwoord: farmacokinetiek, veiligheid, verdraagzaamheid

Uitkomstmaten

Primaire uitkomstmaten

Safety, tolerability and plasma and urine pharmacokinetics of TMC435350 after single oral doses from 50 mg up to 1200 mg or up to MTD.

During the MRD-part an ultra-sound of the hart (Echo cardiogram) will be collected at screening and during the study (at approximately day 6) and in case it is deemed necessary based on the previous ultrasounds, possibly on day 8 and at both post-study screening visits.

Pat. group (7) an ultra-sound of the hart (Echo cardiogram) will be collected at screening, at arrival of the clinical unit and during the study (at approximately day 6) and in case it is deemed necessary based on the previous ultrasounds, possibly on day 8 and at both post-study screening visits.

Secundaire uitkomstmaten

Safety, tolerability and plasma and urine pharmacokinetics of TMC435350 after 5 days of consecutive dosing for twice daily doses from 50 mg up to 400 mg or up to the MTD

Food effect on the safety, tolerability and plasma and urine pharmacokinetics of a single oral dose of 200 mg TMC435350, unless the PK and safety data from previous sessions prove otherwise.

Safety, tolerability and plasma and urine pharmacokinetics of a single dose of 400 mg TMC435350 when given in the presence of a low dose of ritonavir (100 mg twice daily for 2 days), provided the initial pharmacokinetic data support this, unless the PK and safety data from previous sessions prove otherwise.

Toelichting onderzoek

Achtergrond van het onderzoek

The drug TMC435350 is a new, investigational study drug that may eventually be used for the treatment of hepatitis-C infections. The study drug is a protease inhibitor (PI), a class of drugs that selectively inhibit the replication of the virus thereby inhibiting the progression of hepatitis-C infection.

Doel van het onderzoek

The purpose of this study is to investigate how safe the study drug (TMC435350) is and how well it is tolerated. The study will also investigate how quickly and to what extent the study drug is absorbed and eliminated from the body either after a period of fasting as well as after intake of breakfast. Depending on the first study results the effects of the study drug will as well be investigated when administered together with ritonavir. Ritonavir is a medicine that is available on the market for the treatment of HIV-1 infections. It is available as Norvir. This medicine is known for it*s influence on the processing of drugs in the body.

Onderzoeksopzet

This study is a randomized, double blind, placebo-controlled study to determine

the safety, tolerability and pharmacokinetics of TMC435350 after single and multiple oral intakes in healthy subjects, followed by an open label repeated dosing session in 6 HCV-genotype -1 infected patients (non placebo controlled).
This study consists of two parts. In the first part (group 1 and 2, 9 volunteers each) a single doses of the drug will be administered and in the second part (group 3, 4, 5 and 6, 9 volunteers each) multiple doses will be administered. Patient group (7) consist of 6 Subjects who will receive multriple dosing of TMC435350.
SRD: First Part
The subjects who participate in group 1 will receive a single dose of 50, 200 or 800 mg TMC435350 or placebo on day 1 of period 1, 2 and 3 respectively, followed by a dose of 200 mg TMC 435350 or placebo on Day 1 of period 4. A placebo is a solution without the active ingredient.
The subjects who participate in group 2 will receive a single dose of 100, 400 or 1200 mg TMC435350 or placebo on day 1 of period 1, 2 and 3 respectively, followed by a dose of 400 mg TMC 435350 or placebo on Day 3 of period 4. In this period (period 4) the subjects will receive a dose of 100 mg ritonavir twice daily, as well, on Day 1 to 5.
It may be the case that in the periods 4 the dose will be adjusted to one of the previous used doses. This will be decided based on the results obtained during the previous dosing.
Second Part
MRD: The subjects who participate in group 3, 4, 5 or 6 will receive multiple daily doses of 50, 100, 200 or 400 mg or placebo, respectively, split over two administrations each day during 4 days and a single dose on Day 5. Based upon the results from the previous groups it might be decided to provide the full daily dose once daily.
Group 7: Starts after completion of the healthy volunteers sessions. This is an open
label treatment in HCV-genotype 1 infected patients (N=6). The dose regimen will be selected which was shown to be safe in healthy volunteers and as close as possible to a maximum tolerated dose, which will be adminstered for 5 days. TMC435350 will be administered as an oral solution. Ritonavir will be administered in the form of a capsule.
Full PK profiles of TMC435350 will be determined up to 72 hours after the last dose. Safety and tolerability will be evaluated continuously and documented (safety report)), with 24 hours interim PK data after the last dose, before stepping up to the next dose and between each session. Dose escalation will continue only if the previous dose was found safe and tolerable by the investigator, sponsor and METC.

Onderzoeksproduct en/of interventie

The single dose escalation part of the trial will consist of 6 sessions (Sessions Ia to VIa) and the trial population will include 2 panels of 9 healthy subjects each (Panels 1 and 2). The dose of the test drug will be consecutively escalated. Doses of 50 mg, 100 mg, 200 mg, 400 mg, 800 mg and 1200 mg of TMC435350 or placebo will be administered as a single oral

administration alternating over the 2 panels. In each session, 6 subjects will receive active treatment and 3 subjects will receive placebo after a standardized breakfast. The treatment schedule will ensure that over 3 sessions each subject will receive active treatment twice and placebo once. A washout period of at least 10 days will be respected between consecutive TMC435350 or placebo dosings within each panel. Subjects of Panel 1 will have an additional session to investigate food effect: a single dose of TMC435350 will be tested in fasted conditions (Session VIIa). Food effect will be investigated for the 200 mg dose in Panel 1, unless the pharmacokinetic (PK) and safety data from previous sessions prove otherwise. Subjects of Panel 2 will have an additional session to investigate potential effects of twice daily (bid) dosing of 100 mg ritonavir on the pharmacokinetics, safety and tolerability of a single dose of TMC435350 (Session VIIIa), unless PK enhancement by boosting with ritonavir (Norvir®) is not expected from the PK data obtained in previous sessions. PK enhancement with ritonavir will be investigated for the 400 mg dose in Panel 2, unless the PK and safety data from previous sessions prove otherwise, and this dose will be co-administered on Day 3 of a 5 day regimen of 100 mg ritonavir b.i.d. For Session VIIa (Panel 1) and Session VIIIa (Panel 2) the same randomization scheme as in the session of the selected dose will be used. Multiple dosing will be started when Sessions Ia (single dose of 50 mg), IIa (single dose of 100 mg) and IIIa (single dose of 200 mg) are found to be safe and tolerable. The multiple dose escalation part of the trial will consist of 4 consecutive sessions (Sessions Ib to IVb) in 4 panels of 9 healthy subjects each (Panels 3, 4, 5 and 6). In each session, 6 subjects will receive active treatment and 3 subjects will receive placebo. TMC435350 or placebo will be administered during 5 consecutive days. After completion of the healthy volunteers sessions, an open label sessions will be added in HCV-genotype-1 infeced patients. TMC435350 will be administered during 5 consecutive days. The dose regimen will be selected which was shown to be safe in the healthy volunteers group. The final dose selection will be presented to the METC for approval.

Inschatting van belasting en risico

The associated risks to this study are the occurence of possible side effects of the use of TMC435350 and or in combination with Ritanovir. The burden of the subjects are the confinement periods in the study unit, venapunction, the insertion of the canula and an echo of the heart will be recorded. All subjects will be carefully monitored regarding possible adverse events by experienced study personel and physicians.
For HCV infected patients, there is a risk of development of resistance to TMC435350. The short term nature of the study makes this less likely. In addition, studies with other PIs for the treatment of HCV have shown that, when resistance develops, it rapidly reverses to wild type virus upon discontinuation of the compound.

Contactpersonen

Publiek

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Wetenschappelijk

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Locaties

Landen waar het onderzoek wordt uitgevoerd

Netherlands

Deelname eisen

Leeftijd
Volwassenen (18-64 jaar)
65 jaar en ouder

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

Gezonde mannen en vrouwen tussen de 18 en 55 jaar,
Niet-roker tenminste 3 maanden voorafgaande aan de screening visite.
Normaal gewicht, met een BMI-index van 18-30 kg/m2. Normaal ECG.
Patiënten:
Pat. met een leeftijd tussen 18-70 jaar, uitersten inclusief.
Pat. met chronische genotype 1 HCv-infectie, die niet reageerd op voorgaande behandelingen met interferon/ribavirin.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

Bekend met hart ritme arritmieën of verlenging van QTc-interval > 450 ms, bekend met risico factors voor Torsade de Pointes of cardiomyopathie verschijnselen bevestigd door een Graad 1 of hoger in verlaging van EF/SF.
Vrouw behalve indien minimaal 2 jaar postmenopausaal, chirurgisch gesteriliseerd of baarmoeder verwijderd.
Lijdend aan: ernstige aandoening zoals bijvoorbeeld hepatitis A, B, of C infectie of kanker of HIV/AIDS.
Indien gedurende de 30 dagen voorafgaand aan de start van dit onderzoek aan een ander geneesmiddelenonderzoek is deelgenomen.
Indien gedurende de 60 dagen voor start van dit onderzoek bloed gegeven.
Patiënten:
Pat. geinfecteerd met HIVV-1; HIV-2 of iedere andere lever infectie anders dan HCV.
mannelijke pat. met een vrouwelijke partner in de vruchtbare leeftijd die niet instemmen om betrouwbare anticonceptie methode te gebruiken gedurende 90 dagen na de laatste toediening van het onderzoeksmiddel.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blindering:	Dubbelblind
Controle:	Placebo
Doel:	Behandeling / therapie

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	03-02-2007
Aantal proefpersonen:	60
Type:	Werkelijke startdatum

In onderzoek gebruikte producten en hulpmiddelen

Soort:	Geneesmiddel
Merknaam:	Norvir
Generieke naam:	Ritanovir
Registratie:	Geregistreerd voor de te bestuderen indicatie/dosering

Ethische beoordeling

Goedgekeurd WMO Datum:	08-01-2007
Soort:	Eerste indiening
Toetsingscommissie:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Goedgekeurd WMO Datum:	23-01-2007
Soort:	Amendement
Toetsingscommissie:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Goedgekeurd WMO Datum:	23-01-2007
Soort:	Eerste indiening
Toetsingscommissie:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Goedgekeurd WMO Datum:	23-04-2007
Soort:	Amendement
Toetsingscommissie:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Goedgekeurd WMO Datum:	16-05-2007
Soort:	Amendement
Toetsingscommissie:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Goedgekeurd WMO Datum:	21-05-2007
Soort:	Amendement

Toetsingscommissie:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
EudraCT	EUCTR2006-006455-12-NL
CCMO	NL15888.056.06