RESPIRE - A Randomized, Double-Blind, Placebo-Controlled, Multi-Centre Clinical Trial to Evaluate the Safety and Efficacy of ATR-002 in Adult Hospitalized Patients with COVID-19

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• To demonstrate the efficacy of ATR-002 versus placebo in addition to standard of care based on the clinical severity status in adult hospitalized patients with COVID-19• To show that ATR-002 in addition to standard of care shortens the time to...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON50897

Source
ToetsingOnline

Brief title
Safety and Efficacy of ATR-002 for Hospitalized Patients with COVID-19

Condition

- Viral infectious disorders
- Respiratory tract infections

Synonym
COVID-19, lung disease

Research involving
Human

Sponsors and support

Primary sponsor: Atriva Therapeutics GmbH
Source(s) of monetary or material Support: - Meneldor (investment fund focused on early stage biotech companies) - High-Tech Gründerfonds (HTGF);a Germany-based seed investor for innovativetechnologies and business models - Private Investors and Atriva Managment and founders - European Investment Bank

Intervention

Keyword: ATR-002, COVID-19, Infectious disease, Respiratory disease

Outcome measures

Primary outcome

• Population: All study participants fulfilling the inclusion and exclusion

criteria

• Target variable: Clinical severity status on a 7-point ordinal scale at Day 15

• Estimator: Odds ratio of ATR-002 in addition to standard of care versus

placebo in addition to standard of care with 95%

confidence interval

• Fulfillment of In-/exclusion criteria on day 1

• Target variable on day 15

Secondary outcome

• Population defined as above

• Target variables:

- Time from randomization to discharge from hospital

- Time to discharge from hospital or to score of <=2 maintained for 24 hours in

NEWS2, whichever occurs first

- Time to resolution of fever, defined as <=36.6°C (axilla), <=37.2°C (oral) or

<=37.8°C (rectal or tympanic) for at least 24 hours without

antipyretics for 24 hours

- Time to SpO2 >94% on room air maintained for 24 hours

- Clinical severity status over the hospital period calculated as AUC from the

7-point ordinal scale at Days 3, 5, 8, 11, 15 and 30

- Survival time up to Day 30

Study description

Background summary

ATR-002 is a small molecule inhibitor of MEK1 and MEK2 (members of the Ras/Raf/MEK/ERK signaling pathway) that is being developed for the treatment of viral infection, based on the finding that replication of some viruses in host cells depends on an active Raf/MEK/ERK pathway. The antiviral activity of ATR-002 was primarily established in models of influenza (Laure et al, 2020). In addition, the host-cell based mechanism of action suggests a much broader antiviral activity, which has subsequently been demonstrated in various viruses such as hantavirus, respiratory syncytial virus (RSV) and the newly identified SARS virus, SARS-CoV-2.
Based on recent preclinical studies with SARS-CoV-2 performed in laboratories at the Universities of Tuebingen (Prof. Oliver Planz) and Muenster (Prof. Stephan Ludwig), ATR-002 emerges as a possible treatment option in patients suffering from the coronavirus disease 2019 (COVID-19) - the lung disease resulting from infection with SARS-CoV-2.
The clinical spectrum of SARS-CoV-2 infection appears to be wide. Mild infection occurs at the time of inoculation and early establishment of the disease, with mild and often nonspecific symptoms such as malaise, fever, and a dry cough. In patients who can keep the virus limited to this stage of COVID-19, prognosis and recovery is excellent (Siddiqi and Mehra, 2020).
For patients who progress to established pulmonary disease, viral multiplication and localized inflammation in the lung is the norm. During this stage, patients develop a viral pneumonia, with cough, fever and possibly hypoxia. Over the course of the disease, dyspnea occurs after approximately 2 weeks. Imaging with chest X-ray or computerized tomography reveals bilateral infiltrates or ground glass opacities. Markers of systemic inflammation may be elevated, but not remarkably so. It is at this stage that most patients with COVID-19 need to be hospitalized for close observation and management. Treatment primarily consists of supportive measures and available antiviral therapies, once available. It is possible that patients will progress to require mechanical ventilation (Siddiqi and Mehra, 2020).

The current outbreak caused by SARS-CoV-2 is a threat that is rapidly escalating and spreading around the globe. Numerous treatments for COVID-19 are undergoing evaluation in clinical trials. Preliminary data have shown that dexamethasone reduced 28*day mortality among patients with COVID-19 receiving invasive mechanical ventilation or oxygen at randomization; however, mortality was not reduced in patients who were not receiving respiratory support (Horby et al, 2020). Remdesivir has received conditional marketing authorization in Europe for COVID-19 patients with pneumonia requiring supplemental oxygen as treatment of these patients was associated with sooner recovery compared with placebo, although no effect was seen in patients with mild-to moderate disease (European Medicines Agency, June 2020). There is still an unmet medical need as, at the time of writing this clinical trial protocol, no highly potent specific drug treatment to fight COVID-19 is available.
ATR-002 was generally safe and well tolerated in healthy subjects in a Phase 1 clinical trial involving 70 healthy participants, in which the safety and pharmacology of various doses of ATR-002 were assessed in single ascending dose and multiple ascending dose settings (Section 4.3 of the clinical study protocol).

Study objective

• To demonstrate the efficacy of ATR-002 versus placebo in addition to standard of care based on the clinical severity status in adult hospitalized patients with COVID-19
• To show that ATR-002 in addition to standard of care shortens the time to clinically relevant improvement of COVID-19 for a hierarchically ordered sequence of time-to-event endpoints
• To show that the primary endpoint extended as AUC has a more favorable level under ATR-002 compared to placebo in addition to standard of care over the initial trial period of 30 days in adult hospitalized patients with COVID-19
• To explore whether survival time will be prolonged under ATR-002 compared to placebo in addition to standard of care during the initial 30 days of the trial period in adult hospitalized patients with COVID-19

Study design

This is a Phase 2, multi-center, randomized, double-blind, controlled, parallel group, two-arm clinical trial (ATR-002 vs. placebo).
The study will assess the efficacy and safety of ATR-002 versus a matching placebo, as well as pharmacokinetics of ATR-002 in adult hospitalized patients with COVID-19. Study participants will additionally receive throughout the clinical trial any treatment that is considered standard of care as per local standards.
To minimize bias, the clinical trial will be randomized and double-blind. Following screening procedures, eligible study participants will be centrally assigned to randomized investigational medicinal product

(IMP) using Interactive Response Technology (IRT). The
control group will receive matching placebo to the treatment (ATR-002) group.
Drug concentration information will not be reported
to study sites or blinded study personnel until the clinical trial has been
unblinded.
An independent Data Monitoring Committee will convene in accordance with
clinical trial progress, i.e. after 20 study participants
have been treated and then again after each 50 study participants have been
treated. In addition, special meetings can take place
if concerns about the safety of study participants arise.

Intervention

The clinical trial comprises a screening period of up to approximately 24 hours
(on Day -1), followed by a 6-day treatment period
on Days 1 to 6, and follow-up at defined time points up to Day 90.
Study participants will receive IMP (ATR-002 or placebo) orally once daily for
6 days. The daily dose of ATR-002 will be 900 mg on
Day 1 and 600 mg on Days 2 to 6.

Study burden and risks

Treatment with ATR-002 may lead to undesired effects or symptoms. The following
undesired effects and symptoms are known to
date:
Stomach pain
Diarrhea
Dizziness
Headaches
Rash
As with any new investigational medicinal product, treatment with ATR-002 may
also result in new, so far unknown side effects.
The procedures conducted within the scope of this clinical trial may also be
associated with risks or elicit symptoms, e.g., malaise,
during smear tests or blood withdrawals.
Temporary, mild conditions may arise at the spot where the needle is inserted
into the body for blood withdrawals, such as
bruising, swelling and/or nerve damage or local infections in rare cases.
For this reason, the patient is being asked to inform the study team of any
malaise, any illness and any injury that arises during the
clinical trial. If these are severe, he/she must contact the study team as soon
as possible (by telephone if needed).
No highly potent specific drug treatment is currently available for COVID-19.
As such, there is an unmet medical need to respond
to this global pandemic.
Based on the known mode of action of ATR-002, it is possible that study

participants who receive the drug may experience
symptomatic benefit and reduced likelihood of progression to more severe forms
of the disease. However, there is no guarantee
that participation in the current clinical trial will help the study
participant.
Participation in this clinical trial may lead to closer monitoring of a study
participant*s condition, irrespective of his/her
randomization arm.

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. Capable of giving signed informed consent as described in Section 10.1.3 of
the protocol, which includes compliance with the requirements and restrictions

listed in the informed consent form (ICF) and in this protocol.
2. Study participant must be at least 18 years of age at the time of signing the ICF.
3. Study participants with a laboratory confirmed diagnosis of SARS-CoV-2 infection presenting as moderate -to-severe COVID-19 requiring hospitalization for COVID-19 (Clinical Severity Status [3] or [4]) and for medical reasons (see Section 8 of the protocol). Patients presenting to the hospital without a laboratory confirmed SARS-CoV-2 infection will be tested locally for SARS-CoV-2 during the screening period.
For sites in the EU: A CE certified SARS-CoV-2 PCR test kit is required to confirm infection.
For sites outside the EU: SARS-CoV-2 PCR test kits certified according to local regulations are required to confirm infection.
4. Body weight at least 50 kg and have a body mass index (BMI) >= 18.0 kg/m2 and < 40.0 kg/m2.
5. Male or female.
6. A female study participant is eligible to participate if she is not pregnant or breastfeeding, and one of the following conditions applies:
a. She is not a WOCBP as defined in Section 10.3.1 of the protocol.
b. Is a WOCBP and is using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.3.2 of the protocol during the IMP period and for at least 4 weeks after the last dose of IMP. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of IMP.
7. A WOCBP must have a negative urine pregnancy test within 24 hours before the first dose of IMP, see Section 8.3.5 of the protocol.
a. If a urine pregnancy test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required locally. In such cases, the participant must not be randomized if the serum pregnancy result is positive.
b. If a serum pregnancy test is required as per local regulations, a serum pregnancy test is required locally. In such cases, the participant must not be randomized if the serum pregnancy result is positive.
c. The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetectable pregnancy.
8. A male study participant is eligible to participate if:
a. He is azoospermic
b. The partner is not a WOCBP as defined in Section 1.1.1 of the protocol.
c. The partner is a WOCBP and is using a contraceptive method that is highly effective, with a failure rate of <1%, as described in Section 10.3.2 of the protocol during the IMP period and for at least 90 days after the last dose of IMP. The investigator should evaluate the potential for contraceptive method failure (e.g., noncompliance, recently initiated) in relationship to the first dose of IMP.
d. He acknowledges that sperm donation is prohibited from the first dose of IMP

until at least 90 days after the last dose of IMP.

Exclusion criteria

1. Patient*s clinical condition is worsening rapidly.
2. Requiring ICU admission or ventilator support at screening or at randomization.
3. Suspected bacterial, fungal, viral, or other infection (besides COVID-19).
4. History of any of the following: malignant disease, autoimmune disease, or severe liver, kidney, blood, cardiac, pulmonary, neurological, or endocrine disease as judged by the investigator. The medical monitor should be contacted by the investigator.
5. History of hypertension should have hypertension adequately controlled (BP < 140/90 mmHg) with appropriate anti-hypertensive treatment.
6. Clinically significant cardiac conduction abnormalities, including QTc prolongation of > 450 milliseconds.
7. Family history of Long QT Syndrome.
8. Heart failure class 3, or 4, as defined by the New York Heart Association (NYHA).
9. History of acute coronary syndrome (including myocardial infarction), coronary angioplasty, or stenting within 24 weeks prior to screening.
10. Patients with implanted defibrillators or permanent pacemakers.
11. Poorly controlled diabetes mellitus with an HbA1c > 7.5 %.
12. Renal disease including glomerulonephritis, nephritic syndrome, Fanconi Syndrome, or renal tubular acidosis.
13. Renal failure requiring renal replacement therapy or moderate renal impairment as defined by having an estimated glomerular filtration rate (eGFR, CKD-EPI) < 45 ml/min/1.73m2.
14. Chronic Obstructive Pulmonary Disease (COPD) GOLD C, or D, or hospitalization for exacerbation of COPD within 24 weeks prior to screening.
15. Other chronic lung diseases including cystic fibrosis, neuromuscular diseases, severe chest wall deformities, interstitial lung diseases, outpatient chronic non-invasive ventilation due to chronic respiratory failure.
16. Asthma with a symptom control level of "uncontrolled", according to current GINA guidelines.
17. Currently suffering from diseases that seriously affect the immune system, such as: human immunodeficiency virus (HIV) infection, or the blood system, or splenectomy, or organ/ stem cell transplantation.
18. Known Hepatitis B or C infection.
19. Any medical condition, physical examination finding or laboratory abnormality that, in the opinion of the investigator, might confound the results of the study or pose an additional risk to the patient.
20. Alanine transaminase (ALT) or aspartate transaminase (AST) > 3.0 x ULN.
21. Total bilirubin > 1.0 x ULN (>=1.5 x ULN total bilirubin if known Gilbert*s syndrome).

22. Taking concomitant medication metabolized by CYP2C8 and/ or CYP2C9 and listed as *prohibited* in Section 10.5 of the protocol.
23. Taking concomitant medication of any experimental treatment or use of marketed medications including off-label use, that are intended as specific treatment for COVID-19. Any such treatments must be washed out for 30 days or at least 5 half-lives prior to randomization, whichever is longer, unless a formal written standard of care policy document requires otherwise. Inclusion needs to be approved by the investigator and medical monitor.
24. Taking medication that may seriously affect the immune system, e.g. chemotherapy, unless considered and documented as standard of care (e.g. corticosteroids) to treat COVID-19.
25. Currently participating in other clinical trials or previous treatment with an investigational medicinal product within 5 half-lives or 30 days (whichever is longer) prior to randomization.
26. Known allergy or hypersensitivity to the IMP (including excipients).
27. Study participant is pregnant or breastfeeding.
28. Patient has been committed to an institution by virtue of an order issued either by the judicial or the administrative authorities.
29. Patient is an employee of the sponsor, or an employee of any third-party organization involved into the clinical trial, or an employee of the clinical trial site, or is dependent on the investigator.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	ATR-002
Generic name:	ATR-002

Ethics review

Approved WMO Date:	24-03-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	28-05-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-03-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-03-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2020-004206-59-NL
ClinicalTrials.gov	NCT04776044
CCMO	NL77121.100.21