Anti-COVID19 AKS-452 Phase I/II VaccinaTion Study (ACT-Study)

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Objective: Evaluation of safety and initial efficacy of a novel fusion-protein based anti-COVID19 vaccine in healthy volunteers.

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

Summary

ID

NL-OMON51213

Source
ToetsingOnline

Brief title
ACT-Study

Condition

- Viral infectious disorders

Synonym
COVID-19

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Akston Biosciences Corporation

Intervention

Keyword: AKS-452, COVID-19, SARS-CoV-2, Vaccin

Outcome measures

Primary outcome

Phase I: safety / immunogenicity

Phase II: safety / immunogenicity and initial efficacy as expressed by neutralizing IgG titers / seroconversion.

Secondary outcome

1. To evaluate the inhibitory/neutralization potency of the SP/RBD-specific IgG titers induced by AKS-452 and to estimate peak titers and duration of the response.

2. To evaluate the Th1/Th2 immune response profile.

To achieve these objectives, the following will be measured:

a. Anti-SARS-CoV-2 SP/RBD IgG titers at days 0, 28, 56, 90, and 180.

extra time points booster study: day 180+28, day 180+56.

b. Serum titer inhibition of recombinant ACE2-SP/RBD binding and/or neutralization of live SARS-CoV-2 virus infection of live cells (Plaque Reduction Neutralization Test, PRNT) at days 0, 28, 56, 90, and 180.

extra time points booster study: day 180+28, day 180+56.

c. T-cell responses measured ex vivo using PBMCs to measure SP/RBD-specific T cell production of IFN-g and Th1/Th2/Th17 related cytokines via ELISpot or other Ag-specific flowcytometric-based assays on days 0, 7, 28, 35, 56, 90, and

180.

extra time points booster study: day 180+28, day 180+56.

Study description

Background summary

Rationale: Every decade in the twenty-first century has experienced a new major coronavirus epidemic; SARS in the 2000s, MERS in the 2010s, and now (in 2020) Coronavirus Disease 2019 (COVID-19) caused by the SARS-COV-2 virus. This novel COVID-19 is a severe and acute respiratory illness caused by infection with the SARS-CoV-2 virus. The first COVID-19 case was reported in Wuhan, China in December 2019 and as of 18 November 2020, there has been approximately 56 million (M) cases world-wide to date (quantified as SARS-Cov-2 virus confirmed and unconfirmed *probable*), in which there are 18.5M active cases, 36M recovered cases, and 1.3M fatal cases attributed to COVID-19 (COVID-19 Dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University; https://www.covidtracker.com/). Consequently, to address this pandemic crisis, there is an immediate need for solutions that can accurately quantify the level of neutralizing anti-SARSCoV-2 Abs in individuals and therapeutically induce and/or amplify the level of neutralizing anti-SARS-CoV-2 Abs across the population. The expectation of the foreseeable future is that natural and vaccine-induced immunity most likely will not be long-lived [4, 7-10], and therefore a cost-effective and safe vaccine administered as frequently as every 6 months, if necessary, is required to maintain robust immunity among the population. Due to the apparent increased transmissibility of SARS-CoV-2, a global security priority is to advance and stockpile coronavirus vaccines as quickly as possible, inevitably requiring significant international funding and relaxing of regulatory paths in a responsible manner. Given the challenges of a recombinant SARS-Cov-2 SP subunit vaccine to induce a strong protective immune response in an immunologically naïve human population, the SP Ag must be modified and/or formulated with additional immune-enhancing features to overcome the activation thresholds of naïve T and B cells. Akston, the subsidising party of the study, has implemented the following features into its COVID-19 vaccine that are major advantages over most other such vaccines in development, in which the Therapeutic Product Profile (TPP) describes details of its clinical candidate, AKS-452:

1. The use of the smaller focused antigenic portion of SP, the RBD
2. Recombinant fusion of RBD with human IgG1 Fc (SP/RBD-Fc)
3. Emulsification of SP/RBD-Fc in the water-in-oil adjuvant, Montanide ISA 720

In summary, the Fc moiety on AKS-452 is designed to act as a mild adjuvant via inducing activation signaling to the APC via Fc*Rs and is designed to work in concert with a strong classical adjuvant, such as Montanide ISA 720, to enhance the duration of Ag exposure to APCs and perhaps direct Ag entry into lymph nodes locally and systemically where additional APCs reside. As a consequence, the Fc moiety in combination with an adjuvant is expected to create a dramatic dose-sparing potential for both the Ag and adjuvant such that the risk of reactogenicity (a safety concern) is dramatically reduced; i.e., too much adjuvant that overactivates many APCs and other innate immune cells can lead a systemic inflammatory reaction termed reactogenicity. Such reactogenicity is induced acutely after injection and is not mediated by T and B cells.

Study objective

Objective: Evaluation of safety and initial efficacy of a novel fusion-protein based anti-COVID19 vaccine in healthy volunteers.

Study design

Study design: Single center, open-label, phase I dose-finding and safety study combined with a phase II, safety / efficacy study, on the biological activity against COVID-19 under study to warrant more extensive development towards a phase III clinical study.

Intervention

We designed a phase 1 and 2 clinical study design by including 6 dosing cohorts, with subcutaneous (s.c.) administration alone. Consequently, phase 1 will be a classical 6x3 dose-finding design, after which we will assess safety after each dosing cohort (n=3 subjects). The following stopping-rule will be applied (see also flow-chart): any SAE or AE <=3 (according to NCI Common Terminology Criteria for Adverse Events [CTCAE]) attributable to AKS-452.
In case none of the included subjects has an AE<=3 or SAE attributable to AKS-452, we will expand each dosing cohort with an additional 7 patients. After completing the 6 cohorts with a total maximum of 10 patients each (overall 60 patients), a safety assessment during the interim analysis between Phase I and II will be executed. On the basis of this safety assessment conducted on each cohort and a minimum project seroconversion rate of 70% for each cohort (where seroconversion is defined as a true positive based on the SP/RBD IgG ELISA assay positive/negative cutoff criteria using the quantitative cut-off value defined by the assay kit batch expressed in µg/mL. The positive/negative cutoff value was established as 1.313 µg/mL from the validation analysis for the current lot of assay kits, but it should be noted that for each new lot of assay kits, Akston QC performs a re-validation of the cutoff value in order to maintain clinical agreement from lot-to-lot), we will determine the optimal single-dose and the optimal two-dose cohorts for the single-dose s.c. regimen

and two-dose s.c. regimen, respectively, for the Phase II study. If two dosing cohorts are eligible for the subsequent phase 2 study, the lowest dose-regimen will be selected. This has been modified in the Research Protocol accordingly.

The phase 1 participants who received a single dose injection (cohort 1,3,5) will be offered to receive a booster vaccine with the 'naked' AKS-452 (without the adjuvant Montanide ISA 720) at day 180 of the phase 1 study.

Statistical Re-assessment:
• With a seroconversion rate of 90%, 26 participants in phase 2 dosing cohort are sufficient to reach with a confidence interval of 95% a seroconversion rate of 70-98%. The minimal seroconversion rate of 90% is realistic since in both selected dosis regimes (i.e. 2x45 ug and 1x90 ug) a 100% seroconversion rate in phase 1 was observed.
• When a seroconversion rate of 100% is observed in phase II, this will be associated with a 95% confidence interval of 87-100% seroconversion.

With the above mentioned re-assessment we conclude to include a total of 52 participants in phase 2.

Study burden and risks

The burden of participating in the study will be the number of site visits and possible travelling for subjects in phase I/II, study investigations such as blood samples for measurement of immunogenicity, physical examination prior to inclusion / exclusion, and physical discomfort related to the subcutaneous injection of AKS-452. The risk associated with exposure to a novel vaccine for a 1st in-human phase I/II clinical study are pain/swelling/redness/bleeding/infection/granuloma formation at the injection site, mild fever, chills, feeling tired, headache, muscle and joint aches, syncope, and an allergic reaction which are all well within the tolerable range for a novel vaccine like AKS-452. The benefit, in case of a safe and sufficient immunogenicity provoking vaccine, is for protecting health care workers, future vulnerable and frail elderly, and patients undergoing large surgical procedures for instance oncology, transplantation etc. Moreover, providing protection in co-morbid citizens (I.e., diabetes, overweight, cardiovascular disease etc) and ultimately, creating another leverage to returning societies back to their previous health care system capacities and economic growth world-wide.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9700 RB
NL
Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9700 RB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Age 18-85 years (extremes included), males and females
- SARS-CoV-2 serology (an anti-SARS-Cov-2 SP-specific IgG ELISA):
o Tests negative for IgG titer and no known prior SARS-Cov-2 infection
- Body mass index (BMI) between 19.0 and 30.0 kg/m2, inclusive
- General good health, without significant medical illness, as determined via physical exam findings, ECG or vital signs
o Note: one retest of vital functions and ECG is allowed within the screening window
- No clinically significant laboratory abnormalities as determined by the investigator
o Note: one retest of lab tests is allowed within the screening window
- Informed Consent Form signed voluntarily before any study-related procedure is performed, indicating that the subject understands the purpose and procedures required for the study and is willing to participate in the study
- Willing to adhere to the prohibitions and restrictions specified in this protocol
- For phase I: No invitation is received to get a registered vaccine within the first 2 months after the moment of participation in this study.

For phase II this criterium will be abandoned as the whole population will have received an invitation to get a registered vaccine. Therefore, a participant should agree not to receive a registered vaccine within 28 days after receiving the last AKS-452 vaccine. For the booster study with the naked AKS-452 (non-adjuvanted), the participants should waive their right to receive a registered vaccine within the first 56 days after receiving the booster vaccine.
- Negative hepatitis panel (including hepatitis B surface Ag and anti-hepatitis C virus Abs) and negative human immunodeficiency virus Ab and Ag screens at screening
- Female subjects should fulfil one of the following criteria:
o At least 1 year post-menopausal (amenorrhea >12 months and/or follicle-stimulating hormone >30 mIU/mL) at screening;
o Surgically sterile (bilateral oophorectomy, hysterectomy, or tubal ligation);
o Will use adequate forms of contraceptives from screening to discharge.
- Female subjects of childbearing potential and male subjects who are sexually active with a female partner of childbearing potential must agree to the use of an effective method of birth control from screening to discharge
o Note: medically acceptable methods of contraception that may be used by the subject and/or partner include combined oral contraceptive, contraceptive vaginal ring, contraceptive injection, intrauterine device, etonogestrel implant, double barrier, sterilization and vasectomy
- Female subject has a negative pregnancy test at screening and upon check-in at the clinical site.
o Note: pregnancy testing will consist of a serum pregnancy test at screening and urine pregnancy tests at other (dosing) visits, in all women.

Exclusion criteria

- Pregnant or breast feeding females
- Evidence of clinically significant neurologic, cardiac, pulmonary, hepatic, hematologic, rheumatologic, endocrine, autoimmune, or renal disease
- Any laboratory test which is abnormal, and which is deemed by the Investigator(s) to be clinically significant
- Behavioral or cognitive impairment or psychiatric disease that in the opinion of the investigator affects the ability of the subject to understand and cooperate with the study protocol
- Current alcohol/illicit drug/nicotine abuse or addiction: history or evidence of current drug use or addiction (positive drug screen for amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine, or opiates) or signs of excessive use of alcohol at screening and Day -2.
- Presence of any febrile illness (T > = 38.0°C or lab confirmed viral disease (PCR)) or symptoms suggestive of a viral respiratory infection within 1 weeks prior to vaccination
- Use of corticosteroids (excluding topical preparations for cutaneous or nasal

use) or use of immunosuppressive drugs within 30 days before inoculation
- A history of anaphylaxis, history of allergic reaction to vaccine, known allergy to one of the components in AKS-452. Mild allergies without angio-edema or treatment need can be included if deemed not to be of clinical significance (including but not limited to allergy to animals or mild seasonal hay fever)
- A history of asthma within the past 10 years, or a current diagnosis of asthma or reactive airway disease associated with exercise
- Receipt of a licensed vaccine within 4 weeks prior to viral inoculation
- Received any (experimental) SARS-CoV-2 vaccine or drug
- Receipt of blood or blood-derived products (including immunoglobulin) within 6 months prior to vaccination.
- Receipt of another investigational agent within 30 days or 5 times the product half-life (whichever is longest) prior to vaccination
- Shares household with/works with immunocompromised individual(s), adults with significant cardiopulmonary disease, persons with significant asthma, institutionalized elderly or elderly with functional disability
- Deprived of freedom by an administrative or court order or in an emergency setting
- Any condition that in the opinion of the principal investigator (PI) would jeopardize the safety or rights of a person participating in the trial or would render the person unable to comply with the protocol.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-04-2021
Enrollment:	116
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	AKS-452

Ethics review

Approved WMO Date:	22-02-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-03-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-06-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-07-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-08-2021
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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	EUCTR2020-005997-82-NL
ClinicalTrials.gov	NCT04681092
CCMO	NL76321.000.20

Study results

Date completed: 09-02-2022

Actual enrolment: 112

Summary results
Trial is onging in other countries