Phase 1/2, dose-escalation study to evaluate the safety, tolerability and efficacy of a single intravenous infusion of SPK-3006 in adults with late-onset Pompe disease

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3.1 Primary ObjectiveTo evaluate the safety and tolerability of a single IV dose of SPK-3006 administered at escalating dose levels to participants with clinically moderate LOPD.3.2 Secondary ObjectivesTo evaluate potential efficacy and bioactivity...

Ethical review	Approved WMO
Status	Pending
Health condition type	Metabolic and nutritional disorders congenital
Study type	Interventional

Summary

ID

NL-OMON55024

Source
ToetsingOnline

Brief title
Study to investigate SPK-3006 in adults with late-onset Pompe disease

Condition

- Metabolic and nutritional disorders congenital

Synonym
Pompe Disease

Research involving
Human

Sponsors and support

Primary sponsor: Spark Therapeutics
Source(s) of monetary or material Support: Industry

Intervention

Keyword: gene therapy, late-onset Pompe Disease, LOPD, SPK-3006

Outcome measures

Primary outcome

3.4 Primary Endpoints

The primary endpoints of this study include the following:

• Incidence of adverse and serious adverse events (AEs/SAEs), clinically significant abnormal laboratory values, change in vital signs, change in physical examination (PE), vector shedding in bodily fluids, and liver function tests

• Immune responses against the AAV capsid (neutralizing antibody [NAb] assay) and GAA transgene product (binding and NAb assays)

Secondary outcome

3.5 Secondary Endpoints

Secondary endpoints include the following:

• Changes from baseline in the Six-Minute Walk Test (6MWT)

• Changes from baseline in the Forced Vital Capacity (FVC)

• Peak and steady-state vector-derived GAA enzyme levels assessed by total GAA protein and activity measured in circulation

• Biomarkers of muscle injury and glycogen accumulation (creatine kinase [CK], urine glucose tetrasaccharide [Hex 4])

3.6 Exploratory Endpoints

Exploratory endpoints will assess changes from baseline in the following:

• Other muscle function tests including Gait, Stairs, Gower, Chair (GSGC) and

Rasch built Medical Research Council (MRC)

• Other respiratory function tests including sniff nasal inspiratory pressure

(SNIP), and maximum inspiratory and expiratory pressures (MIP and MEP)

• Muscle biopsy (optional and at selected study centers)

• qMRI of muscles (at selected study centers)

• Liver health biomarkers

• FluoroSpot assay (cellular immune response to AAV-Spark100 or GAA)

• Lysosomal health biomarker (βHexosaminidase [βHexo])

• Activities measured utilizing biosensors (wearable devices)

• Health outcome measures including the below patient reported outcomes:

o Short Form-36 Health Survey (SF-36)

o Rasch-built Pompe-specific Activity (R-PAct) scale

o Fatigue Severity Scale (FSS)

• Patient Reported Outcomes Measurement Information System (PROMIS) item banks

Study description

Background summary

Late onset Pompe disease (LOPD, glycogen storage disease type 2) patients experience the consequences of intracellular glycogen accumulation resulting from deficient activity of acid alpha glucosidase enzyme (GAA). While many tissues may be affected, in LOPD the most frequent and debilitating clinical consequences arise from the inability to normally clear tissue glycogen from skeletal muscle including respiratory muscle, resulting in myocyte death, loss

of motor function and respiratory failure.
ERT with alglucosidase alfa, a recombinant human acid α-glucosidase, is currently the only disease-specific therapy approved for the treatment of Pompe disease in the United States (US) and European Union (EU). In contrast to the substantial effects of ERT in IOPD, the clinical benefits of ERT in LOPD are less conclusive.
Based on the unsatisfactory clinical outcomes in a large proportion of patients, adverse drug reactions, the frequency and duration of treatment, and substantial economic burden associated with ERT, a significant unmet medical need exists for patients with Pompe disease.
Gene therapy with SPK-3006 could potentially overcome many of the clinical limitations associated with ERT for the treatment of LOPD.

Study objective

3.1 Primary Objective
To evaluate the safety and tolerability of a single IV dose of SPK-3006 administered at escalating dose levels to participants with clinically moderate LOPD.

3.2 Secondary Objectives
To evaluate potential efficacy and bioactivity of SPK-3006.

3.3 Exploratory Objectives
To evaluate additional muscle function and respiratory measures, muscle biopsies (optional and at selected study centers), quantitative magnetic resonance imaging (qMRI) of muscles (at selected study centers), biomarkers of liver health and lysosomal health, immune responses against AAV-Spark100 and GAA, as well as health outcome measures.

Study design

4.1 Overall Design
This is a Phase 1/2, prospective, multinational, multicenter, open-label, non-randomized, first-in- human, dose-escalation study to evaluate the safety, tolerability and exploratory efficacy of a single intravenous infusion of SPK-3006 in adults with clinically moderate, LOPD (as defined in the inclusion criteria).

After provision of written informed consent, screening assessments may begin. The study design includes a screening period that may extend for a period of up to 14 weeks to allow sufficient time for assessment of all screening criteria and scheduling of SPK-3006 infusion. Sirolimus therapy will begin on Day -6 prior to dosing and continue through week 12. All participants will be monitored for approximately 60 months (±4 weeks) (End-of-Study) after SPK-3006 infusion (see Schedule of Assessments).

Intervention

4.1.2 Study Intervention
Assessments and procedures to be performed on Dosing Day (Day 0) are shown in the Schedule of Assessments. Participants will receive a single intravenous infusion of SPK-3006 at an infusion center staffed with the necessary personnel and equipment to address any urgent medical event (e.g., hypersensitivity reactions, including anaphylaxis) that may occur. The infusion center will have access to a local ICU. The complete dose of SPK-3006 will be infused via infusion pump over approximately 60 minutes. Vital signs will be measured prior to infusion of SPK-3006, at designated timepoints during infusion - infusion start, 30 minutes after start and end of infusion (all approximately ±10 minutes), and at designated timepoints during the post-infusion observation period on Day 0, [i.e., 2 hours, 3.5 hours, 5 hours (all approximately ±10 minutes), and 24 hours (±1) hour) after the start of SPK-3006 infusion]. Sites may choose to have participants stay overnight to logistically accommodate Day 0 and Day 1 procedures and timepoints (see Schedule of Assessments). Such a hospitalization will not be considered an SAE unless an untoward event meeting the definition of an SAE occurs.

Study burden and risks

Exams that will be done and repeated at most of the visits:
- physical exam (these require a hospital visit, of PE is not applicable for a visit, that visit can be completed at patient's home)
- ECG
- Liver ultrasound
- FibroScan
- 6MWT
- pulmonary function tests (FVC)
- drug dispense log (receive/complete/review)
- ECHO,
- blood and urine analysis (incl pregnancy test if applicable)
- SARS-CoV-2 test
- collection biosensors
- other muscle function tests ,
- review potential Adverse events
- Questionnaires,
- dispense Sirolimus (to lower the chance that an immune reaction cancels the effect of the study drug)
- Infusion SPK-3006
- ERT infusion and log to complete

The side effects of PCV in humans are unknown as this is a first-in-men study. Participants will be closely monitored during and up to 5 hours after the IV administration of SPK-3006 and during the follow-up visits. Participants will

also be informed of early signs and symptoms of hypersensitivity reactions.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

1. Be able to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information (PHI) in accordance with national and local privacy regulations;
2. Are male or female >=18 years of age with a confirmed diagnosis (e.g., GAA genetic testing) of LOPD, or based on a documented deficiency of GAA enzyme activity;
3. Have received a marketed ERT for at least the previous 24 months and maintained a stable dose, frequency and compliance for the past 6 months with no dose variation and no longer improving on ERT;
4. Have clinically moderate LOPD characteristics
a. Be able to walk >=75 meters on the 6MWT (assistive devices permitted) but less than 500 meters assessed at two timepoints prior to initiating

immunosuppression (Day -6) with <10% variance between the assessments. If the variance is >=10%, a third timepoint will be collected;
b. Have a percentage of the predicted FVC >=30% and <=80% in the upright position;
5. Agree to use reliable contraception for a minimum of 6 months after administration of SPK-3006 or 12 weeks after the final dose of sirolimus, whichever occurs later. Female candidates of child-bearing potential must have a negative pregnancy test prior to initiating immunosuppression (Day -6) and on Day 0 prior to administration of SPK-3006. See Section 13 (Appendix 1) for guidance on reliable contraception and the definition of women of child-bearing potential (WOCBP);
6. Agree to refrain from blood, plasma, platelets, egg or sperm, and organ donation after receiving SPK-3006.

Exclusion criteria

1. Have active hepatitis B and/or C;
All candidates must be screened for both active hepatitis B and C, regardless of prior known history.
a. Screening for hepatitis B.
All candidates must have a single sample at Screening for each of the following tests: hepatitis B surface antigen (HBsAg), total hepatitis B core antibody (anti-HBc), and a nucleic acid test for hepatitis B virus DNA (HBV-DNA viral assay).A candidate is not eligible if either HbsAg is positive or HBV-DNA is positive/detectable.
i. A candidate is not eligible if either HBsAg is positive or HBV-DNA is positive/detectable.
ii. A candidate is eligible if the anti-HBc is positive and both HBsAg and HBV-DNA are negative, as this would be consistent with a prior infection of hepatitis B. Anti-HBc must be obtained in all candidates to discriminate between acute infection and possible reactivation of hepatitis B during the trial in candidates with no prior history of hepatitis B.
iii. A candidate who is currently undergoing antiviral therapy for chronic hepatitis B is not eligible.
b. Screening for hepatitis C:
iv. A candidate who is currently undergoing antiviral therapy for chronic hepatitis C is not eligible.
v. All other candidates, including those who have never been treated or who have completed antiviral therapy for chronic hepatitis C must have a nucleic acid test for hepatitis C viral RNA (HCV-RNA single load assay) at Screening.
• A candidate is not eligible if the HCV-RNA load assay is positive/detectable.
• Candidates treated with anti-viral therapy for chronic hepatitis C, must have completed anti-viral therapy at least 6 months prior to Screening and have a negative HCV-RNA at Screening.
• Candidates with a documented or self-reported history of hepatitis C must have a single negative HCV-RNA at Screening.

2. Have significant underlying liver disease. A candidate is not eligible if any of the following pre-existing diagnoses, which are indicative of significant underlying liver disease, are present in the medical record:
• Liver cirrhosis;
• Portal hypertension; or
• Hepatic encephalopathy
• Gamma-glutamyl transferase (GGT) >1.2X upper limit of normal (ULN) adjusted for age and gender; or
• Bilirubin >1.2X ULN adjusted for age and gender. Candidates with asymptomatic elevated bilirubin (e.g., Gilbert syndrome) can be considered after discussion with the Sponsor Medical Monitor.
All candidates who do not have the pre-existing diagnoses listed above must have the following assessments performed at screening:
• Measurement of serum albumin. A candidate is not eligible if the serum albumin level is below the testing laboratory*s lower limit of normal;
• Liver fibrosis >= stage 3. The following results are indicative of fibrosis >= stage 3 and exclude the candidate from participation:
- FibroScan, with a score > 8.3 kPa units
- FibroTest/ FibroSURE with a result > 0.48
- AST-Platelet Ratio Index (APRI) >1;
Of note, if results from more than one modality for evaluation of liver fibrosis are available (e.g., results from both FibroScan and FibroSURE are available) the result from FibroScan should be consulted for determination of liver fibrosis as it will take precedence over other modalities.Human immunodeficiency virus infection;
3. Have human immunodeficiency virus (HIV) infection;
4. Have a prior hypersensitivity to recombinant human GAA (rhGAA);
5. Have pre-existing AAV-Spark100 Neutralizing Antibody titers >1:1;
6. Have high titer antibody responses to rhGAA (anti-GAA >1:30,000);
7. Had participated in a clinical study with an investigational drug in the past 6 months (vaccination studies are accepted; observation studies are accepted after discussion with the Medical Monitor);
8. Requires any invasive ventilation or requires noninvasive ventilation while awake and upright;
9. Had any change to respiratory muscle strength training within 90 days prior to informed consent (for participants receiving respiratory muscle strength training) or initiation of respiratory muscle strength training prior to Day 0;
10. Received any prior vector or gene transfer agent;
11. Require concomitant use of a medication that is contraindicated with sirolimus (see Section 19.6.4.1), such as, medication known to be a strong or moderate inducer or inhibitor of CYP3A4 - excluded only during the sirolimus immunosuppressive period;
12. Received live vaccines within 30 days prior to informed consent to at least 52 weeks after receiving SPK-3006 infusion
13. Used a systemic immunosuppressive agents (e.g., corticosteroids) within 30 days prior to informed consent and to Day 0 prior to SPK-3006 administration;
14. Have an active malignancy (except non-melanoma skin cancer);

15. Have a history of liver cancer;
16. Are a pregnant or nursing female;
17. Have any evidence of an active infection at the time of SPK-3006 infusion;
18. Have a known allergy or hypersensitivity to SPK-3006 investigational product, sirolimus, or corticosteroids;
19. Have any concurrent clinically significant condition that would not allow the potential participant to complete the follow-up examinations during the course of the study, or other condition that, in the opinion of the Investigator and/or Medical Monitor, makes the candidate unsuitable for participation in the study;
20. Are unable or unwilling to comply with the visit schedule and study assessments described in the clinical protocol.

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2021
Enrollment:	2
Type:	Anticipated

Ethics review

Approved WMO

Date:	06-05-2020
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO Date:	06-01-2021
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	14-07-2021
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)
Approved WMO Date:	20-01-2022
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	EUCTR2019-001283-30-NL
ClinicalTrials.gov	NCT04093349

Register	ID
CCMO	NL72791.000.20