A Randomized, Double-blind, Placebo-controlled, Repeat-dose, Multicenter Trial to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of HZN-825 in Patients with Diffuse Cutaneous Systemic Sclerosis

Published: 25-11-2021
Last updated: 05-04-2024

Primary Objective:The primary objective is to demonstrate the efficacy of 1 or 2 dose regimens of HZN-825 versus placebo in subjects with diffuse cutaneous SSc, as determined by a comparison of change in forced vital capacity (FVC) % predicted after…

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

Summary

ID

NL-OMON49927

Source
ToetsingOnline

Brief title
HZNP-HZN-825-301 / Beacon

Condition

- Autoimmune disorders

Synonym
Diffuse Cutaneous Systemic Sclerosis, Disease characterized by skin hardening (fibrosis) and problems in many organs of the body

Research involving
Human

Sponsors and support

Primary sponsor: Horizon Therapeutics Ireland DAC
Source(s) of monetary or material Support: Horizon Therapeutics Ireland DAC

Intervention

Keyword: Diffuse Cutaneous Systemic Sclerosis, HZN-825, Phase 2b/3

Outcome measures

Primary outcome

Change in FVC % predicted from Baseline to Week 52

Secondary outcome

1. Change from Baseline in HAQ-DI at Week 52.

2. Change from Baseline in MDGA at Week 52.

3. Change from Baseline in PTGA at Week 52.

4. Change from Baseline in the Physical Effects subscale of the SSPRO-18 at

Week 52.

5. Change from Baseline in the Physical Limitations subscale of the SSPRO-18 at

Week 52.

6. Proportion of subjects with an mRSS decrease of >=5 points and 25% from

Baseline at Week 52.

7. Responder rate (defined as ACR-CRISS [predicted probability] of at least

0.6) at Week 52.

8. Proportion of subjects with an improvement in >=3 of 5 core measures from

Baseline: >=20% in mRSS, >=20% in HAQ-DI, >=20% in PTGA, >=20% in MDGA and >=5% for

FVC % predicted at Week 52 (ACR-CRISS-20).

Study description

Background summary

Diffuse cutaneous SSc is a rare and devastating autoimmune disease characterized by skin fibrosis, beginning on the fingers and face, that rapidly becomes generalized with internal organ manifestations of fibrosis. The disease carries a high morbidity and mortality rate; patients with diffuse cutaneous SSc have a 10-year survival rate of 55%. Death is most often caused by lung, heart and kidney involvement.

Currently, there is no effective treatment or cure for generalized SSc. Treatment depends on the symptoms that are present and the organs that are affected and may include medication and surgery. To date, all available therapeutic options (e.g., corticosteroids, methotrexate, cyclophosphamide, azathioprine and mycophenolate mofetil) have demonstrated only limited efficacy and/or have safety issues that impact their use and are not indicated for use in patients with SSc. One treatment, nintedanib, was approved, although it only slows the decline of pulmonary function in adults with interstitial lung disease (ILD) associated with SSc. Thus, there is a substantial unmet clinical need for an effective and well-tolerated treatment for SSc.

HZN-825 is under investigation as a novel therapy for SSc because it selectively antagonizes LPAR1, which has been shown to be associated with skin, pulmonary, cardiac, peritoneal and tubulointerstitial fibrosis, and may be a new therapeutic target for treating fibrotic diseases, including SSc.

Study objective

Primary Objective:
The primary objective is to demonstrate the efficacy of 1 or 2 dose regimens of HZN-825 versus placebo in subjects with diffuse cutaneous SSc, as determined by a comparison of change in forced vital capacity (FVC) % predicted after 52 weeks of treatment.

Secondary Objectives:
1. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on Health Assessment Questionnaire-Disability Index [HAQ-DI] after 52 weeks of treatment.
2. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on Physician Global Assessment (MDGA) after 52 weeks of treatment.
3. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on Patient

Global Assessment (PTGA) after 52 weeks of treatment.
4. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on the Physical Effects subscale of the scleroderma skin patient-reported outcome (SSPRO-18) after 52 weeks of treatment.
5. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on the Physical Limitations subscale of the SSPRO-18 after 52 weeks of treatment.
6. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on the modified Rodnan skin score (mRSS), after 52 weeks of treatment.
7. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on American College of Rheumatology-Composite Response Index in Systemic Sclerosis (ACR-CRISS), defined as improvement from Baseline in mRSS, HAQ-DI, PTGA, MDGA and FVC % predicted after 52 weeks of treatment.
8. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on ACR-CRISS-20, defined as improvement in >=3 core set measures from Baseline of >=20% in mRSS, >=20% in HAQ-DI, >=20% in PTGA,>=20% in MDGA and >=5% in FVC % predicted after 52 weeks of treatment.
9. Assess safety and tolerability of HZN-825 based on adverse events (AEs), the adverse event of special interest (AESI) (orthostatic hypotension), concomitant medication use, vital signs, 12-lead electrocardiogram (ECG) and clinical safety laboratory evaluations (hematology, chemistry, inflammatory parameters, coagulation panel and urinalysis).
10. Evaluate the pharmacokinetics (PK) of HZN-825 and metabolite(s).

Exploratory Objectives:
1. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on the SSPRO-18 after 52 weeks of treatment.
2. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on University of California Los Angeles Scleroderma Clinical Trial Consortium Gastrointestinal Tract (UCLA SCTC GIT 2.0) after 52 weeks of treatment.
3. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on Raynaud*s phenomenon using the Raynaud*s Assessment.
4. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on Scleroderma HAQ (SHAQ) at Week 52.
5. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on change from Baseline in Systemic Sclerosis Quality of Life Questionnaire (SScQoL) scores.
6. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on change from Baseline in SF-12®Health Survey (SF-12) scores.
7. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on change from Baseline in pain and pain component scale scores.
8. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on change from Baseline in fatigue based on the Functional Assessment of Chronic Illness Therapy - Fatigue Scale (FACIT-F) score.
9. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on change from Baseline in protein expression of markers of inflammation and fibrosis in skin biopsies.
10. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on change

from Baseline in transcriptomics associated with LPAR1 pathway, inflammation and fibrosis in skin biopsies.
11. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on change from Baseline in lung fibrosis after 52 weeks of treatment in subjects with suitable Baseline high resolution computed tomography (HRCT).
12. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on change from Baseline in diffusing capacity of the lungs for carbon monoxide (DLCO) after 52 weeks of treatment.
13. Evaluate the effect of 2 dose regimens of HZN-825 versus placebo on change from Baseline in serum and plasma biomarkers associated with LPAR1 pathway, inflammation and/or fibrosis.

Study design

This is a randomized, double-blind, placebo-controlled, repeat-dose, multicenter trial. Subjects will be screened within 4 weeks prior to the Baseline (Day 1) Visit. Approximately 300 subjects who meet the trial eligibility criteria will be randomized on Day 1 in a 1:1:1 ratio to receive HZN-825 300 mg QD, HZN-825 300 mg BID or placebo for 52 weeks. Randomization will be stratified according to Screening use of mycophenolate mofetil (yes/no) and presence of interstitial lung disease (ILD) (yes/no) based on a Screening HRCT scan.

The trial will include up to a 4-week Screening Period and a 52-week Double-blind Treatment Period. Subjects will take their first dose of trial drug at the clinic and will return to the clinic for trial visits at Week 4 and every 6 weeks thereafter until Week 52. All subjects who complete the Double-blind Treatment Period (Week 52) will be eligible to enter a 52-week extension trial (HZNP-HZN-825-302). Subjects not entering the extension will return to the clinic for a Safety Follow-up Visit 4 weeks after the last dose of trial drug.

If a subject prematurely discontinues trial drug, he/she will be asked to remain in the trial, participating in the scheduled trial visits through Week 52. If a subject prematurely discontinues trial drug and does not wish to continue in the trial, he/she will be asked to return for a clinic visit and undergo the Week 52 assessments.

Intervention

Subjects will take 2 tablets of trial drug orally in the morning and evening with a meal.

Group A: HZN-825 300 mg QD regimen: 2 HZN-825 tablets in the morning and 2 placebo tablets in the evening
Group B: HZN-825 300 mg BID regimen: 2 HZN-825 tablets in the morning and 2

HZN-825 tablets in the evening
Group C: Placebo regimen: 2 placebo tablets in the morning and 2 placebo tablets in the evening

Study burden and risks

The following side effects are common:
- Headache
- Orthostatic hypotension (blood pressure dropping when standing which can lead to feeling of dizziness)
- Flatulence (gas)
- Abdominal pain

The following side effects noted in previous studies were rare and can be serious:
- There was one serious side effect while taking HZN 825 of fainting in a patient with a medical history of this in childhood.
- One participant on the HZN-825 300 mg twice a day dose experienced nausea and abdominal pain that led to stopping the study.

There is always a chance that an unexpected or serious side effect of an allergic reaction may happen. This can happen to people who take this or any other drug. Some symptoms of allergic reactions are the following:
- Rash
- Wheezing and difficulty breathing
- Dizziness and fainting
- Swelling around the mouth, throat, or eyes
- A fast pulse
• Sweating

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. Written informed consent.
2. Male or female between the ages of 18 and 75 years, inclusive, at Screening.
3. Meets the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for SSc with a total score of >=9 (Van den Hoogen et al., 2013).
4. Classified as having skin involvement proximal to the elbow and/or knee (diffuse cutaneous SSc subset by LeRoy and Medsger, 2001).
5. At the time of enrollment, less than 36 months since the onset of the first SSc manifestation, other than Raynaud's phenomenon.
6. Skin thickening from SSc in the forearm suitable for repeat biopsy.
7. mRSS units >=15 at Screening.
8. FVC >=45% predicted at Screening, as determined by spirometry.
9. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the trial.

Exclusion criteria

1. Positive for anti-centromere antibodies.
2. Diagnosed with sine scleroderma or limited cutaneous SSc.
3. Diagnosed with other autoimmune connective tissue diseases, except for fibromyalgia, scleroderma-associated myopathy and secondary Sjogren's syndrome.
4. Scleroderma renal crisis diagnosed within 6 months of the Screening Visit.
5. Any of the following cardiovascular diseases:
a. uncontrolled, severe hypertension (>=160/100 mmHg) or persistent low blood pressure (systolic blood pressure <90 mmHg) within 6 months of Screening,
b. myocardial infarction within 6 months of Screening,
c. unstable cardiac angina within 6 months of Screening.

6. DLCO <40% predicted (corrected for hemoglobin). If severe acute respiratory syndrome coronavirus2 (SARS-CoV-2) exposure is of clinical concern for any subject, consider using a DLCO up to 6 months before the Screening Visit.
7. Pulmonary arterial hypertension (PAH) by right heart catheterization requiring treatment with more than1 oral PAH-approved therapy or any parenteral therapy. Treatment is allowed for erectile dysfunction and/or Raynaud's phenomenon/digital ulcers.
8. Corticosteroid use for conditions other than SSc within 4 weeks prior to Screening (topical steroids for dermatological conditions and inhaled/intranasal/intra-articular steroids are allowed).
9.Use of any other non-steroid immunosuppressive agent, small biologic molecule, cytotoxic or anti-fibrotic drug within 4 weeks of Screening, including cyclophosphamide, azathioprine (Imuran®) or other immunosuppressive or cytotoxic medication.
10. Known active bacterial, viral, fungal, mycobacterial or other infection, including tuberculosis or atypical mycobacterial disease (fungal infections of nail beds are allowed).
11. Use of a United States Food and Drug Administration-approved agent for SSc or an investigational agent for any condition within 90 days or 5 half-lives, whichever is longer, prior to Screening or anticipated use during the course of the trial.
12. Malignant condition in the past 5 years (except successfully treated basal/squamous cell carcinoma of the skin or cervical cancer in situ).
13. Women of childbearing potential or male subjects not agreeing to use highly effective method(s) of birth control throughout the trial and for 1 month after last dose of trial drug. Male subjects must refrain from sperm donation and females from egg/ova donation for this same time period. Women are considered of childbearing potential if
they are not postmenopausal and not surgically sterile (documented bilateral salpingectomy, bilateral oophorectomy, or hysterectomy). A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.
14. Pregnant or lactating women.
15. Current drug or alcohol abuse or history of either within the previous 2 years, in the opinion of the Investigator or as reported by the subject.
16. Previous enrollment in this trial or participation in a prior HZN-825 or SAR100842 clinical trial.
17. Known history of positive test for human immunodeficiency virus.
18. Active hepatitis (hepatitis B: positive hepatitis B surface antigen and positive anti-hepatitis B core antibody [anti-HBcAb] and negative hepatitis B surface antibody [HBsAb] or positive for HBcAb with a positive test for HBsAb and with presence of hepatitis B virus DNA at Screening; hepatitis C: positive

anti-hepatitis C virus [anti-HCV] and positive RNA HCV).
19. Current alcoholic liver disease, primary biliary cirrhosis or primary sclerosing cholangitis or moderate (Child-Pugh B) to severe (Child-Pugh C) hepatic impairment by Child-Pugh scoring system.
20. Previous organ transplant (including allogeneic and autologous marrow transplant).
21. International normalized ratio >2, prolonged prothrombin time >1.5 × the upper limit of normal (ULN) or partial thromboplastin time >1.5 × ULN at Screening.
22. Alanine aminotransferase or aspartate aminotransferase > × ULN.
23. Estimated glomerular filtration rate < 30 mL/min/1.73 m2 at Screening.
24. Total bilirubin >2 × ULN. Subjects with documented diagnosis of Gilbert's syndrome may be enrolled if their total bilirubin is <=3.0 mg/dL.
25.Any other condition that, in the opinion of the Investigator, would preclude enrollment in the trial.

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:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	HZN-825

Generic name:	HZN-825

Ethics review

Approved WMO Date:	25-11-2021
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	31-01-2022
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	20-12-2022
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	EUCTR2020-005764-62-NL
ClinicalTrials.gov	NCT04781543
CCMO	NL78637.028.21