A phase 1, first-in-human, 2-part, randomized, double-blind, placebo controlled, single ascending dose and sequential, open-label, multiple ascending dose study to evaluate the safety, tolerability, pharmacodynamics, and pharmacokinetics of VIS171 in healthy participants and participants with autoimmune disease(s)

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The purpose of this first-in-human (FIH) study is to assess the safety, tolerability, pharmacodynamics (PD), and pharmacokinetics (PK) of subcutaneous (SC) VIS171 in healthy participants (single ascending dose [SAD] - Part A) as well as in...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON51485

Source
ToetsingOnline

Brief title
VIS171

Condition

- Hepatic and hepatobiliary disorders
- Autoimmune disorders

Synonym
AIH, autoimmune disease(s), autoimmune hepatitis

Research involving
Human

Sponsors and support

Primary sponsor: Parexel Nederland
Source(s) of monetary or material Support: Visterra Inc.

Intervention

Keyword: AIH, Autoimmune hepatitis, VIS171

Outcome measures

Primary outcome

Objectives and Endpoints - Part A (Single Ascending Dose)

Objectives Endpoints

Primary:

· To evaluate the safety and tolerability of VIS171.

Primary endpoint:

· Incidence and severity of TEAEs.

Objectives and Endpoints - Part B (Multiple Ascending Dose)

Objectives Endpoints

Primary:

· To Endpoint evaluate the safety and tolerability of VIS171.

Primary:

· Incidence and severity of TEAEs.

Secondary outcome

Secondary part A:

· To determine the PD effect of VIS171.

· To assess the PK of VIS171.

Secondary Endpoint:

· Mean fold change from baseline in immune cell types, including the following:

· Absolute number (cells/µL) and frequency (%) of Treg.

· Absolute number (cells/µL) and frequency (%) of helper T cells, cytotoxic T

cells, and natural killer cells.

· Pharmacokinetic parameters:

· Cmax, tmax, AUClast, and AUC*.

Secondary part B:

· To determine the PD effect of VIS171.

· To assess the PK of VIS171.

· To evaluate the

immunogenicity of VIS171.

Secondary Endpoint:

· Mean fold change from baseline in immune cell types, including the following:

· Absolute number (cells/µL) and frequency (%) of Treg.

· Absolute number (cells/µL) and frequency (%) of helper T cells, cytotoxic T

cells, and natural killer cells.

· Pharmacokinetic parameters:

· Cmax, tmax, and AUCtau.

· Characterization of ADA to VIS171 over time.

Study description

Background summary

Rationale: VIS171 is under development for the treatment of autoimmune diseases with an underlying mechanism attributed to T cell dysregulation. VIS171 is a fusion protein containing modified human interleukin-2 (IL-2) and a human antibody fragment crystallizable (Fc) domain. Nonclinical studies have demonstrated that VIS171 has a
robust and specific effect on regulatory T cell (Treg) expansion. The purpose of this first-in-human (FIH) study is to assess the safety, tolerability, pharmacodynamics (PD), and pharmacokinetics (PK) of subcutaneous (SC) VIS171 in healthy participants (single ascending dose [SAD] - Part A) as well as in participants with autoimmune diseases (multiple ascending dose [MAD] - Part B). The autoimmune diseases that will be included in Part B (MAD) are systemic lupus erythematosus (SLE), autoimmune hepatitis (AIH), immune-mediated focal segmental glomerulosclerosis (FSGS), and alopecia
areata (AA). These diseases share an underlying mechanism of diminished Treg responses contributing to disease pathogenesis and have been evaluated in prior clinical studies investigating low-dose recombinant or modified human IL-2. The data obtained from this FIH study will inform dose selection for subsequent clinical development and will help prioritize indications for further study.

Study objective

The purpose of this first-in-human (FIH) study is to assess the safety, tolerability, pharmacodynamics (PD), and pharmacokinetics (PK) of subcutaneous (SC) VIS171 in healthy participants (single ascending dose [SAD] - Part A) as well as in participants with autoimmune diseases (multiple ascending dose [MAD] - Part B).

Study design

Study Design: This is a phase 1, multicenter, 2-part combined SAD and MAD FIH study to investigate the safety, tolerability, PD, and PK of SC VIS171 in healthy participants (Part A - SAD) and in participants with an autoimmune inflammatory disease(s) (SLE, AIH, FSGS, or AA) (Part B - MAD). For Part A, participants will be enrolled at a single study site in New Zealand. For Part

B, participants will be enrolled from approximately 20 study sites in up to 10 countries

Intervention

Intervention Groups and Duration: In Part A, participants in each cohort will receive a single SC dose of VIS171 or placebo on Day 1. The starting dose in Part A is 1 jig/kg. The proposed doses for Part A are 1, 4, 8, 16, and 32 jig/kg in Cohorts 1, 2, 3, 4, and 5, respectively.
The dosing frequency in Cohorts 1 and 2 in Part B will be once every 2 weeks for 8 weeks (total of 4 doses). The doses for Cohorts 1 and 2 in Part B will be derived from Part A. The dosing frequency for Cohort 3 in Part B will be determined from Cohorts 1 and 2 of Part B, and may be increased to once every week for 8 weeks (up to 8 doses).

Study burden and risks

2.3.1. Risk Assessment
VIS171 has not been evaluated in humans.
The active component of VIS171, IL-2, has been investigated in a clinical setting for over 30 years and has a well-understood safety profile at a wide range of doses. Recombinant human IL-2 (aldesleukin) has been a Food and Drug Administration-approved therapy for metastatic melanoma and metastatic renal carcinoma since 1992. Furthermore, in the past 30 years, there has been an appreciation for the opportunity for low-dose IL-2 regimens to treat autoimmune diseases prompting many academic and exploratory studies.
It is documented that IL-2 (high-dose infusion regimens) used in oncology treatment can cause a reaction that may include dermatologic toxicity, low blood pressure, increased heart rate or arrhythmias, shortness of breath, nausea, diarrhea and joint and muscle stiffness.
· Dermatologic toxicity caused by higher doses of IL-2 generally manifests as erythema, and pruritus that can develop on the face and neck and progress to the trunk. Participants in this study will be reminded to protect their skin from extreme sun exposure, harsh lotions or detergents, and other skin irritants while participating in the study.13
· High-dose IL-2 therapy has been associated with reversible reduction in kidney function, attributed at least in part to hemodynamic changes resulting in acute kidney injury.14,15,16 In vitro studies have indicated the potential for IL-2 to harm podocytes. Notably, however, the Protein Atlas suggests that IL-2 receptor is minimally expressed on healthy human podocytes.17 A meta-analysis concluded that low-dose recombinant IL-2 administered subcutaneously had a favorable safety profile, and did not identify kidney injury as a parameter of concern.13 While the sponsor does not believe low-dose modified IL-2 (VIS171) carries a risk of kidney injury, healthy participants will be monitored closely for the development of nonorthostatic albuminuria. Studies with low-dose IL-2 consistently found reduced toxicity relative to

high-dose treatment, as demonstrated by a lack of serious adverse events (SAEs) in the majority of low-dose studies.2,6,9,18
The safety of VIS171 was determined in vivo in 2 non-GLP and 2 GLP studies in cynomolgus monkeys and rats. Cynomolgus monkeys are relevant for evaluating VIS171 safety as well as pharmacological activity, based on similar binding profiles of human and cynomolgus monkey IL-2 and its receptors. Rats have been used historically to assess the safety of IL-2-containing compounds, and VIS171 is active in rats.
VIS171 was well tolerated in cynomolgus monkeys and rats. In the GLP studies, animals were dosed once weekly for 12 weeks in the rat study and 8 weeks in the cynomolgus monkey study. The NOAELs were determined to be 6000 .tg/kg in the GLP rat study and 300 .tg/kg in the GLP cynomolgus monkey study. In the cynomolgus monkey study dermatological reactions were observed in a dose dependent fashion. All were monitorable and resolved when treatment was discontinued. There were no VIS171-related changes to urinalysis parameters.
The potential for VIS171 to stimulate cytokine release was evaluated in an in vitro cytokine release assay using whole blood and in each in vivo study conducted. Overall, the in vitro human whole blood assays and the in vivo cynomolgus monkey data both indicated that VIS171 has a low risk for cytokine release in humans.
Monitoring for potential adverse events (AEs) is incorporated into the design of this study through safety assessments of physical examinations, vital sign measurements, electrocardiograms (ECGs), clinical laboratory assessments (hematology, serum chemistry, coagulation, urinalysis, urine albumin/creatinine ratio [uACR; Part A and Part B (participants with AIH and AA)], and urine protein/creatinine ratio [uPCR; Part A]), and AE solicitation. Brief physical examinations will include evaluations of the skin, so that the skin is frequently observed and any risk is identified early. As described in Section 4.1.1 (Part A) and Section 4.1.2 (Part B), a Safety Monitoring Committee (SMC) will be reviewing all available safety data and PD data during this study prior to each dose escalation and prior to the start of Part B.

Contacts

Public
Parexel Nederland

Herman Heijermansweg 20
Amsterdam 1077WL
NL
Scientific
Parexel Nederland

Herman Heijermansweg 20

Amsterdam 1077WL
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Summary of Key Inclusion and Exclusion Criteria:
Inclusion Criteria
Male or female participant between 18 and 55 years of age, inclusive, at the screening
visit (Part A and Part B [participants with AIH, FSGS, and AA]) or between 18 and
75 years of age, inclusive, at the screening visit (Part B [participants with SLE]). Body
mass index between 17 and 35 kg/m2, inclusive, at the screening visit.
Additional inclusion criteria:
* Part A: Healthy, as determined by prestudy medical evaluation (medical history,
physical examination, vital signs, 12-lead electrocardiogram, and clinical laboratory
evaluations), as judged by the principal investigator.
* Part B (participants with SLE only): Diagnosis of adult SLE according to the 2019
American College of Rheumatology classification criteria for at least 6 months prior
to signing the informed consent form (ICF) and an estimated glomerular filtration rate
(eGFR) >= 30 mL/min/1.73 m2 (calculated using the Chronic Kidney Disease
Epidemiology Collaboration [CKD-EPI] formula [2021]).
* Part B (participants with AIH only): Adult meeting criteria for autoimmune hepatitis

(simplified diagnostic criteria) and must have completed induction therapy with standard of care (eg, steroids) and be on maintenance therapy (eg, azathioprine and/or
low dose steroids).

Exclusion criteria

Key Exclusion Criteria
Receipt of high dose corticosteroid therapy within 4 weeks prior to screening as either
(a) intravenous (IV) pulse corticosteroid therapy or (b) daily oral corticosteroid therapy of
>= 1 mg/kg or 80 mg/day prednisone (or equivalent), receipt of belimumab within 6 months prior to screening, history of treatment with rituximab or ocrelizumab (or other
B cell-depleting agent) within 12 months prior to screening, history of cytotoxic
medications (eg, cyclophosphamide) within the preceding 12 months, and receipt of
blood products within 6 months prior to screening.
Participants with uncontrolled hypertension (systolic blood pressure [SBP] > 140 mmHg,
diastolic blood pressure [DBP] > 90 mmHg in any position) or symptomatic hypotension,
any chronic infectious disease, or participants with a positive urine drug or alcohol breath
screen test result at screening or Day *1.
Current symptoms of infection, diagnosis of Coronavirus Disease 2019 (COVID-19) (reverse transcription polymerase chain reaction [RT-PCR], antigen testing, or clinical
diagnosis) in 21 days prior to screening, or ongoing diagnosis of *Long-COVID* symptoms due to a prior COVID-19 infection.
Received a vaccination, other than COVID-19 vaccination, during the 30 days prior to
administration of the first dose of study intervention. A COVID-19 vaccination cannot be
received within 7 days prior to the first dose of study intervention and until 14 days after
the last dose.
Additional exclusion criteria:
* Part B (participants with SLE only): Presence of life- or organ-threatening manifestations of lupus requiring intense immunosuppressive therapy, organ support
systems, or plasmapheresis. Lupus cerebritis, or active severe or unstable neuropsychiatric SLE.

* Part B (participants with AIH only): Advanced cirrhosis/liver disease.
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* Part B (participants with FSGS only): Steroid resistant nephrotic syndrome defined as
absence of complete or partial remission following at least 12 weeks of full dose
corticosteroid therapy. Known secondary causes of FSGS (eg, genetic/familial, viral,
reflux uropathy, toxic causes [eg, bisphosphonates]).
* Part B (participants with AA only): Participant has concomitant hair loss of another
form, including but not limited to traction alopecia, central centrifugal cicatricial
alopecia, lichen planopilaris, frontal fibrosing alopecia, or androgenetic alopecia.
Presence of other severe autoimmune diseases - requiring additional immunosuppressive treatment.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL
Recruitment status:	Will not start
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	VIS171
Generic name:	VIS171

Ethics review

Approved WMO Date:	29-09-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-02-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-11-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-11-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2021-006246-12-NL
CCMO	NL81691.091.22