CLINICAL STUDY PROTOCOL
FOR TEPEZZA (teprotumumab-trbw; HZN-001)

Protocol Number: HZNP-TEP-001

A Randomized, Double-Blind, Placebo-Controlled, Repeat-Dose, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics, and Explore Efficacy of TEPEZZA in Patients with Diffuse Cutaneous Systemic Sclerosis

Date: 02 February 2022

Version 5.0, Amendment 4
IND 147532

Sponsor:
Horizon Therapeutics U.S.A., Inc.
1 Horizon Way
Deerfield, IL 60015

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CONFIDENTIAL

PROTOCOL

1 TITLE PAGE

Study Title:	A Randomized, Double-Blind, Placebo-Controlled Repeat-Dose, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics, and Explore Efficacy of TEPEZZA in Patients with Diffuse Cutaneous Systemic Sclerosis
Protocol Number:	HZNP-TEP-001
Version:	5.0, Amendment 4
IND	147532
Investigational Product:	TEPEZZA (teprotumumab-trbw; HZN-001)
Indication:	Diffuse Cutaneous Systemic Sclerosis
Sponsor:	Horizon Therapeutics U.S.A., Inc. 1 Horizon Way Deerfield, IL 60015
Development Phase:	1
Sponsor's Responsible Medical Officer:	PPD Horizon Therapeutics U.S.A., Inc. 1 Horizon Way Deerfield, IL 60015
Sponsor Signatory:	PPD Horizon Therapeutics U.S.A., Inc.
Approval Date:	02 February 2022

CONTACT IN THE EVENT OF AN EMERGENCY

Any death, life-threatening event or other serious adverse event experienced by a subject during the course of the study, whether or not judged drug-related, must be reported within 24 hours of knowledge of the event by entering the information into the electronic case report form (eCRF). If unable to access the eCRF, the event must be reported by submitting the completed Serious Adverse Event Form via email or fax to the contacts provided below.

Fax: PPD
Email: clinicalsafety@horizontherapeutics.com

SPONSOR SIGNATURE PAGE

Protocol Number:	HZNP-TEP-001
Version:	5.0, Amendment 4
Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Repeat-Dose, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics, and Explore Efficacy of TEPEZZA in Patients with Diffuse Cutaneous Systemic Sclerosis
Version Date:	02 February 2022

Approved by:

PPD

PPD
Horizon Therapeutics U.S.A., Inc.

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PPD
Horizon Therapeutics U.S.A., Inc.

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Number: HZNP-TEP-001

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Version Date: 02 February 2022

I agree to conduct the study according to the protocol named above. I fully understand that any changes instituted by the Principal Investigator without previous discussion with the Sponsor constitute a violation of the protocol, unless necessary to eliminate an immediate hazard to the safety or well-being of a subject.

I acknowledge that I have read and understand the protocol named above and agree to carry out all of its terms in accordance with applicable regulations and laws.

I assure that the study drug supplied by the Sponsor will be used only as described in the protocol named above.

Signature:

_____ _____

Name Date
Study Center
Address
City State Country

SUMMARY OF CHANGES
Protocol HZNP-TEP-001
Version 5.0 Amendment 4, incorporating Protocol Version 4.0

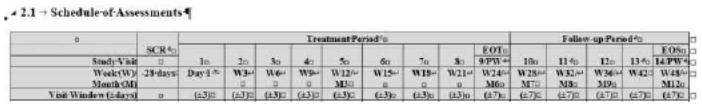
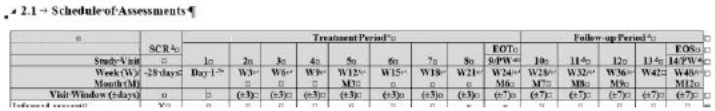
Additions, revisions and clarifications to Version 4.0 of the protocol include:

- Changing the responsible study statistician.
- Removing inclusion criterion 5. The primary objective of this study is to evaluate the safety of TEPEZZA in patients with dcSSc. Inclusion criterion 5 restricts study enrollment to subjects who lack improvement or have worsening disease on current therapy, which is a small subset of patients eligible for this study. Removal of this inclusion criterion will allow for a more representative study population.
- Adding Plaquenil® as an example of an anti-malarial in exclusion criterion 7 and revising exclusion criterion 7 to improve clarity.
- Modifying exclusion criteria 19 and 20 to be less restrictive (i.e., platelets $<100\times10^3/\mu L$ instead of $<120\times10^3/\mu L$ and hemoglobin <8 g/dL instead of <10 g/dL). TEPEZZA is not expected to increase bleeding during CCI; thus, lower platelet and hemoglobin levels are appropriate.
- CCI
- Removing the ±3-day visit window from the Day 1 Visit, as a visit window is not applicable for the Day 1 Visit.
- Emphasizing that subjects are encouraged to remain in the study even if study drug has been discontinued.
- Clarifying which personnel may be unblinded for the Week 24 primary analyses.
- Correcting minor typographical errors (changes are not detailed below).

SUMMARY TABLE OF CHANGES
Protocol Version 4.0, Amendment 3 (12 July 2021) to Protocol Version 5.0, Amendment 4 (02 February 2022)

Text Version 4.0, Amendment 3 12 July 2021	Amended Text Version 5.0, Amendment 4 02 February 2022	Reason for Change
SPONSOR SIGNATURE PAGE Approved by:¶ PPD Date¤	**SPONSOR SIGNATURE PAGE** Approved by:¶ PPD Date¤	*The responsible study statistician was changed.*
Synopsis – Inclusion Criteria and Section 9.3.1 Inclusion Criteria 5. Based on data available through medical history and/or medical records, the subject should have had: a. worsening of sclerodermatous skin involvement in one or more body areas (including any new areas of involvement) within the last 6 months prior to the Screening Visit, b. and/or the presence of a tendon friction rub at Screening, c. and/or no improvement in sclerodermatous skin involvement (defined as an improvement of >3 units) within the last 6 months prior to the Screening Visit.	**Synopsis – Inclusion Criteria and Section 9.3.1 Inclusion Criteria** Criterion deleted	*Inclusion criterion 5 restricts study enrollment to subjects who lack improvement or have worsening disease on current therapy, which is a small subset of patients eligible for this study. Removal of this inclusion criterion will allow for a more representative study population.*

Text Version 4.0, Amendment 3 12 July 2021	Amended Text Version 5.0, Amendment 4 02 February 2022	Reason for Change
Synopsis – Exclusion Criteria and Section 9.3.2 Exclusion Criteria 7. Use of any other non-steroid immunosuppressive agent, cytotoxic or anti-fibrotic drug within 4 weeks of Screening other than an anti-malarial. This includes cyclophosphamide, azathioprine (Imuran®), methotrexate or other immunosuppressive or cytotoxic medication except mycophenolate mofetil (CellCept) or mycophenolic acid (Myfortic), which are permitted with use according to inclusion criterion.	**Synopsis – Exclusion Criteria and Section 9.3.2 Exclusion Criteria** 7. Use of a non-steroidal immunosuppressive agent, cytotoxic or anti-fibrotic drug within 4 weeks of Screening, including cyclophosphamide, azathioprine (Imuran®), methotrexate or other immunosuppressive or cytotoxic medication. Exceptions are mycophenolate mofetil (CellCept) and mycophenolic acid (Myfortic), which are permitted according to inclusion criterion 8, and anti-malarials (e.g., hydroxychloroquine [Plaquenil®]).	*To provide an example of an anti-malarial drug and improve clarity of text*
Synopsis – Exclusion Criteria and Section 9.3.2 Exclusion Criteria 19. Platelets <120×10^3/µL. 20. Hemoglobin <10 g/dL.	**Synopsis – Exclusion Criteria and Section 9.3.2 Exclusion Criteria** 19. Platelets <100×10^3/µL. 20. Hemoglobin <8 g/dL.	*TEPEZZA is not expected to increase bleeding during skin biopsy; thus, lower platelet and hemoglobin levels are appropriate.*
Synopsis – Statistical Analyses Efficacy CCI [redacted] Quality of Life QOL data will be analyzed using the intent-to-treat analysis set.	**Synopsis – Statistical Analyses** Efficacy CCI [redacted] Quality of Life QOL data will be analyzed using the full analysis set.	CCI [redacted]

Text Version 4.0, Amendment 3 12 July 2021	Amended Text Version 5.0, Amendment 4 02 February 2022	Reason for Change
Section 2.1 Schedule of Assessments 	**Section 2.1 Schedule of Assessments** 	*A visit window is not applicable for the Day 1 Visit.*
Section 9.3.3 Removal of Subjects from Treatment or the Study All subjects are free to withdraw from study participation at any time, for any reason and without prejudice to their further medical care. In addition, the Investigator may terminate a subject from treatment or from the study at any time, if further participation in the study is not in the best interest of the subject.	**Section 9.3.3 Removal of Subjects from Treatment or the Study** All subjects are free to withdraw from study participation at any time, for any reason and without prejudice to their further medical care. Subjects who prematurely discontinue study drug during the Treatment Period will be encouraged to continue study participation, particularly returning for the Week 24 (end of treatment) assessments, and continue in the 24-week Follow-up Period. Subjects who discontinue study drug due to an AE should be followed until resolution or stabilization of the AE, or an adequate explanation for the event is obtained. If further participation in the study is not in the best interest of the subject, the Investigator may terminate a subject from treatment or from the study.	*To emphasize that subjects are encouraged to remain in the study even if study drug has been discontinued*
Section 9.4.8 Blinding and Unblinding All investigative site staff directly involved in this study will remain blinded from Screening through analysis of the follow-up data and all site close-out visits. The Sponsor and its designees will be unblinded after the database lock following completion of all subjects in the double-blind Treatment Period.	**Section 9.4.8 Blinding and Unblinding** All investigative site staff and Sponsor personnel directly involved in this study will remain blinded from Screening through analysis of the follow-up data and all site close-out visits (i.e., through Week 48). Select Sponsor personnel/designees may be unblinded after the database lock following completion of all subjects in the double-blind Treatment Period.	*To clarify which personnel may be unblinded for the Week 24 primary analyses*

Text Version 4.0, Amendment 3 12 July 2021	Amended Text Version 5.0, Amendment 4 02 February 2022	Reason for Change
Section 9.4.9 Concomitant Therapy and Restricted Medications *Use of any non-steroid immunosuppressive agent, cytotoxic or anti-fibrotic drug, other than mycophenolate mofetil, mycophenolic acid or an anti-malarial ¤ | 4 weeks prior to Screening through study completion ¤	**Section 9.4.9 Concomitant Therapy and Restricted Medications** *Use of any non-steroid immunosuppressive agent, cytotoxic or anti-fibrotic drug, other than mycophenolate mofetil, mycophenolic acid or an anti-malarial (e.g., hydroxychloroquine [Plaquenil®]) ¤ | 4 weeks prior to Screening through study completion. ¤	*To provide an example of an anti-malarial drug and improve clarity of text*
Section 9.6.2 Analysis Sets • CCI [redacted]	**Section 9.6.2 Analysis Sets** • CCI [redacted]	CCI [redacted]
Section 9.6.3.2 Efficacy Endpoint Analyses CCI [redacted]	**Section 9.6.3.2 Efficacy Endpoint Analyses** CCI [redacted]	CCI [redacted]
Section 9.6.3.3 Quality-of-Life Analyses CCI [redacted]	**Section 9.6.3.3 Quality-of-Life Analyses** CCI [redacted]	CCI [redacted]

Text Version 4.0, Amendment 3 12 July 2021	Amended Text Version 5.0, Amendment 4 02 February 2022	Reason for Change
Section 9.6.5 Interim Analyses No interim analyses are planned. The primary analysis time point for this study is Week 24. Therefore, the database will be locked after all subjects complete Week 24 assessments or withdraw from study prematurely prior to Week 24 for primary analyses. However, the study team and study site personnel will remain blinded until the completion of the study in order to complete the analysis of remaining time points, including Week 48.	**Section 9.6.5 Interim Analyses** No interim analyses are planned. The primary analysis time point for this study is Week 24. Therefore, the database will be locked after all subjects complete Week 24 assessments or withdraw from study prematurely prior to Week 24 for primary analyses. Select Sponsor personnel/designees may be unblinded after the database lock for the Week 24 analyses.	*To clarify which personnel may be unblinded for the Week 24 primary analyses*

2 SYNOPSIS

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Repeat-Dose, Multicenter Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics, and Explore Efficacy of TEPEZZA in Patients with Diffuse Cutaneous Systemic Sclerosis	
Protocol Number: HZNP-TEP-001	**Phase**: 1
Protocol Version: 5.0	
Test Drug: TEPEZZA (teprotumumab-trbw; HZN-001)	**Indication**: Diffuse Cutaneous Systemic Sclerosis
Number and Country of Study Sites: Up to 12 study centers in the United States	

Objectives:
The overall objective is to evaluate the safety, tolerability and effect on insulin-like growth factor-1 (IGF-1), inflammatory and fibrotic biomarkers of TEPEZZA (teprotumumab-trbw; HZN-001), a fully human monoclonal antibody (mAb) inhibitor of the IGF-1 receptor (IGF-1R), administered once every 3 weeks (q3W) for 24 weeks in the treatment of subjects with diffuse cutaneous systemic sclerosis (dcSSc).

Primary Objective
The primary objective is to evaluate the safety of TEPEZZA versus placebo on the proportion of subjects who experience a treatment-emergent adverse event (TEAE) through Week 24 in subjects with dcSSc.

Other Objectives

CCI

[redacted]

Objectives (continued):

Pharmacokinetic and Anti-drug Antibody (ADA) Objectives

1. Evaluate the pharmacokinetics (PK) of teprotumumab.
2. Evaluate the immunogenicity of TEPEZZA.

Safety and Tolerability Objectives

To assess safety and tolerability of TEPEZZA based on TEAEs, adverse events of special interest (AESI) (hyperglycemia, hearing impairment, infusion reaction, new onset or exacerbation of inflammatory bowel disease), concomitant medication use, vital signs, clinical safety laboratory evaluations and inflammatory laboratory evaluations.

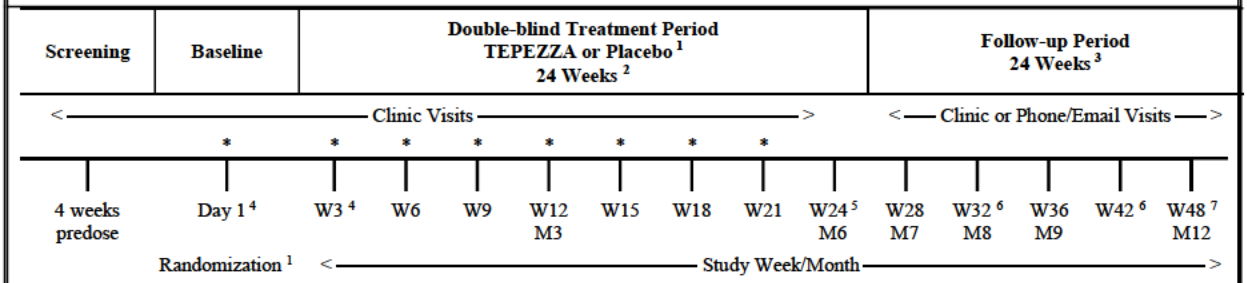
Study Design:

This is a randomized, double-blind, placebo-controlled, repeat-dose, multicenter study. Subjects will be screened for the study within 4 weeks prior to the Baseline (Day 1) Visit. Approximately 25 subjects who meet the study eligibility criteria will be randomized on Day 1 in a 3:2 ratio to receive 8 infusions of TEPEZZA (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) or placebo q3W. During the 24-week double-blind Treatment Period, study drug will be infused on Day 1 (Baseline) and Weeks 3, 6, 9, 12, 15, 18 and 21 with a comprehensive visit at Week 24 (end of treatment). All study drug dosing will be performed at the clinic or infusion center under the supervision of clinic staff or nurses. At any scheduled infusion, the infusion rate may be reduced or the dose may be interrupted or held based on tolerability (see Section 9.4.6.3.2 for details). On each dosing day, scheduled assessments (except for adverse event [AE] and concomitant medication use monitoring, which will be monitored throughout the clinic visit) will be completed prior to study drug infusions. After each of the first 2 infusions, subjects will be contacted by phone/email the following day. Additional phone/email contacts and clinic visits may also be conducted for any subject experiencing an infusion-associated event.

At the end of the Treatment Period (Week 24), subjects will enter a 24-week Follow-up Period, during which study drug will not be administered and a clinic visit will be scheduled for Weeks 28, 36 and 48. A phone call or email at Weeks 32 and 42 will occur to inquire how the subject is doing and women of childbearing potential will be asked if they have missed a menstrual cycle and will have a serum pregnancy test, if required.

Subjects who prematurely discontinue prior to completing the Treatment Period will return to the clinic and undergo the scheduled Week 24 assessments; such subjects will also be encouraged to continue in the 24-week Follow-up Period. An overview of the study design is presented in the schematic below and details of study activities are provided in Section 2.1, *Schedule of Assessments*.

Study Design (continued):



* Infusion of study drug
AE=adverse event; M=Month; q3W=every 3 weeks; W=Week

1. Subjects will be randomized in a 3:2 ratio (15 TEPEZZA and 10 placebo) to receive:
   a. TEPEZZA (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions); or
   b. Placebo (placebo q3W for all 8 infusions).
2. Visit windows are ±3 days for Weeks 3 to 21, inclusive.
3. Visit windows are ±7 days for Weeks 24 to 48, inclusive.
4. All subjects will be contacted by phone/email the day following the first (Day 1) and second (Week 3) infusions for safety and tolerability assessments; additional phone/email contacts will occur the day after any clinic visit where a subject experiences an infusion-related AE.
5. If a subject prematurely discontinues prior to completing the 24-week Treatment Period, he/she will return to the clinic and undergo the Week 24 assessments. Subjects will be encouraged to continue in the 24-week Follow-up Period.
6. All subjects will be contacted via phone or email at Weeks 32 and 42 to inquire how subjects are doing and to ask women of childbearing potential about their menstrual cycle.
7. If a subject prematurely discontinues prior to completing the 24-week Follow-up Period, he/she will return to the clinic and undergo the Week 48 assessments.

Subject Population:

Approximately 25 male and non-pregnant female subjects between the ages of 18 and 80 years, inclusive, with dcSSc will be enrolled.

Inclusion Criteria:

Eligible subjects must meet/provide **all** of the following criteria:

1. Written informed consent.
2. Male or female between the ages of 18 and 80 years, inclusive, at Screening.
3. Meets the 2013 American College of Rheumatology/European League Against Rheumatism classification criteria for systemic sclerosis (SSc) with a total score of ≥9 [Van den Hoogen, 2013].
4. Classified as having skin involvement proximal to elbow, knee, face and neck (dcSSc subset by LeRoy and Medsger, 2001).
5. At the time of enrollment, no more than 60 months must have elapsed since the onset of the first dcSSc manifestations, other than Raynaud's phenomenon.
6. Skin thickening from dcSSc in the forearm suitable for repeat biopsy.
7. mRSS units ≥10 and ≤45 at Screening.
8. Subjects will be allowed to take CellCept® (mycophenolate mofetil) up to 3 g/day or Myfortic® (mycophenolic acid) up to 2.14 g/day and low-dose prednisone (≤10 mg/day or equivalent dosing of glucocorticoids). Subjects taking CellCept or Myfortic have been doing so for ≥20 weeks and the dose must have been stable for ≥16 weeks prior to the Day 1 Visit. Prednisone must have been at a stable dose for ≥4 weeks prior to the Day 1 Visit.
9. Diabetic subjects must have glycated hemoglobin (HbA1c) ≤8.0%, with no new diabetic medication (oral or insulin) or more than a 10% change in the dose of a currently prescribed diabetic medication within 60 days prior to Screening.
10. Women of childbearing potential (including those with an onset of menopause <2 years prior to Screening, nontherapy-induced amenorrhea for <12 months prior to Screening or not surgically sterile [absence of ovaries and/or uterus]) must have a negative serum pregnancy test at Screening and negative urine pregnancy tests at all protocol-specified timepoints (i.e., prior to each dose and throughout the subject's participation in the Follow-up Period); subjects who are sexually active with a non-vasectomized male partner must agree to use 2 reliable forms of contraception during the study, one of which is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be started at least one full cycle prior to Baseline and continue for 180 days after the last dose of study drug. Highly effective contraceptive methods (with a failure rate <1% per year), when used consistently and correctly, include implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomized partner.
11. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the study.

Exclusion Criteria:

Subjects will be ineligible for study participation if they meet **any** of the following criteria:

1. Diagnosed with limited cutaneous SSc or sine scleroderma.
2. Diagnosed with other autoimmune connective tissue diseases, except for fibromyalgia, scleroderma-associated myopathy and Sjogren's syndrome.
3. Scleroderma renal crisis diagnosed within 6 months of the Screening Visit, characterized by abrupt onset of hypertension and acute kidney injury (see Section 9.5.1.1).
4. FVC <50% predicted, diffusing capacity of the lungs for carbon monoxide (DLCO) <40% predicted or pulmonary arterial hypertension (PAH) by right heart catheterization requiring treatment with more than one oral PAH-approved therapy or parenteral therapy (intermittent use of phosphodiesterase-5 inhibitors are allowed for erectile dysfunction and/or Raynaud's phenomenon/digital ulcers).
5. Corticosteroid use for conditions other than dcSSc within 4 weeks prior to Screening (topical steroids for dermatological conditions and inhaled steroids are allowed).
6. Previous treatment with rituximab (Rituxan® or MabThera®) within 12 months prior to the first infusion.
7. Use of a non-steroidal immunosuppressive agent, cytotoxic or anti-fibrotic drug within 4 weeks of Screening, including cyclophosphamide, azathioprine (Imuran®), methotrexate or other immunosuppressive or cytotoxic medication. Exceptions are mycophenolate mofetil (CellCept) and mycophenolic acid (Myfortic), which are permitted according to inclusion criterion 8, and anti-malarials (e.g., hydroxychloroquine [Plaquenil®]).
8. Use of biologics or small molecules approved for rheumatoid arthritis, psoriatic arthritis and other rheumatic diseases within 4 weeks prior to Screening.
9. Use of 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 study.
10. Malignant condition in the past 5 years (except successfully treated basal/squamous cell carcinoma of the skin or cervical cancer in situ).
11. Pregnant or lactating women.
12. 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.
13. Biopsy-proven or clinically suspected inflammatory bowel disease (e.g., diarrhea with or without blood or rectal bleeding associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence for more than 4 weeks without a confirmed alternative diagnosis OR endoscopic or radiologic evidence of enteritis/colitis without a confirmed alternative diagnosis).
14. Known hypersensitivity to any of the components of TEPEZZA or prior hypersensitivity reactions to mAbs.
15. Previous enrollment in this study or participation in a prior teprotumumab-trbw clinical study.
16. Human immunodeficiency virus, untreated or positive viral load for hepatitis C or hepatitis B infections.
17. Previous organ transplant (including allogeneic and autologous marrow transplant).
18. Alanine aminotransferase or aspartate aminotransferase >2.5 times the upper limit of normal or estimated glomerular filtration rate of <30 mL/min/1.73m^2 at Screening.
19. Platelets <100×10^3/μL.
20. Hemoglobin <8 g/dL.
21. Any other condition that, in the opinion of the Investigator, would preclude inclusion in the study.

Dose Regimen/Route of Administration:

All study drug dosing will be performed at the clinic or infusion center under the supervision of clinic staff or nurses. On Day 1 of the double-blind Treatment Period, subjects will be randomized in a 3:2 ratio to receive infusions of either:

1. TEPEZZA (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions),
   or
2. Placebo (q3W for all 8 infusions).

The infusion rate may be reduced and the dose may be interrupted or held based on tolerability (see Section 9.4.6.3.2 for details). The first and second infusions will be administered over approximately 90 minutes (but not less than 80 minutes). Subsequent infusions will be administered over approximately 60 minutes (but not less than 50 minutes), providing there are no significant infusion-associated events.

Dosage Form and Strength Formulation:

TEPEZZA 500 mg will be provided in single-dose, 20-mL glass vials as a freeze-dried powder. Each vial of TEPEZZA will be reconstituted with 10 mL of sterile water for injection. The resulting solution will have a concentration of 47.6 mg/mL TEPEZZA. Reconstituted TEPEZZA solution will be further diluted in 0.9% (w/v) sodium chloride (NaCl) solution prior to administration.

Doses up to 1800 mg will be administered in a total infusion volume of 100 mL and those above 1800 mg will be administered in a total infusion volume of 250 mL. To maintain a constant volume in the infusion bags, a volume equal to the volume of TEPEZZA to be placed into the infusion bag will be first removed from the infusion bag using a sterile syringe and needle. The appropriate volume of reconstituted drug product solution based on the subject`s dose and body weight will be withdrawn and the TEPEZZA drug product solution will be diluted with normal saline (0.9% NaCl) in the infusion bag.

Placebo will consist of a normal saline (0.9% NaCl) solution and will be administered in 100 mL or 250 mL infusion bags, as appropriate, per weight-based dosing volumes.

Duration of Treatment and Follow-up:

The planned duration of the Treatment Period is 24 weeks (6 months). At Week 24, all subjects will be encouraged to enter a 24-week Follow-up Period.

Criteria for Evaluation:

CCI [redacted]

Criteria for Evaluation (continued):

CCI [redacted]

Statistical Analyses:

Primary Endpoint

The proportion of subjects who experience a TEAE (as defined by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]) through Week 24 in subjects with dcSSc.

Efficacy Endpoints

CCI [redacted]

Quality-of-Life Endpoints

CCI [redacted]

Pharmacokinetic and ADA Endpoints

1. PK of teprotumumab.
2. The incidence of ADA and titer levels.

Safety and Tolerability Endpoints

1. Incidence of TEAEs and AESI (hyperglycemia, hearing impairment, infusion reaction, new onset or exacerbation of inflammatory bowel disease).
2. Vital signs: change from Baseline at each scheduled visit.
3. Clinical safety laboratory tests: change from Baseline at each scheduled visit.

Statistical Analysis of Efficacy and Safety Parameters

Primary

The primary analysis will be conducted using the safety analysis set, consisting of all subjects who receive at least 1 dose of study drug (full or partial dose of TEPEZZA or placebo). The number and percentage of subjects who experience a TEAE will be summarized by treatment group.

Efficacy

CCI [redacted]

Statistical Analyses (continued):

CCI

[redacted]

CCI

[redacted]

Quality of Life

CCI

[redacted]

Safety and Tolerability

Safety analyses will be performed using the safety analysis set.

The number and percentage of subjects in each treatment group reporting at least one occurrence of a TEAE, a TEAE of grade 3 or higher, a serious TEAE, a TEAE related to study drug, an AESI and a TEAE resulting in discontinuation of treatment will be summarized by treatment group. TEAEs will additionally be summarized by system organ class and preferred term.

Concomitant medications will be summarized by Anatomical Therapeutic Chemical Level 4 term and preferred term using counts and percentage of subjects for each treatment group.

Descriptive summaries of observed and change from Baseline values will be presented for each vital sign parameter by treatment group and visit. A shift table for weight gain and weight loss as well as hypertension by NCI-CTCAE grade and visit will be summarized by treatment group.

Safety laboratory parameters (chemistry [including HbA1c], hematology, CCI [redacted] and urinalysis) and change from Baseline (if applicable) will be summarized by visit and treatment group using descriptive statistics. The laboratory values will be categorized as low, normal and high based on their normal ranges. Shift tables using categories of low, normal and high from Baseline to each visit will be summarized by treatment group. Additionally, a shift table for glucose by NCI-CTCAE grade and visit will be summarized by treatment group. Summaries will be provided separately for hyperglycemia.

Sample Size Estimate:

For a TEAE that occurs in 20% of TEPEZZA-treated subjects in the dcSSc population, a sample size of 15 subjects provides approximately 95% probability that the TEAE will be observed at least once.

This study is not powered to detect a statistically significant difference in the proportion of CCI responders unless the difference is very large. For example, if 10% of all placebo subjects were responders and 75% of all TEPEZZA subjects were responders, this study would have 87% power to detect that difference (α=0.05, 2-tailed).

2.1 Schedule of Assessments

		Treatment Period [2]									Follow-up Period [3]				
	SCR [1]									EOT					EOS
Study Visit		1	2	3	4	5	6	7	8	9/PW [4]	10	11 [5]	12	13 [5]	14/PW [6]
Week (W)/ Month (M)	-28 days	Day 1 [7]	W3	W6	W9	W12/ M3	W15	W18	W21	W24/ M6	W28/ M7	W32/ M8	W36/ M9	W42	W48/ M12
Visit Window (±days)			(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)
Informed consent	X														
Review inc/exc criteria	X	X													
Demographics	X														
Medical history [8]	X [9]	X													
Weight	X	X	X	X	X	X	X	X	X	X			X		X
Height	X														
Randomization [10]		X													
Study drug infusion		X	X	X	X	X	X	X	X						
Phone (email) contact for safety (day after infusion) [11]		X	X												
Efficacy assessments															
CCI															
[redacted]			X	X	X	X	X	X	X	X			X		X
CCI		X		X		X				X			X		X
CCI [redacted]	X [13]					X				X					X
CCI		X				X				X			X		X
CCI		X				X				X			X		X
CCI		X				X				X			X		X
QOL assessments															
CCI [redacted]		X								X			X		X
CCI [redacted]		X								X			X		X
Safety assessments															
Pregnancy test [14]	X	X	X	X	X	X	X	X	X	X	X		X		X
Physical examination	X	X	X			X				X					X
Vital signs [15]	X	X [15]	X [15]	X	X	X	X	X	X	X	X		X		X
12-lead ECG [16]	X														
Clinical laboratory tests															
Chemistry (including glucose)	X	X	X	X	X	X	X	X	X	X	X		X		X
CCI		X					X			X					X
CCI [redacted]		X					X			X					X
Hematology	X	X	X	X	X	X	X	X	X	X	X		X		X

	SCR [1]	Treatment Period [2]									Follow-up Period [3]				
Study Visit		1	2	3	4	5	6	7	8	EOT 9/PW [4]	10	11 [5]	12	13 [5]	EOS 14/PW [6]
Week (W)/ Month (M)	-28 days	Day 1 [7]	W3	W6	W9	W12/ M3	W15	W18	W21	W24/ M6	W28/ M7	W32/ M8	W36/ M9	W42	W48/ M12
Visit Window (±days)			(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±3)	(±7)	(±7)	(±7)	(±7)	(±7)	(±7)
Coagulation [17]	X														
HbA1c [18]	X					X				X					
Urinalysis	X	X	X	X	X	X	X	X	X	X	X		X		X
ADA/NAb samples [19]		X	X			X		X		X			X		X
AE, SAE assessment [20]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior/concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
CCI [redacted]		X	X							X					
PK samples [22]		X	X			X		X		X			X		
Biomarker samples [23]		X	X			X		X		X					
CCI [redacted]		X	X			X		X		X					
Contact (phone/email)[5]												X		X	

CCI [redacted]; ADA=anti-drug antibody; AE=adverse event; dcSSc= diffuse cutaneous systemic sclerosis; ECG=electrocardiogram; EOS=End of Study; EOT=End of Treatment; CCI [redacted] exc=exclusion; CCI [redacted]; CCI [redacted]; HbA1c=glycated hemoglobin; CCI [redacted] CCI [redacted]; inc=inclusion; M=month; CCI [redacted] CCI [redacted]; NAb=neutralizing antibody; CCI [redacted]; PK=pharmacokinetic; CCI [redacted]; PW=premature withdrawal; q3W=once every 3 weeks; QOL=quality of life; SCR=Screening; SAE=serious adverse event; CCI [redacted]; W=Week

Footnotes:

1. Screening procedures can take place over more than 1 day/clinic visit provided consent is obtained first and all assessments are completed within the designated window.
2. Double-blind Treatment Period. Subjects will receive TEPEZZA (10 mg/kg for the first infusion and 20 mg/kg for remaining infusions) or placebo (q3W).
3. Subjects will participate in a 24-week Follow-up Period.
4. If a subject prematurely discontinues study drug during the Treatment Period, he/she will return for a clinic visit and undergo the Week 24 assessments. Subjects will be encouraged to continue in the 24-week Follow-up Period.
5. All subjects will be contacted via phone or email at Weeks 32 and 42 to assess AEs, concomitant medications and to inquire if the subject has missed a menstrual cycle. If a menstrual cycle has been missed, the subject will have a serum pregnancy test performed per Section 9.5.7.2.
6. If a subject prematurely discontinues from the study prior to completing the 24-week Follow-up Period, he/she will return for a clinic visit and undergo the Week 48 assessments.
7. On Day 1 (Baseline), subjects will be randomized and receive the first dose of study drug. Baseline assessments will be performed prior to dosing.
8. Medical history including dcSSc history and treatment, as well as substance use history.
9. CCI [redacted]

10. Subjects will be randomized in a 3:2 ratio to receive either TEPEZZA (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions) or placebo (q3W for all 8 infusions).
11. Phone (or email) contact by research staff focusing on safety and tolerability aspects will be made the day after (within 24 hours) the infusion for the first and second infusions, and thereafter as deemed appropriate. In addition, subjects who experience an infusion-associated event after any subsequent infusion will also be contacted by phone (or email) by research staff the day after the infusion, and thereafter as deemed appropriate.
12. CCI [redacted]
13. If the subject has had the test <3 months prior to Screening, then the Screening spirometry need not be performed.
14. Serum pregnancy test at Screening and Week 48 (or as needed). Urine pregnancy tests prior to dosing at all other visits, as applicable. Perform for female subjects of childbearing potential (including those with an onset of menopause <2 years prior to Screening, non-therapy-induced amenorrhea for <12 months prior to Screening or not surgically sterile [absence of ovaries and/or uterus]).
15. Vital signs (blood pressure, heart rate, respiratory rate, temperature) will be measured at all clinic visits. Vital signs will be measured pre- and post-infusion on Day 1 and Week 3 and pre-infusion on all other dosing days. Additional vital signs will be monitored if infusion-associated AEs occur (see Section 9.5.7.4 for details).
16. Additional ECGs will be assessed, as needed.
17. CCI [redacted]
18. HbA1c must be ≤8.0% for randomization. If the HbA1c is elevated and considered clinically significant at any time point after Screening, it will be repeated approximately every 90 days until it returns to normal or Baseline value.
19. Blood samples for immunogenicity testing will be collected pre-infusion on Day 1 and Weeks 3, 12 and 18; a single sample will be collected at Weeks 24, 36 and 48. If a sample is ADA positive after confirmatory and reactive titer testing, the sample will then be tested for NAb.
20. AEs that occur after signing the informed consent form and prior to dosing on Day 1 will be considered Baseline signs/symptoms. AEs occurring or worsening after initiation of the infusion on Day 1 through 3 weeks (21 days) after last dose of study drug will be considered treatment-emergent AEs. AEs occurring after 3 weeks (21 days) after last dose of study drug through Week 48 will be considered follow-up AEs. All AEs and SAEs that occur from the signing of informed consent through Week 48 will be recorded.
21. CCI [redacted]
22. PK samples will be collected pre- and post-infusion on Day 1 and Weeks 3, 12 and 18; a single sample will be collected at Weeks 24 and 36.
23. CCI [redacted]

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4 LIST OF ABBREVIATIONS

Abbreviation	Definition
CCI [redacted]	[redacted]
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
AUC	area under the concentration-time curve
CFR	Code of Federal Regulations
C_{max}	maximum serum concentration
CRO	contract research organization
dcSSc	diffuse cutaneous systemic sclerosis
DLCO	diffusing capacity of the lungs for carbon monoxide
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
CCI [redacted]	[redacted]
FDA	Food and Drug Administration
FVC	forced vital capacity
GCP	Good Clinical Practice
CCI [redacted]	[redacted] – [redacted]
HbA1c	glycated hemoglobin
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
HZN-001	TEPEZZA, teprotumumab-trbw
IBD	inflammatory bowel disease
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IGF-1	insulin-like growth factor-1
IGF-1R	insulin-like growth factor-1 receptor
IGFBP	insulin-like growth factor binding protein
IND	Investigational New Drug

Abbreviation	Definition
IRB	Institutional Review Board
IV	intravenous
mAb	monoclonal antibody
CCI [redacted]	[redacted]
CCI [redacted]	[redacted]
NAb	neutralizing antibody
NaCl	sodium chloride
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PAH	pulmonary arterial hypertension
CCI [redacted]	[redacted]
PK	pharmacokinetic
CCI [redacted]	[redacted]
q3W	once every 3 weeks
QOL	quality of life
SAE	serious adverse event
SSc	systemic sclerosis
TEAE	treatment-emergent adverse event
TED	thyroid eye disease
CCI [redacted]	[redacted]
US	United States
U.S.A.	United States of America
USP	United States Pharmacopeia

Abbreviations that appear only in figures and tables are defined with the relevant figures and tables.

5 ETHICS

5.1 Institutional Review Board/Independent Ethics Committee

The Principal Investigator (Investigator), the Sponsor and/or contract research organization (CRO) authorized by the Sponsor will submit this protocol, any protocol modifications and the informed consent form (ICF) and all applicable study documentation to be used in this study to the appropriate Institutional Review Board (IRB) or Independent Ethics Committee (IEC) for review and approval/favorable opinion. A letter confirming the IRB/IEC approval/favorable opinion of the protocol, the subject ICF and applicable study documentation, a list of the IRB/IEC members involved in the vote, as well as a statement that the IRB/IEC is organized and operates according to Good Clinical Practice (GCP) and the applicable laws and regulations, must be forwarded to the Sponsor or its designee **prior to** the enrollment of subjects into the study. A copy of the approved ICF will also be forwarded to the Sponsor or its designee. Appropriate reports on the progress of the study will be made to the IRB/IEC and the Sponsor or its designee by the Investigator in accordance with applicable governmental regulations and in agreement with the policy established by the Sponsor.

5.2 Ethical Conduct of the Study

The Investigators will ensure that this study is conducted in a manner that fully conforms with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Tripartite Guideline or with local law if it affords greater protection to the subject. For studies conducted in the United States (US) or under a US Investigational New Drug program, the Investigator will additionally ensure adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 Code of Federal Regulations (CFR), subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects" and part 56, "Institutional Review Boards."

5.3 Subject Information and Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable by local regulations), to obtain signed informed consent from each subject prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study.

The Investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The ICF and any other written information provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject

information and/or the written ICF. The Investigator will inform the subject of changes in a timely manner and will ask the subject to confirm his/her participation in the study by signing the revised ICF. Any revised written ICF and written information must receive the IRB/IEC`s approval/favorable opinion in advance of use.

All signed ICFs are to remain in the Investigator's site file or, if locally required, in the subjects' notes/files of the medical institution.

The electronic case report forms (eCRFs) for this study contain a section for documenting all subject informed consent(s) and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the ICF should be reviewed and updated if necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

5.4 Compensation for Health Damage of Subjects/Insurance

The Sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

5.5 Confidentiality

All records identifying the subject will be kept confidential and to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the Sponsor. Only the subject number will be recorded in the eCRF and if the subject name appears on any other document, it must be obliterated before a copy of the document is supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the Sponsor, IRB/IEC or regulatory authorities may inspect their medical records to verify the information collected and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The Investigator will maintain a list to enable subjects to be identified.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The Sponsor of this study is Horizon Therapeutics U.S.A., Inc. (Horizon). Horizon personnel will serve as the Medical Monitor (see Section 17.1 for details). The Sponsor will be responsible for timely reporting of serious adverse events (SAEs) to regulatory authorities as required. The Sponsor will be responsible for timely reporting of SAEs and any other new pertinent safety information to all Investigators as required.

The study will be conducted at up to 12 study centers in the U.S. and the Coordinating Investigator will be PPD (Table 6.1). Prior to initiation of the study, each Principal Investigator will provide the Sponsor or its designee with a fully executed and signed Food and Drug Administration (FDA) Form 1572 and a Financial Disclosure Form. Financial Disclosure Forms will also be completed by all Sub-Investigators listed on Form 1572. It is the responsibility of the Investigators or Sub-Investigators to advise the Sponsor of any change in the relevant financial interests that occur during the study and the 1-year period following its completion.

Table 6.1 lists other organizations that are critical to the conduct of the study, with a brief description of their roles:

Table 6.1 Table of Non-Sponsor Study Responsibilities

Study Responsibility	Person/Organization
Coordinating Investigator	PPD
Contract research organization (feasibility, project management and monitoring)	PPD
Central safety laboratory	PPD
Clinical drug supply and distribution	PPD

7 INTRODUCTION

7.1 Background

7.1.1 Diffuse Cutaneous Systemic Sclerosis

The term scleroderma is used to describe the presence of thickened, hardened skin. Scleroderma is the cardinal feature of systemic sclerosis (SSc). Patients with SSc are commonly classified into 2 distinct subsets on the basis of the pattern of skin involvement. Diffuse cutaneous SSc (dcSSc) is dominated by rapidly progressive fibrosis of the skin, lungs and other internal organs. By contrast, limited cutaneous SSc is dominated by vascular manifestations and skin and organ fibrosis is generally limited and slow to progress [Varga, 2007].

The involvement of multiple organs is the distinguishing hallmark of dcSSc and accounts for much of the morbidity and mortality associated with the disease [Asano, 2017; Varga, 2007; Volkmann, 2019]. Immune perturbations and vascular injury precede and contribute to the development of fibrosis, which, in turn, further exacerbates vascular and immune damage [Asano, 2015; Bhattacharyya, 2011; Varga, 2007; Volkmann, 2019]. The disease is considered incurable and dcSSc carries the highest risk of fatality of the connective tissue diseases, with 55% survival at 10 years [Mayes, 2003; Varga, 2007].

There is no clear understanding of the initial disease triggers but it is generally accepted that genetic, epigenetic modifications and/or environmental factors cause an injury to the vasculature leading to a complex pathogenesis involving immune activation, inflammation, small vessel damage and an increase in the synthesis and deposition of extracellular matrix components resulting in multiorgan fibrosis [Asano, 2015; Asano, 2017; Volkmann, 2019]. This complex pathogenesis includes but is not limited to activation of dermal fibroblasts, skewing of T helper populations to a Th2/Th17 phenotype, differentiation of macrophages to an M2 phenotype, increased infiltration of plasmacytoid dendritic cells, endothelial-to-mesenchymal transition, epithelial cell activation and differentiation of various cell types into myofibroblasts [Asano, 2017].

SSc is highly heterogeneous in its multisystem clinical manifestations, including Raynaud's phenomenon, cutaneous telangiectasia, nail fold capillary alterations, pulmonary arterial hypertension (PAH), gastric antral vascular ectasia and scleroderma renal crisis with malignant hypertension [Varga, 2007]. The disease severity varies among patients and follows a variable and unpredictable course and response to treatment [Varga, 2007; Bhattacharyya, 2011; Volkmann, 2019].

SSc has a worldwide distribution and is more frequent in women than men [Mayes, 2003]. Based on incidence and survival rates, an estimated 75,000–100,000 individuals in the US have SSc [Varga, 2007].

The goal of skin fibrosis treatment is the restoration of abnormally activated dermal fibroblasts producing the excessive amount of extracellular matrix [Asano, 2017]. However, the complexity

and heterogeneity of the disease pose unique challenges for the development of effective therapies.

7.1.2 Insulin-like Growth Factor-1 Receptor (IGF-1R)

The insulin-like growth factor-1 receptor (IGF-1R) is a tyrosine kinase cell surface receptor that shares approximately 60% overall homology with the insulin receptor [Schumacher, 1991]. When activated by its ligands, insulin-like growth factor (IGF)-1 and IGF-2, IGF-1R regulates important cellular activities involving cell proliferation, differentiation and inflammation [Khandwala, 2000; Li, 2018; Ullrich, 1986].

Increasing evidence provides support to the role of the IGF-1/IGF-1R pathway in the pathogenesis of dcSSc including the presence of elevated levels of IGF-1 and associated binding proteins in serum and skin of diseased individuals, ability of IGF-1R stimulation to cause fibroblast migration, proliferation and differentiation into myofibroblasts and the requirement for IGF-1R signaling for M2 macrophage polarization. Additionally, preclinical evidence in mice supports a role for the IGF-1R receptor in lung fibrosis following injury.

Key data supporting the involvement of IGF-1R in the dcSSc pathogenesis:

1. IGF-1 protein levels as well as protein levels of one of its binding partners, insulin-like growth factor binding protein (IGFBP)-3, are elevated in the serum of patients with dcSSc as compared with healthy controls and patients with systemic lupus erythematosus or limited cutaneous SSc [Hamaguchi, 2008].
2. Ribonucleic acid levels of IGF-1 and another binding partner, IGFBP-5, have also been shown to be elevated in skin fibroblasts derived from SSc patients [Feghali, 1999; Hamaguchi, 2008].
3. IGF-1 ribonucleic acid and protein levels were found to be elevated in the skin and serum of patients with Morphea, a chronic disorder with sclerotic plaques and increased fibrosis [Fawzi, 2008].
4. Case reports have noted where treatment with an IGF-1 antagonist, octreotide, resolved either refractory pretibial myxedema with Graves' disease or skin sclerosis in a patient with carcinoid syndrome [Pavlovic, 1995; Shinohara, 2000].
5. In vitro studies have demonstrated that IGF-1 stimulated differentiation of fibroblasts into myofibroblasts [Hung, 2013].
6. In animal models of acute lung injury, IGF-1R blockade following injury increases survival and decreases time for fibrosis resolution, hydroxyproline content and the number of myofibroblasts and alpha smooth muscle actin expressing cells, in the lungs [Choi, 2009; Hung, 2013].
7. In a model of bleomycin-induced lung injury, mice with conditional IGF-1R deletion in lungs showed reduced mortality, reduced alveolar damage and reduced erythrocytes, neutrophils, macrophages and lymphocytes in bronchoalveolar lavage fluid as well as prevented vascular permeability changes [Pineiro-Hermida, 2017].
8. IGF-1R has also been shown to be important in M2 macrophage polarization. IGF-1 is highly expressed in M2 macrophages as compared to M0/M1 macrophages [Spadaro, 2017]. IGF-1R has also been shown to influence the macrophage activation process as mice with the IGF-1R gene knocked out in cells of the myeloid lineage

showed decreased ability to induce the M2 polarization process, reduced transcripts associated with an M2 phenotype as well as an increase in responsiveness to interferon gamma, a phenotype normally observed in M1 macrophages [Barrett, 2015; Spadaro, 2017].

7.1.3 TEPEZZA

TEPEZZA (teprotumumab-trbw), a fully human monoclonal antibody (mAb), is an IGF-1R inhibitor that received approval from the FDA for the treatment of thyroid eye disease (TED) in January 2020.

In vitro, IGF-1R antagonists have shown the ability to block signaling through multiple signal transduction pathways (e.g., extracellular-signal-regulated kinase pathway, mitogen activated protein kinase), decrease the expression of cytokines and reduce secretion of disease related glycosaminoglycan [Chen, 2014; Pritchard, 2003; Smith, 2004; Tsui, 2008]. TED and dcSSc have common disease features including activation of fibroblasts, elevated levels of inflammatory cytokines, infiltration of immune cells into disease tissue and excessive synthesis of extracellular matrix components [Bahn, 2010; Boschi, 2005; Smith, 2010]. By blocking signaling and down-regulating IGF-1R in fibroblasts, myofibroblasts, fibrocytes and cells of the immune system, TEPEZZA has the potential to specifically target the key underlying pathophysiology of dcSSc, thereby reducing the severity and progression of the disease.

7.1.3.1 Physiochemical Properties

The human variable regions of TEPEZZA were derived from a hybridoma obtained from a transgenic HCo7 mouse immunized with recombinant human IGF-1R protein. The antibody is made up of 2 heterodimers, each composed of a heavy and light polypeptide chain. The 4 peptide chains are linked by disulfide bonds. The antibody bears a single carbohydrate chain in the constant region of both heavy chains. The manufacture of teprotumumab-trbw drug substance consists of fermentation cell culture and purification. A stable antibody-producing cell line was established in the Chinese hamster ovary cell line CHO-DG44. Current product specifications for planned studies are as follows:

Generic Name/USAN:	Teprotumumab-trbw
Company Drug Code:	HZN-001
Chemical Abstracts Service Number:	89957-37-9
Drug Product:	Each vial delivers 500 mg TEPEZZA formulated with 20 mmol/L Histidine-Histidine Chloride, 250 mmol/L trehalose and 0.01% polysorbate 20 (w/v) as a lyophilized powder packaged in a 20 mL clear, glass vial.
Chemical Name:	Immunoglobulin G1 anti-(human insulin-like growth factor 1 receptor) (human monoclonal heavy chain), disulfide with human monoclonal light chain, dimer
Chemical Structure:	H2L2 polypeptide structure consisting of 2 light chains and 2 heavy chains held together by disulfide bonds
Molecular Weight:	148 kDA
Appearance:	White to off-white powder for reconstitution

USAN=United States Adopted Name.

7.1.3.2 Safety Pharmacology

In the repeat-dose toxicity studies at dose levels up to 75 mg/kg twice weekly for 7 weeks or 75 mg/kg once weekly for up to 39 weeks, there were no findings from clinical observations, physical examinations (including measurements of vital signs such as heart rate, respiration rate and body temperature) or electrocardiogram (ECG) examinations at various intervals that suggested potential effects of TEPEZZA in central nervous, respiratory or cardiovascular systems. An overview of the nonclinical safety pharmacology studies is provided in the current version of the Investigator's Brochure.

7.1.3.3 Nonclinical Pharmacokinetics

Teprotumumab showed low systemic clearances and long terminal half-lives following intravenous (IV) administration in both rats and monkeys, consistent with pharmacokinetic (PK) characteristics of mAbs. No gender differences were apparent for any dose level tested in either species. Metabolism of antibodies is generally known, i.e., degradation to smaller peptides and amino acids (Ryman, 2017); as a result, TEPEZZA is not expected to be involved in classical drug-drug interactions. An overview of the nonclinical PK studies is provided in the current version of the Investigator's Brochure.

7.1.3.4 Clinical Experience

7.1.3.4.1 Efficacy

To date, TEPEZZA has been studied in 2 independent, randomized, double-blind, placebo-controlled, parallel-group, multicenter studies that evaluated the efficacy and safety of TEPEZZA (Phase 2 Study TED01RV and Phase 3 Study HZNP-TEP-301) for the treatment of TED and an open-label extension of Study HZNP-TEP-301 (Study HZNP-TEP-302). TEPEZZA received approval from the FDA for the treatment of TED in January 2020.

The effectiveness of TEPEZZA in the treatment of TED has been demonstrated in randomized, double-blind, placebo-controlled Studies TED01RV and HZNP-TEP-301. Subjects who met eligibility criteria were randomized in a 1:1 ratio (stratified by tobacco use status) to receive 8 infusions of TEPEZZA (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) or placebo administered once every 3 weeks (q3W). TEPEZZA resulted in statistically significant and clinically relevant improvements in measures that assessed multiple facets of TED (proptosis, inflammation as measured by Clinical Activity Score, diplopia and quality of life [QOL]). Consistent results were shown across all efficacy endpoints and all subpopulations.

Data from the off-treatment Follow-up Period in Study HZNP-TEP-301 showed that the response to treatment achieved for the primary and secondary responder endpoints at the end of the Double-Masked Treatment Period was also observed for the majority of the teprotumumab subjects at the end of the 48-week off-treatment Follow-up Period.

Results of Study HZNP-TEP-302 demonstrated efficacy of teprotumumab in subjects who had TED for a longer period of time than in the original Phase 2 and Phase 3 trials. The majority of

eligible subjects for this open-label extension trial were randomized to placebo in Study HZNP-TEP-301 and were also non-responders in Study HZNP-TEP-301. The duration of TED before the first dose of teprotumumab in these subjects in Study HZNP-TEP-302 was an average of 6 months longer than in Study HZNP-TEP-301 (12 vs. 6 months); however, similar efficacy was observed in those who transitioned from placebo in Study HZNP-TEP-301 to teprotumumab in Study HZNP-TEP-302, indicating that teprotumumab is as efficacious in subjects with longer TED duration. In addition, results indicate that, although sample sizes were small, additional treatment with teprotumumab has potential to benefit patients who were previous proptosis non responders after 6 months of initial treatment or who relapsed in off-treatment follow up. There were no new safety signals identified in subjects in this trial, including those subjects who received additional treatment with teprotumumab.

TEPEZZA has not been studied in the dcSSc population.

7.1.3.4.2 Pharmacokinetics

Characteristics

The PK of teprotumumab (IV infusion) was derived from a Phase 1 study in oncology subjects (Study BO19373) and Phase 2 and 3 studies in subjects with TED (TED01RV and HZNP-TEP-301), using both non-compartmental and population PK analyses.

The PK of teprotumumab was characterized in 96 oncology subjects and 83 TED subjects at doses of 1 to 20 mg/kg. Overall, the PK characteristics of teprotumumab were consistent with other immunoglobulin G1 mAbs, with low systemic clearance (0.334 L/day), low volume of distribution (3.94 L for central compartment and 4.21 L for peripheral compartment) and long elimination half-life (geometric mean of 19.9 days in TED subjects) [Dirks, 2010; Ryman, 2017]. Target-mediated drug disposition was saturated at higher doses of TEPEZZA (≥3 mg/kg) and teprotumumab PK were linear at the clinical dose range (10 to 20 mg/kg) in TED subjects.

Population PK analysis indicated that weight, age, sex and race had no effect on teprotumumab exposures. Female subjects had a 14.5% higher maximum serum concentration (C_{max}), but similar area under the concentration-time curve (AUC) compared to male subjects, which is not considered clinically relevant. Covariates including smoking status, mild or moderate renal impairment and hepatic function (total bilirubin, aspartate aminotransferase and alanine aminotransferase) did not have any impact on teprotumumab PK.

Drug-drug interactions between TEPEZZA and thyroid medications (e.g., levothyroxine, propylthiouracil) commonly used by TED subjects are not expected, as TEPEZZA and small molecule drugs do not share common or overlapping clearance pathways [Zhou, 2011].

Immunogenicity of TEPEZZA was assessed in serum samples in Studies TED01RV and HZNP-TEP-301. There was no clinically relevant immunogenic response observed after administration of TEPEZZA. No subjects treated with teprotumumab in Study HZNP-TEP-302 were positive for anti-drug antibodies.

7.1.3.4.3 Pharmacodynamics

Total serum IGF-1 levels were increased after TEPEZZA treatment at all dose regimens tested in oncology subjects (1 to 16 mg/kg q3W and 1 to 9 mg/kg once weekly), suggesting that TEPEZZA blocked the binding of IGF-1 to its receptor IGF-1R at the clinical doses evaluated.

7.1.3.4.4 Safety

7.1.3.4.4.1 Thyroid Eye Disease Studies

TEPEZZA was generally well tolerated at the dose investigated (10 mg/kg for the first dose followed by an IV infusion of 20 mg/kg q3W for a total of 8 doses) in the TED population, with more than 90% of subjects completing the 24-Week Double-blind Treatment Period. Among the 121 subjects exposed to TEPEZZA across Studies TED01RV, HZNP-TEP-301 and HZNP-TEP-302, no deaths occurred and few subjects experienced treatment-emergent adverse events (TEAEs) that were serious (8/121 subjects, 6.6%), severe or higher in intensity (4/121 subjects, 3.3%) or led to discontinuation of study drug (6/121 subjects, 5.0%).

The most commonly reported TEAEs among subjects treated with TEPEZZA in the Double-blind Treatment Period (incidence ≥5.0% and greater than placebo) were *Muscle spasms* (26.2%), *Nausea* (16.7%), *Alopecia* (15.5%), *Diarrhoea* (13.1%), *Dry skin* (9.5%), *Fatigue* (9.5%), *Dysgeusia* (8.3%), *Headache* (8.3%), *Hyperglycaemia* (7.1%) and *Weight decreased* (6.0%). Each of these commonly reported TEAEs in the Double-blind Treatment Period were nonserious, mild or moderate in intensity and did not result in discontinuation from study drug, with the exception of 1 event of *Diarrhoea* (likely exacerbation of pre-existing inflammatory bowel disease (IBD), which was serious, severe and led to discontinuation of study drug) and 1 event of *Headache* (severe). Among the events of *Diarrhoea* reported, no events of new-onset IBD have been observed. TEAEs associated with hyperglycemia (*Hyperglycaemia* or *Blood glucose increased*) were more likely to occur in subjects with pre-existing diabetes mellitus or impaired glucose tolerance; the events were managed with medications for glycemic control as needed.

TEAEs associated with hearing impairment (reported as *Deafness*, *Hypoacusis*, *Eustachian tube dysfunction*, *Hyperacusis*, *Autophony* or *Eustachian tube patulous*) were observed in teprotumumab-treated subjects (9.5%) in the Double-Masked Population compared to no reports among placebo-treated subjects. All of these events were nonserious, mild or moderate in intensity, and none led to premature discontinuation of study drug; these events usually improved or resolved.

Infusion reactions were observed in 3 TEPEZZA-treated subjects in the TED clinical program; these events were managed with symptomatic treatment and all events resolved without complication.

No clinically significant changes in laboratory values, vital signs or ECGs were observed in subjects treated with TEPEZZA in the Double-blind Treatment Period. Over the 24-Week Double-blind Treatment Period, a greater proportion of TEPEZZA subjects (18.4%) had a

≥5% decrease in weight compared with placebo subjects (2.5%). In addition, no significant anti-teprotumumab-trbw antibodies were detected up to 48 weeks after the final administration of TEPEZZA.

Data from the off-treatment Follow-up Period in Study HZNP-TEP-301 showed no significant change in the safety profile of teprotumumab through approximately 1 year off treatment, which was also demonstrated in the same off-treatment Follow-up period in Study TED01RV.

The safety profile observed in Study HZNP-TEP-302 was consistent with the results of previous Phase 2 and 3 studies of teprotumumab in TED. Teprotumumab was well tolerated and demonstrated an acceptable safety profile in the TED population in Study HZNP-TEP-302, including subjects who were retreated with teprotumumab after receiving teprotumumab in Study HZNP-TEP-301.

7.1.3.4.4.2 Oncology Studies

TEPEZZA was originally developed by F. Hoffman-La Roche Ltd. for the treatment of patients with advanced solid tumors, including sarcoma. Development for this indication was discontinued based on insufficient clinical efficacy and was not based on any observed safety issues.

In the oncology program, over 700 subjects were treated with TEPEZZA at dose levels ranging from 1 to 27 mg/kg q3W to 1 to 9 mg/kg once weekly. Taking into consideration progression of disease and prior/concomitant treatment with cytotoxic agents, TEPEZZA was generally well-tolerated with a safety profile similar to that seen in the TED population. Safety data from the oncology program are presented in the current version of the Investigator's Brochure.

7.1.3.4.4.3 Diabetic Macular Edema Studies

In a study conducted in 5 subjects with diabetic macular edema who were treated with TEPEZZA (Study DME01RV), the most frequent TEAEs included events associated with hyperglycemia (4 subjects; *Blood sugar increased*, *Blood glucose increased* and *Hyperglycaemia*) and *Dizziness* (2 subjects). No subjects experienced serious TEAEs. Two subjects withdrew early from the study prior to the last infusion due to hyperglycemia. No additional studies of TEPEZZA have been conducted or planned in subjects with diabetic macular edema.

7.1.3.4.4.4 Adverse Events of Special Interest

Following a comprehensive review of the safety data from the TEPEZZA studies conducted in TED, the following adverse events of special interest (AESI) have been identified for the current study:

- Hyperglycemia
- Hearing impairment
- Infusion-associated events, including anaphylactic reaction
- New onset or exacerbation of IBD

An overview of the AESIs, including general precautions, is presented in the following paragraphs.

Hyperglycemia

In nonclinical studies, there was no *in vitro* cross-reactivity of TEPEZZA with the insulin receptor. TEPEZZA clinical studies in TED have shown a higher incidence of hyperglycemia in subjects treated with TEPEZZA compared to placebo. Subjects with pre-existing diabetes mellitus (who were under appropriate glycemic control upon study entry) or impaired glucose tolerance were more likely to experience an event of hyperglycemia after exposure to TEPEZZA.

Subjects with known controlled diabetes mellitus are allowed to participate in studies with TEPEZZA. Glycated hemoglobin (HbA1c) levels should be monitored regularly in these subjects. Investigators are strongly encouraged to adjust their subjects' diabetes management to the individual, balancing complications due to diabetes and hyperglycemia. A reasonable goal is HbA1c levels ≤7% [American Diabetes Association, 2019a]. However, it is also acceptable to set a higher goal of ≤8% in older individuals [Huang, 2008].

Hearing Impairment

Adverse reactions of middle to high range sensorineural hearing loss have been reported in both healthy volunteers and subjects with malignancies who received as little as 1 dose of various IGF-1R mAbs.

In the TEPEZZA TED clinical program as of the data cutoff of 19 June 2020, 14 (11.6%) of the 121 subjects exposed to TEPEZZA have experienced events associated with hearing impairment, with no reports of hearing impairment in subjects who received placebo. Each of these events were nonserious, mild or moderate in intensity and none led to premature discontinuation of study drug; these events usually improved or resolved. If possible, subjects should avoid ototoxic drugs while receiving teprotumumab.

Infusion-related and Anaphylactic Reactions

A total of 3 subjects were identified by the Sponsor adjudication process as having experienced infusion-related reactions during treatment with TEPEZZA for TED. The associated symptoms included transient increases in blood pressure, feeling hot, tachycardia, headache, dyspnea and muscular pain. The reactions occurred during or within 1.5 hours after the first or second infusion in 2 of the subjects and during the fifth infusion in the remaining subject. The reactions were considered mild or moderate in intensity and were treated with a glucocorticoid and/or antihistamine. Each of the reactions resolved without sequelae. Among the 3 subjects, 2 were discontinued from treatment and 1 was pre-medicated prior to study drug infusions with diphenhydramine, dexamethasone, famotidine and acetaminophen and completed all subsequent infusions at a slower infusion rate without reoccurrence of infusion reaction.

Treatment with mAbs may cause infusion-associated symptoms such as fever, chills, hypotension, shortness of breath, skin rash and headache. Such reactions typically occur during

or shortly after the infusion of mAbs and are usually associated with the first infusion. Their incidence and severity typically decrease with subsequent infusion. Severe infusion-associated reactions might be clinically indistinguishable from anaphylactic reactions.

New Onset or Exacerbation of Inflammatory Bowel Disease

Exacerbation and suspected exacerbation of underlying IBD occurred in 2 subjects in the TED Phase 2 study. Subjects with IBD were excluded from Study HZNP-TEP-301 (Phase 3) and will be excluded from this study. No events suggestive of new onset IBD were observed in the TED Phase 3 studies.

7.2 Rationale for this Study

dcSSc 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 dcSSc have a 10-year survival rate of 55% [Mayes, 2003; Varga, 2007]. Death is most often caused by lung, heart and kidney involvement [Hao, 2017; Pokeerbux, 2019; Tyndall, 2010].

Currently, there is no effective treatment or cure for dcSSc. 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., steroids, methotrexate, cyclophosphamide, azathioprine and mycophenolate mofetil) have demonstrated only limited efficacy and/or have safety issues that impact their use. Thus, there is a substantial unmet clinical need for a safe and effective treatment for dcSSc.

By blocking signaling and downregulating IGF-1R in fibroblasts, myofibroblasts, fibrocytes and cells of the immune system, TEPEZZA has the potential to specifically target the key underlying pathophysiology of dcSSc, thereby reducing the severity and progression of the disease. The current study was designed to evaluate the safety, tolerability and effect of TEPEZZA on IGF-1, inflammatory and fibrotic biomarkers in subjects with dcSSc.

7.3 Rationale for Dose Selection

The selected dose regimen for dcSSc subjects is the same as that studied in TED subjects (i.e., an initial single dose of 10 mg/kg followed by 20 mg/kg q3W). In the Phase 2 and Phase 3 TED studies, this selected regimen was highly effective, generally well tolerated and provided TEPEZZA concentrations maintaining >90% saturation of IGF-1R throughout the dosing interval in all subjects. Given the apparent similarity of mechanical- and immune-mediated drivers of disease in dcSSc to those in TED, maintaining >90% saturation of IGF-1R throughout the dosing interval would be an appropriate strategy in dcSSc as well.

8 STUDY OBJECTIVES

The overall objective of this study is to evaluate the safety, tolerability and effect on IGF-1, inflammatory and fibrotic biomarkers of TEPEZZA (teprotumumab-trbw; HZN-001), a fully

human mAb inhibitor of the IGF-1R, administered q3W for 24 weeks in the treatment of subjects with dcSSc.

8.1 Primary Objective

The primary objective is to evaluate the safety of TEPEZZA versus placebo on the proportion of subjects who experience a TEAE through Week 24 in subjects with dcSSc.

8.2 Other Objectives

CCI

CCI

8.3 Pharmacokinetic and Anti-drug Antibody Objectives

1. Evaluate the PK of teprotumumab.
2. Evaluate the immunogenicity of TEPEZZA.

8.4 Safety and Tolerability Objectives

To assess safety and tolerability of TEPEZZA based on treatment-emergent adverse events (TEAEs), AESIs (hyperglycemia, hearing impairment, infusion reaction, new onset or exacerbation of IBD), concomitant medication use, vital signs, clinical safety laboratory evaluations and inflammatory laboratory evaluations.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study will be conducted at up to 12 sites in the United States.

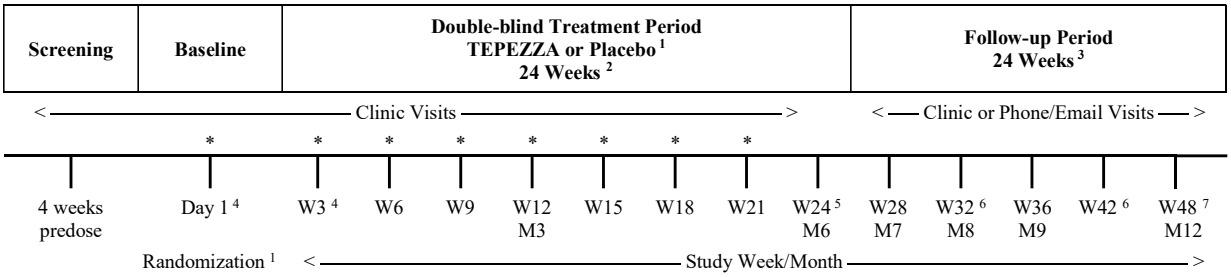
This is a randomized, double-blind, placebo-controlled, repeat-dose, multicenter study. Subjects will be screened for the study within 4 weeks prior to the Baseline (Day 1) Visit. Approximately 25 subjects who meet the study eligibility criteria will be randomized on Day 1 in a 3:2 ratio to receive 8 infusions of TEPEZZA (10 mg/kg for the first infusion and 20 mg/kg for the remaining 7 infusions) or placebo q3W. During the 24-week double-blind Treatment Period, study drug will be infused on Day 1 (Baseline) and Weeks 3, 6, 9, 12, 15, 18 and 21 with a comprehensive visit at Week 24 (end of treatment). All study drug dosing will be performed at the clinic or infusion center under the supervision of clinic staff or nurses. At any scheduled infusion, the infusion rate may be reduced or the dose may be interrupted or held based on tolerability (see Section 9.4.6.3.2 for details). On each dosing day, scheduled assessments (except for adverse event [AE] and concomitant medication use monitoring, which will be monitored throughout the clinic visit) will be completed prior to study drug infusions. After each of the first 2 infusions, subjects will be contacted by phone/email the following day. Additional phone/email contacts and clinic visits may also be conducted for any subject experiencing an infusion-associated event.

At the end of the Treatment Period (Week 24), subjects will enter a 24-week Follow-up Period, during which study drug will not be administered and a clinic visit will be scheduled for Weeks 28, 36 and 48. A phone call or email at Weeks 32 and 42 will occur to inquire how the subject is doing and women of childbearing potential will be asked if they have missed a menstrual cycle and will have a serum pregnancy test, if required.

If a subject prematurely discontinues prior to completing the Treatment Period, he/she will return to the clinic and undergo the Week 24 assessments; such subjects will also be encouraged to continue in the 24-week Follow-up Period. If a subject prematurely discontinues prior to completing the 24-week Follow-up Period, he/she will return to the clinic and undergo the Week 48 assessments.

An overview of the study design is presented in Figure 9.1 and details of study activities are provided in Section 2.1, *Schedule of Assessments*.

Figure 9.1 Schematic of Study Design



* Infusion of study drug
AE=adverse event; M=Month; q3W=every 3 weeks; W=Week

1. Subjects will be randomized in a 3:2 ratio (15 TEPEZZA and 10 placebo) to receive:
   a. TEPEZZA (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions); or
   b. Placebo (placebo q3W for all 8 infusions).
2. Visit windows are ±3 days for Weeks 3 to 21, inclusive.
3. Visit windows are ±7 days for Weeks 24 to 48, inclusive.
4. All subjects will be contacted by phone/email the day following the first (Day 1) and second (Week 3) infusions for safety and tolerability assessments; additional phone/email contacts will occur the day after any clinic visit where a subject experiences an infusion-related AE.
5. If a subject prematurely discontinues prior to completing the 24-week Treatment Period, he/she will return to the clinic and undergo the Week 24 assessments. Subjects will be encouraged to continue in the 24-week Follow-up Period.
6. All subjects will be contacted via phone or email at Weeks 32 and 42 to inquire how subjects are doing and to ask women of childbearing potential about their menstrual cycle.
7. If a subject prematurely discontinues prior to completing the 24-week Follow-up Period, he/she will return to the clinic and undergo the Week 48 assessments.

9.2 Discussion of Study Design

This study is a randomized, double-blind, placebo-controlled, repeat-dose, multicenter study in the dcSSc population designed according to standard principles. The measurements used in this study to assess safety and efficacy are established and well-defined.

Because patients with dcSSc have a potential risk of weight loss and malnutrition as manifestations of their disease [Hughes, 2020; Richard, 2019; Baron, 2009; Wojteczek, 2020; Gyger, 2015], weight will be measured frequently in this study. Dosing will be based on the subject's weight on Day 1 for dosing on Day 1 and at Weeks 3, 6 and 9 and on the subject's weight at Week 9 for dosing at Weeks 12, 15, 18 and 21.

Given the teratogenic effects of TEPEZZA noted in a monkey embryo-fetal development toxicity study and the PK profile of teprotumumab (see Section 7.1.3.4.2), female subjects are required to use adequate contraception and report any pregnancies for at least 6 months after the last dose of study drug. Six months after the last dose, the estimated plasma concentration (0.2 µg/mL) is considered reasonably safe with a low risk of teratogenicity. Furthermore, a 6-month waiting period is in line with recommendations given for other teratogens, such as cytostatic chemotherapy.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

Eligible subjects must meet/provide **all** of the following criteria:

1. Written informed consent.
2. Male or female between the ages of 18 and 80 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, 2013].
4. Classified as having skin involvement proximal to elbow, knee, face and neck, dcSSc subset [LeRoy and Medsger, 2001].
5. At the time of enrollment, no more than 60 months must have elapsed since the onset of the first dcSSc manifestations, other than Raynaud's phenomenon.
6. Skin thickening from dcSSc in the forearm suitable for repeat biopsy.
7. mRSS units ≥10 and ≤45 at Screening.
8. Subjects will be allowed to take CellCept® (mycophenolate mofetil) up to 3 g/day or Myfortic® (mycophenolic acid) up to 2.14 g/day and low-dose prednisone (≤10 mg/day or equivalent dosing of glucocorticoids). Subjects taking CellCept or Myfortic have been doing so for ≥20 weeks and the dose must have been stable for ≥16 weeks prior to the Day 1 Visit. Prednisone must have been at a stable dose for ≥4 weeks prior to the Day 1 Visit.
9. Diabetic subjects must have HbA1c ≤8.0%, with no new diabetic medication (oral or insulin) or more than a 10% change in the dose of a currently prescribed diabetic medication within 60 days prior to Screening.
10. Women of childbearing potential (including those with an onset of menopause <2 years prior to Screening, nontherapy-induced amenorrhea for <12 months prior to Screening or not surgically sterile [absence of ovaries and/or uterus]) must have a negative serum pregnancy test at Screening and negative urine pregnancy tests at all protocol-specified timepoints (i.e., prior to each dose and throughout the subject's participation in the Follow-up Period); subjects who are sexually active with a non-vasectomized male partner must agree to use 2 reliable forms of contraception during the trial, one of which is recommended to be hormonal, such as an oral contraceptive. Hormonal contraception must be started at least 1 full cycle prior to Baseline and continue for 180 days after the last dose of study drug. Highly effective contraceptive methods (with a failure rate <1% per year), when used consistently and correctly, include implants, injectables, combined oral contraceptives, some intrauterine devices, sexual abstinence or vasectomized partner.

11. Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the study.

9.3.2 Exclusion Criteria

Subjects will be ineligible for study participation if they meet **any** of the following criteria:

1. Diagnosed with limited cutaneous SSc or sine scleroderma.
2. Diagnosed with other autoimmune connective tissue diseases except for fibromyalgia, scleroderma-associated myopathy and Sjogren's syndrome.
3. Scleroderma renal crisis diagnosed within 6 months of the Screening Visit, characterized by abrupt onset of hypertension and acute kidney injury (see Section 9.5.1.1).
4. FVC <50% predicted, diffusing capacity of the lungs for carbon monoxide (DLCO) <40% predicted or PAH by right heart catheterization requiring treatment with more than one oral PAH-approved therapy or parenteral therapy (intermittent use of phosphodiesterase-5 inhibitors are allowed for erectile dysfunction and/or Raynaud's phenomenon/digital ulcers).
5. Corticosteroid use for conditions other than dcSSc within 4 weeks prior to Screening (topical steroids for dermatological conditions and inhaled steroids are allowed).
6. Previous treatment with rituximab (Rituxan® or MabThera®) within 12 months prior to the first infusion.
7. Use of a non-steroidal immunosuppressive agent, cytotoxic or anti-fibrotic drug within 4 weeks of Screening, including cyclophosphamide, azathioprine (Imuran®), methotrexate or other immunosuppressive or cytotoxic medication. Exceptions are mycophenolate mofetil (CellCept) and mycophenolic acid (Myfortic), which are permitted according to inclusion criterion 8, and anti-malarials (e.g., hydroxychloroquine [Plaquenil®]).
8. Use of biologics or small molecules approved for rheumatoid arthritis, psoriatic arthritis and other rheumatic diseases within 4 weeks prior to Screening.
9. Use of 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.
10. Malignant condition in the past 5 years (except successfully treated basal/squamous cell carcinoma of the skin or cervical cancer in situ).
11. Pregnant or lactating women.
12. 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.
13. Biopsy-proven or clinically suspected IBD (e.g., diarrhea with or without blood or rectal bleeding associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence for more than 4 weeks without a confirmed alternative diagnosis OR

endoscopic or radiologic evidence of enteritis/colitis without a confirmed alternative diagnosis).

14. Known hypersensitivity to any of the components of TEPEZZA or prior hypersensitivity reactions to mAbs.
15. Previous enrollment in this study or participation in a prior teprotumumab-trbw clinical trial.
16. Human immunodeficiency virus, untreated or positive viral load for hepatitis C or hepatitis B infections.
17. Previous organ transplant (including allogeneic and autologous marrow transplant).
18. Alanine aminotransferase or aspartate aminotransferase >2.5 times the upper limit of normal or estimated glomerular filtration rate of <30 mL/min/1.73m^2 at Screening.
19. Platelets <100×10^3/µL.
20. Hemoglobin <8 g/dL.
21. Any other condition that, in the opinion of the Investigator, would preclude inclusion in the study.

9.3.3 Removal of Subjects from Treatment or the Study

All subjects are free to withdraw from study participation at any time, for any reason and without prejudice to their further medical care. Subjects who prematurely discontinue study drug during the Treatment Period will be encouraged to continue study participation, particularly returning for the Week 24 (end of treatment) assessments, and continue in the 24-week Follow-up Period. Subjects who discontinue study drug due to an AE should be followed until resolution or stabilization of the AE, or an adequate explanation for the event is obtained.

If further participation in the study is not in the best interest of the subject, the Investigator may terminate a subject from treatment or from the study.

9.3.3.1 Removal of Subjects from Treatment

The primary reason for discontinuation from study drug should be recorded on the eCRF using one of the following categories:

- Adverse event. The subject experiences an AE that imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue receiving treatment because of an AE. Subjects who discontinue study drug due to an AE will remain in the study unless they withdraw from the study for another reason. AEs requiring permanent study drug discontinuation per the protocol include:
    - A drug-related anaphylactic reaction.
    - Severe drug-related hyperglycemia (e.g., blood glucose >250 mg/dL) that does not abate to mild or moderate intensity with anti-diabetic treatment (dose may be skipped up to 2 times prior to permanently discontinuing study drug; see Section 9.4.6.3.2 for details).

- Diagnosed or suspected IBD (e.g., diarrhea with or without blood or rectal bleeding associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence for more than 4 weeks without a confirmed alternative diagnosis OR endoscopic or radiologic evidence of enteritis/colitis without a confirmed alternative diagnosis).

- Lack of efficacy. Discontinuation of study drug due to lack of efficacy is at the discretion of the Investigator or subject and may occur if the Investigator determines that study drug administration is not benefitting the subject. Subjects who discontinue study drug due to lack of efficacy will remain in the study unless they withdraw from the study for another reason.
- Withdrawal by subject/guardian. The subject wishes to withdraw from study treatment. The clinical site should attempt to determine the underlying reason for the voluntary withdrawal and document it on the eCRF.
- Study terminated by Sponsor. The Sponsor, IRB/IEC or regulatory agency terminates the study.
- Pregnancy.
- Death.
- Completed. The subject completed treatment.

9.3.3.2 Removal of Subjects from the Study

The primary reason for discontinuation from the study should be recorded on the eCRF using one of the following categories:

- Lost to follow-up. The subject does not return to the clinic for scheduled assessments and does not respond to the site's attempts to contact the subject.
- Withdrawal by subject/guardian. The subject wishes to withdraw from the study. The clinical site should attempt to determine the underlying reason for the voluntary withdrawal and document it on the eCRF.
- Death.
- Completed. The subject completed the study.

If a subject prematurely discontinues from the study during the Follow-up Period, he/she will return for a clinic visit and undergo the Week 48 (end of study) assessments.

9.3.4 Replacement Policy

9.3.4.1 Subjects

In general, no subject prematurely discontinued from the study for any reason will be replaced. An exception may be made for subjects who are unevaluable due to the impact of an event, for example, a pandemic or a natural disaster, and associated restrictions on movement and work.

Subjects unable to receive treatment or be evaluated due to restrictions during the event may be replaced, at the discretion of the Sponsor. This may result in more subjects being enrolled into the study to allow for the planned number to be evaluable for the efficacy and safety analyses.

9.3.4.2 Centers

A center may be closed and/or replaced for the following administrative reasons:

- Excessively slow recruitment.
- Poor protocol adherence.

9.3.4.3 Screen Failures

Subjects who do not meet all of the inclusion criteria or meet any of the exclusion criteria will be considered screen failures. Screen failures may be allowed to rescreen for the study if both the Investigator and Sponsor are in agreement regarding rescreening and if the Investigator determines that the subject can satisfy all of the eligibility criteria.

9.4 Treatments

9.4.1 Treatments Administered

All study drug dosing will be performed at the clinic or infusion center under the supervision of clinic staff or nurses. On Day 1 of the double-blind Treatment Period, subjects will be randomized in a 3:2 ratio to receive infusions of either:

1. TEPEZZA (10 mg/kg on Day 1 followed by 20 mg/kg q3W for the remaining 7 infusions), or
2. Placebo (q3W for all 8 infusions).

The infusion rate may be reduced and the dose may be interrupted or held based on tolerability. The first and second infusions will be administered over approximately 90 minutes (but not less than 80 minutes). Subsequent infusions will be administered over approximately 60 minutes (but not less than 50 minutes), providing there are no significant infusion-associated events.

9.4.2 Identity of Investigational Products

9.4.2.1 TEPEZZA

TEPEZZA (teprotumumab-trbw; HZN-001) is a fully human anti-IGF-1R mAb. The physiochemical properties were previously presented in Section 7.1.3.1. TEPEZZA will be provided in single-dose, 20-mL glass vials as a freeze-dried powder containing, in addition to the drug substance, 20 mmol/L histidine-histidine chloride, 250 mmol/L trehalose and 0.01% polysorbate 20 (w/v).

Prior to administration, each vial containing 500 mg TEPEZZA freeze-dried powder will be reconstituted with 10 mL of sterile water for injection. The resulting solution will have a concentration of 47.6 mg/mL TEPEZZA. Reconstituted TEPEZZA solution will be further

diluted in 0.9% (w/v) sodium chloride (NaCl) solution prior to administration (see Section 9.4.6.3 for details).

9.4.2.2 Placebo

Placebo will consist of a normal saline (0.9% NaCl) solution and will be administered in 100 mL or 250 mL infusion bags, as appropriate, per weight-based dosing volumes.

9.4.3 Labeling

Study drug packaging will be in compliance with Sponsor/CRO standard procedures and will meet all local requirements.

Upon arrival of investigational products at the site, the investigational unblinded pharmacist (or designee in accordance with institutional policies and local regulations) should inspect them for damage and verify proper identity, quantity, integrity of seals and temperature conditions and report any deviations or product complaints to the monitor/Sponsor upon discovery.

9.4.4 Storage

Recommended storage conditions for the freeze-dried TEPEZZA drug product are between 2°C and 8°C (36°F to 46°F), protected from light.

The storage instructions for reconstituted TEPEZZA solution in the vial and the diluted solution in the infusion bag containing 0.9% Sodium Chloride Injection, United States Pharmacopeia (USP) are outlined in the most recent version of the Investigator's Brochure. An Investigational Pharmacy Manual will be provided to all sites to further describe these processes in detail.

At the clinic, all TEPEZZA must be stored in a secure area with limited access, and a daily temperature log of the drug storage area will be maintained every working day; deviations from the specified temperature range will be reported as protocol deviations.

9.4.5 Drug Accountability

The Principal Investigator at each site is responsible for the control of all study drug and delegating infusion bag preparation and drug accountability responsibilities to an unblinded pharmacist (or designee in accordance with institutional policies and local regulations), who must maintain adequate records of the receipt and disposition of all study medication shipped to the study center. Records will include receipt dates, condition at time of receipt, quantities received, quantities dispensed, quantities returned or destroyed and the identification numbers of the subjects who received study medication.

As permitted by site policy, all empty, partially empty and full vials of study drug must be retained by the study center under locked storage until drug accountability has been completed. Periodically throughout the study and at the conclusion of the study, inventory checks and accountability of study materials will be conducted by an unblinded representative of the Sponsor. Once accountability is completed, the Sponsor's representative will authorize the return of study medication (used, partially used and unused vials that were retained by the study

center as permitted by site policy) to the 3rd party vendor (see Table 6.1). The completed Drug Accountability and Drug Return/Destruction Record(s) will be returned to the unblinded CRO manager. The Investigator's copy of the Drug Accountability and Drug Return/Destruction Record(s) must document accurately the return and/or onsite destruction of all study drug supplies and be maintained by the unblinded pharmacist or designee until the study is complete and the database is locked. Records will also include disposition dates and quantities destroyed onsite or returned to the designated facility.

9.4.6 Study Drug Administration and Timing of Dose for Each Subject

9.4.6.1 Description of Clinical Supplies

The clinical supply vendor will supply study drug to clinical sites. Ancillary supplies for dosing will be provided by the study site (i.e., infusion bags containing normal saline, infusion administration sets, syringes, needles, alcohol swabs, gauze pads, bandages and biohazard containers for safe storage of used needles and syringes).

9.4.6.2 Determination of Dose Volume

The volume of study drug to be administered will be determined by the electronic data capture (EDC) system and will be based on the subject's weight. The first dose will be 10 mg/kg, followed by 20 mg/kg q3W for the remaining 7 infusions. Weight will be measured at Screening and on each clinic visit during the double-blind Treatment Period. Dosing on Day 1 and at Weeks 3, 6 and 9 during the double-blind Treatment Period will be based on the weight measured on Day 1. Dosing at Weeks 12, 15, 18 and 21 during the double-blind Treatment Period will be based on the weight measured at Week 9.

9.4.6.3 Details Concerning Timing and Dose Administration

9.4.6.3.1 Preparation and Administration of TEPEZZA

TEPEZZA will be prepared by the site pharmacist (or designee in accordance with institutional policies and local regulations), who is not blinded to the identity of the study medication. Each vial of TEPEZZA will be reconstituted with 10 mL of sterile water for injection. The resulting solution will have a concentration of 47.6 mg/mL teprotumumab-trbw antibody. Reconstituted TEPEZZA solution will be further diluted in 0.9% (w/v) NaCl solution prior to administration by the site pharmacist or designee.

Doses up to 1800 mg will be administered in a total infusion volume of 100 mL and those above 1800 mg will be administered in a total infusion volume of 250 mL. To maintain a constant volume in the infusion bags, a volume equal to the volume of TEPEZZA to be placed into the infusion bag will first be removed from the infusion bag using a sterile syringe and needle. The appropriate volume of reconstituted drug product solution based on the subject`s dose and body weight will be withdrawn and the TEPEZZA drug product solution will be diluted with normal saline (0.9% NaCl) in the infusion bag. Dosing on Day 1 and at Weeks 3, 6 and 9 during the double-blind Treatment Period will be based on the weight measured on Day 1. Dosing at

Weeks 12, 15, 18 and 21 during the double-blind Treatment Period will be based on the weight measured at Week 9.

The infusion is to be administered at room temperature (20°C to 25°C [68°F to 77°F]).

The storage time of reconstituted TEPEZZA solution in the vial and the diluted solution in the infusion bag are outlined in the most recent version of the Investigator's Brochure and in the Investigational Pharmacy Manual provided to the site. If refrigerated prior to administration, allow the diluted solution to reach room temperature prior to infusion.

No incompatibilities between TEPEZZA and polyethylene, polyvinyl chloride, polyurethane or polyolefin bags and IV administration sets have been observed. Exposure of the solution to direct sunlight should be avoided.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Upon reconstitution, TEPEZZA is a colorless or slightly brown, clear to opalescent solution which is free of foreign particulate matter. Discard the solution if any particulate matter or discoloration are observed.

Do not freeze the reconstituted or diluted solution.

Partially used vials should not be re-used.

The first and second IV infusions on Day 1 and Week 3 will be administered over approximately 90 minutes (but not less than 80 minutes) for all subjects; subsequent infusions may be administered over a shorter time period (approximately 60 minutes, but not less than 50 minutes) in the absence of any infusion-associated events. All subjects will be monitored for AEs from the start of infusion through 60 minutes after infusion completion for the first 3 doses; the monitoring period for subsequent doses may be reduced to 30 minutes after infusion completion for subjects who do not experience infusion-associated events.

9.4.6.3.2 Dose Modifications, Interruptions and Delays

All dosing instructions are applicable for TEPEZZA and placebo administration.

Subjects will be monitored for immediate infusion-associated events (e.g., facial flushing, warmth, dyspnea, dizziness, hypertension, hypotension, pruritus) and delayed infusion-associated events (e.g., rash). If immediate infusion-associated events are noted, the infusion rate will be slowed or interrupted, symptomatic treatment (e.g., antipyretics, antihistamines, beta-agonists, oxygen, IV fluid) may be administered and vital signs (temperature, blood pressure, pulse and respiratory rate) will be monitored every 5 minutes until stable and then every 15 minutes for 2 additional determinations. The infusion may be restarted upon complete resolution of symptoms; however, study drug dosing will be permanently discontinued if the event is an anaphylactic reaction.

Following the appearance of either immediate or delayed infusion-associated events, subsequent doses may be pre-treated with diphenhydramine (1 to 1.25 mg/kg IV; maximum of 50 mg), ranitidine (50 mg IV), famotidine (0.5 mg/kg IV), dexamethasone (0.4 mg/kg IV; maximum of 20 mg) and/or acetaminophen (500 mg). All subsequent infusions will be administered over approximately 90 minutes (but not less than 80 minutes) with vital signs monitored every 15 minutes from the start of the infusion through 60 minutes after infusion completion.

If delayed infusion-associated events are noted, subjects may continue dosing at the Investigator's discretion; however, if a rash worsens following repeated dosing or other signs of serum sickness (e.g., delayed fever, myalgias, arthralgias) are present, study drug dosing will be permanently discontinued.

In general, the decision to continue dosing should take into consideration the potential benefit and risk to a subject.

In the event a subject's HbA1c level rises to >8% while in the study, the Investigator must determine the risk versus benefit for each subject to remain in the study.

Increase in blood glucose is a known AE observed in previous clinical trials with TEPEZZA and other IGF-1R antagonists and is known to respond to treatment. Fasting glucose levels (after at least an 8-hour fast) should be tested at Baseline. Hyperglycemia should be promptly investigated and managed. Subjects with recurrent hyperglycemia, defined as a fasting glucose level of ≥126 mg/dL (7.0 mmol/L) or higher, will require evaluation for diabetes mellitus (e.g., fasting glucose, glucose tolerance and HbA1c tests) and appropriate medical management at the discretion of the Investigator [American Diabetes Association, 2019b].

Since a referral for treatment of hyperglycemia may take some time, if the Investigator considers it appropriate to continue the subject in the study, the next scheduled infusion visit may be skipped to allow modified anti-diabetic treatment to show its activity and hyperglycemia to return to mild/moderate level before dosing. The subject would then be dosed at the next scheduled visit (i.e., 6 weeks after the previous infusion). Fasting blood glucose levels must return to mild/moderate severity before the next scheduled infusion. The above process of withholding a scheduled infusion will be permitted only twice during the study.

Any changes to the scheduled dosing interval (q3W) or adjustments in the infusion rate should be reported to the Sponsor/CRO.

9.4.7 Method of Assigning Subjects to Treatment Groups

A randomization schedule will be generated by an unblinded statistician not otherwise associated with the study prior to shipment of any study drug to the clinical sites. On Day 1 of the double-blind Treatment Period, once all Baseline procedures other than administration of drug have been completed, the authorized site personnel will use the EDC system to randomize the subject. The unblinded pharmacist or designee will then use the EDC system to obtain dosing information and dispense the appropriate study drug. Only the pharmacist at the site will have access to dosing information.

9.4.8 Blinding and Unblinding

The pharmacists or designees responsible for preparing the TEPEZZA or placebo solutions for IV administration will not be blinded to the identity of the study drug. Pharmacists/designees will provide study drug in infusion bags (fully diluted for administration) to study site personnel with appropriate blinded labels. The subject, Investigator and all other study site personnel will be blinded to the treatment being administered.

The study blind should be broken only if the safety of a subject is at risk and the treatment plan depends on which medication he or she received. Unless the subject is at immediate risk, the Investigator must make diligent attempts to contact the Sponsor or Sponsor's designee before unblinding the subject's data. If a subject's data are unblinded without prior knowledge of the Sponsor, the Investigator must notify the Sponsor as soon as possible and no later than the next business day. All circumstances surrounding the event must be clearly documented. Please refer to the instructions in the eCRF guidelines for unblinding a subject by the pharmacist.

The Sponsor or designee will unblind the identity of the study medication for an unexpected, drug-related SAE for submission to health authorities and IRB/IEC according to applicable regulatory requirements. However, the results will not be shared with other Sponsor representatives or staff at study sites. Details of subjects who are unblinded during the study will be included in the clinical study report.

Unblinding for independent pharmacological analysis of biological samples or SAE reporting will be performed according to procedures in place to ensure integrity of the data.

All investigative site staff and Sponsor personnel directly involved in this study will remain blinded from Screening through analysis of the follow-up data and all site close-out visits (i.e., through Week 48). Select Sponsor personnel/designees may be unblinded after the database lock following completion of all subjects in the double-blind Treatment Period.

9.4.9 Concomitant Therapy and Restricted Medications

Concomitant treatment with CellCept (mycophenolate mofetil) up to 3 g/day or Myfortic (mycophenolic acid) up to 2.14 g/day and low-dose prednisone (≤10 mg/day) or equivalent dosing of glucocorticoids is allowed during the study. Subjects taking CellCept or Myfortic have been doing so for ≥20 weeks prior to the Day 1 Visit and the dose must have been stable for ≥16 weeks prior to the Day 1 Visit. Prednisone must have been at a stable dose for ≥4 weeks prior to the Day 1 Visit.

Symptomatic treatment (e.g., antipyretics, antihistamines and/or corticosteroids, beta-agonists, oxygen, IV fluid) may be administered to subjects who experience immediate infusion-associated AEs. Following the appearance of either immediate or delayed infusion-associated events, subsequent dosing of study drug may be pre-treated with diphenhydramine (1 to 1.25 mg/kg IV; maximum of 50 mg), ranitidine (50 mg IV), famotidine (0.5 mg/kg IV), dexamethasone (0.4 mg/kg IV; maximum of 20 mg) and/or acetaminophen (500 mg).

Medication use that is restricted during the study is presented in Table 9.1.

Table 9.1 Restricted Medications

Medication	Restricted Time Period
Steroids for conditions other than dcSSc	4 weeks prior to Screening through study completion. Topical steroids for dermatological conditions and inhaled steroids are allowed during the study. Steroid therapy (parenteral/oral) for infusion-associated AEs is allowed (see Section 9.4.9 for details).
Oral or parenteral therapy approved for PAH	Receipt of >1 approved therapy during the study (use of PDE-5 inhibitors are allowed for erectile dysfunction and/or Raynaud's phenomenon/digital ulcers).
Rituximab (Rituxan® or MabThera®)	12 months prior to first infusion through study completion.
Use of any non-steroid immunosuppressive agent, cytotoxic or anti-fibrotic drug, other than mycophenolate mofetil, mycophenolic acid or an anti-malarial (e.g., hydroxychloroquine [Plaquenil®])	4 weeks prior to Screening through study completion.
Biologics or small molecules approved for rheumatoid arthritis, psoriatic arthritis and other rheumatic diseases	4 weeks prior to Screening through study completion.
Investigational agent	90 days or 5 half-lives, whichever is longer, prior to Screening through study completion.
Illicit drug/alcohol use	History of abuse within the past 2 years or abuse during study.

AE=adverse event; dcSSc=diffuse cutaneous systemic sclerosis; IV=intravenous; PAH=pulmonary arterial hypertension; PDE-5=phosphodiesterase-5

Subjects should avoid ototoxic medications and medications that may cause muscle spasm/cramps (such as diuretics or statins) during the study. If a muscle spasm occurs, evaluate for other causes of muscle spasm such as electrolyte abnormalities and dehydration.

All concomitant treatment (for dcSSc and other conditions) in the Treatment Period and the Follow-up Period must be documented in the eCRF.

9.4.10 Treatment Compliance

The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the Investigator.

All infusions of study medication will be administered at the clinic or infusion center under the supervision of clinic staff or nurses. Infusion volumes and start and stop times of the infusions will be recorded in the eCRF.

An inventory of the study medication supplies will be performed by the site or authorized study designee and recorded onto the Drug Accountability Log in the subject's source document records or equivalent.

9.5 Efficacy, Quality-of-Life, Pharmacokinetic and Safety Variables

The Schedule of Assessments is provided in Section 2.1.

9.5.1 Efficacy Variables

9.5.1.1 CCI

[redacted]

- [redacted]
- CCI [redacted]
- CCI
- [redacted]

[redacted]

9.5.1.1.1 CCI [redacted]

[redacted]

CCI [redacted]

9.5.1.1.2 CCI [redacted]

[redacted]

9.5.1.1.3 CCI [redacted] –

[redacted]

9.5.1.1.4 CCI [redacted]

[redacted]

9.5.1.1.5 CCI [redacted]

[redacted]

CCI [redacted]

9.5.1.2 CCI [redacted]

[redacted]

9.5.2 Quality-of-Life Assessments

9.5.2.1 CCI [redacted]

[redacted] CCI

[redacted]

CCI [redacted]

9.5.2.2 CCI [redacted]

[redacted]

9.5.3 Pharmacokinetic Measurements

Blood samples will be collected from all subjects to evaluate PK at the following time points: pre- and post-infusion on Day 1 and Weeks 3, 12 and 18; a single sample will be collected at Weeks 24 and 36.

Instructions for collection, processing, handling, storing and shipping of PK samples will be detailed in a laboratory manual that will be provided to each site prior to site initiation.

9.5.4 Immunogenicity Testing

Blood samples will be collected from all subjects for immunogenicity testing (anti-drug antibodies [ADA] and possibly neutralizing antibodies [NAb]) at the following time points: pre-infusion on Day 1 and Weeks 3, 12 and 18; a single sample will be collected at Weeks 24, 36 and 48.

If a sample is ADA positive after confirmatory and reactive titer testing, the sample will then be tested for NAb.

Instructions for collection, processing, handling, storing and shipping of immunogenicity samples will be detailed in a laboratory manual that will be provided to each site prior to site initiation.

9.5.5 Serum Biomarker Assessments

Blood samples will be collected from all subjects to analyze for biomarkers of the IGF-1 pathway at the following time points: pre-infusion on Day 1 and Weeks 3, 12 and 18; an additional single sample will be collected at Week 24.

Based on the results of the assays, other similar serum biomarkers may be assayed to further explore drug and disease mechanisms. Blood samples collected for analysis of biomarkers may be used for future testing should there be new information about the disease; however, the samples will be stored for no more than 5 years after the study is completed. All samples will be destroyed after all potential biomarkers have been tested or 5 years after the study is complete, whichever comes first.

Instructions for collection, processing, handling, storing and shipping of samples will be detailed in a laboratory manual that will be provided to each site prior to site initiation.

9.5.6 CCI

[redacted]

9.5.7 Safety Variables

Safety will be assessed by AE and concomitant medication use monitoring, physical examination, vital signs, clinical safety laboratory evaluations (complete blood count and chemistry [including HbA1c]), clinical inflammatory laboratory evaluations (CCI [redacted]), pregnancy testing (if applicable) and a screening ECG.

9.5.7.1 Adverse Events

9.5.7.1.1 Definitions

9.5.7.1.1.1 Adverse Event Definition

According to ICH, an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

Pre-existing conditions that worsen during a study are to be reported as AEs.

Unchanged, chronic conditions are **NOT** considered AEs and should not be recorded on the AE pages of the eCRF unless there is a clear exacerbation of a chronic condition.

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the study drug is being studied (i.e., dcSSc). It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. Events that are unequivocally due to disease progression should only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the study drug.

9.5.7.1.1.2 Serious Adverse Event Definition

A TEAE, Baseline event or suspected adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death. This includes any death that occurs during the conduct of a clinical study, including deaths that appear to be completely unrelated to the study drug (e.g., car accidents).
- Life-threatening adverse experience. An AE or suspected adverse reaction is considered life-threatening if, in the view of either the Investigator or the Sponsor, its occurrence places the subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.
- Persistent or significant disability or incapacity.
- Inpatient hospitalization or prolongation of an existing hospitalization.
- Congenital anomaly or birth defect.
- Other medically important event that, according to appropriate medical judgment, may require medical or surgical intervention to prevent one of the outcomes listed above.

Surgical procedures or other therapeutic interventions themselves are not AEs, but the condition for which the surgery/intervention is required is an AE and should be documented accordingly.

Elective surgeries that require hospitalization and treatment received at an emergency room or similar facility will not be considered as SAEs unless one of the definitions of an SAE listed above is met.

In addition, hospitalizations for planned procedures are not considered an AE, unless they are prolonged hospitalizations and emergency room visits <24 hours in duration are not considered hospitalizations.

9.5.7.1.1.3 Non-serious Adverse Event Definition

A non-serious AE includes any AE that is not described in the previous SAE category.

9.5.7.1.1.4 Unexpected Adverse Event Definition

An AE or suspected adverse reaction is considered unexpected if it is not listed in the Reference Safety Information section of the Investigator's Brochure or is not listed with the specificity or

severity that has been observed. Unexpected, as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Reference Safety Information as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

9.5.7.1.1.5 Adverse Events of Special Interest

Based on previous clinical experience with TEPEZZA, the following AESIs are identified for this study (See Section 7.1.3.4.4.4 for further information):

- Hyperglycemia
- Hearing impairment
- Infusion reaction
- New onset or exacerbation of IBD

9.5.7.1.2 Documentation of Adverse Events

Any AEs that occur after signing the ICF and prior to dosing on Day 1 will be considered Baseline signs/symptoms. The TEAE reporting period begins with administration of the first dose of study medication on Day 1 and continues until 3 weeks (21 days) after last dose of study drug. The follow-up AE reporting period begins 21 days after the last dose of study drug through completion of the Follow-up Period (Week 48 or premature withdrawal). All Baseline signs/symptoms, TEAEs and AEs during the Follow-up Period must be recorded in the source documents and on the subject's eCRF. All AEs and SAEs that occur from the signing of informed consent through Week 48 will be recorded.

If the Investigator observes an SAE after study completion that he/she believes was possibly caused by the study medication, the Investigator will report this SAE using the procedures described in Section 9.5.7.1.5.

Detailed information regarding all SAEs must also be recorded on the Serious Adverse Event Reporting Form. Whenever possible, the Investigator should group together into a single term the signs and symptoms that constitute a single diagnosis. For example, cough, rhinitis and sneezing might be grouped together as "upper respiratory infection" if the Investigator is confident of the diagnosis.

9.5.7.1.3 Intensity of Adverse Events

All clinical AEs encountered during the study will be reported on the AE form of the eCRF. Intensity of AEs will be graded on a 5-point scale (mild, moderate, severe, life-threatening, death) and reported in detail on the eCRF.

Intensity	Definition	Corresponding NCI-CTCAE Grade
Mild	discomfort noticed but no disruption of normal daily activity	1
Moderate	discomfort sufficient to reduce or affect daily activity	2
Severe	inability to work or perform normal daily activity	3
Life-threatening	represents an immediate threat to life	4
Fatal	results in death	5

NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events

9.5.7.1.4 Relationship to Study Drug

The relationship of the study drug to each AE will be determined by the Investigator and the Sponsor based on the following definitions:

- No reasonable causal relationship (not related): There is no plausible temporal relationship or there is another explanation that unequivocally provides a more plausible explanation for the event.
- Yes, reasonable causal relationship (possibly related): There is evidence in favor of a causal relationship (i.e., there is a plausible time course) and at least one of the following criteria apply:
    - There is a reasonable pharmacological relationship (or known class effect).
    - There is no other more plausible explanation.
    - There is a positive de-challenge (without active treatment of the event).
    - There is a positive re-challenge.
    - There is a distinguishable dose effect.

Within the reporting requirement under 21 CFR 312.32I(1)(i), the FDA provides the following examples of types of evidence that would suggest a causal relationship between the drug and the AE.

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome).
- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture).

- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

9.5.7.1.5 Reporting and Documenting Serious Adverse Events

All SAEs beginning with the time of signing of the ICF and continuing through Week 48 (end-of-study visit) must be reported. The following steps will be taken to report promptly and document accurately any SAE, whether or not it appears to be related to the study medication:

1. Report the SAE to the Sponsor by entering the information into the eCRF **within 24 hours** after becoming aware that a subject has experienced an SAE. If unable to access the eCRF, the event must be reported by submitting the completed SAE form by email to clinicalsafety@horizontherapeutics.com, fax or telephone **within 24 hours** after becoming aware that a subject has experienced an SAE (see Appendix 17.1 for contact information).

2. Perform appropriate diagnostic tests and therapeutic measures and submit all follow-up substantiating data, such as diagnostic test reports, hospital discharge summaries and autopsy report to the Sponsor's representative.

3. Respond in a timely manner to any queries from Sponsor regarding the SAE.

4. Conduct appropriate consultation and follow-up evaluation until the SAE is resolved, stabilized or otherwise explained by the Investigator.

5. Review each SAE report and evaluate the relationship of the SAE to study treatment. The Sponsor will determine whether the SAE is unexpected in nature.

6. The Investigator must report all AEs or SAEs that meet the criteria for Unanticipated Problems Involving Risks to Human Subjects or Others to the IRB/IEC.

9.5.7.1.6 Follow-up of Adverse Events

Any ongoing study drug-related AE present at the time of study termination, including a clinically significant laboratory test abnormality, will be followed until resolved or until the event stabilizes and the overall clinical outcome has been ascertained.

In the event of unexplained, treatment-emergent, clinically significant abnormal laboratory test results or clinically significant changes in laboratory test results, the tests should be repeated immediately and followed until the values have returned to within the reference range or to Baseline for that subject.

9.5.7.1.7 Medication Errors

A medication error is any unintended failure in the drug treatment process, such as mistakes in the prescribing, dispensing, storing, preparation or administration of a medicine that leads to, or has the potential to lead to, harm to the patient.

All cases of medication errors, which include overdose, will be documented on the eCRF in order to capture this important safety information consistently in the database. AEs associated with a medication error, such as an overdose, or an SAE of overdose are to be reported according to the procedures outlined in Sections 9.5.7.1.2 and 9.5.7.1.5, respectively.

An overdose is defined as a known deliberate or accidental administration of investigational drug to a subject. For this study, any dose of TEPEZZA that is greater than 27 mg/kg q3W over the dose that has been assigned will be considered an overdose.

In the event of drug overdose, the subject is to be treated with symptomatic and supportive care, as required.

9.5.7.1.8 Review of Adverse Events and Emerging New Safety Information

The Sponsor will perform an ongoing review of all AEs and all other emerging new information relevant to the safety of the drug, including periodic review and analyses of their entire safety database.

9.5.7.1.9 Reporting of Investigational New Drug Safety Reports

The Sponsor will notify the US FDA and all Investigators of any new serious risks associated with the drug.

9.5.7.1.10 Development Safety Update Reports

The Sponsor will prepare and submit annual safety reports to the US FDA.

9.5.7.2 Pregnancy Reporting

Pregnancy testing will be performed for women of childbearing potential (including those with an onset of menopause <2 years prior to Screening, non-therapy-induced amenorrhea for <12 months prior to Screening or not surgically sterile [absence of ovaries and/or uterus]) at Screening, prior to dosing on Day 1 and Weeks 3, 6, 9, 12, 15, 18 and 21 and at Weeks 24, 28, 36 and 48. If a subject discontinues study participation during the Follow-up Period prior to the Week 48 Visit, a pregnancy test will be performed at the premature withdrawal visit. A serum pregnancy test will be performed at Screening and at Week 48; urine pregnancy tests will be performed at all other visits, as applicable. Serum pregnancy tests will be analyzed at a central study laboratory and the urine pregnancy tests will be performed locally.

Women of childbearing potential will be contacted via phone or email at Week 32 and Week 42 (or 6 months after last infusion if withdrawn early from treatment) to inquire if they have missed a menstrual cycle and will have a serum pregnancy test performed, if required. The serum pregnancy test may be performed by a local laboratory with the result provided to the Investigator or a subject may return to the clinic for testing by the central laboratory.

If a female subject becomes pregnant during the Treatment Period, she should immediately notify the Investigator and TEPEZZA dosing should be permanently discontinued.

Pregnancies occurring up to 180 days after the last dose must also be reported to the Investigator.

The Investigator should report pregnancies to the Sponsor within 24 hours by submitting the completed pregnancy report form by email to clinicalsafety@horizontherapeutics.com, fax or telephone within 24 hours after becoming aware that the subject has become pregnant (see Appendix 17.1 for contact information). The Investigator should counsel the subject and discuss the possible risks of continuing the pregnancy. If pregnancy continues and the subject signs the pregnancy consent form, monitoring should also continue to the conclusion of the pregnancy.

Subjects should be instructed to continue contraception for 180 days after their last dose of study drug.

9.5.7.3 Medical History

Medical history, including dcSSc history and treatment and substance use history, will be conducted at Screening and on Day 1. The subject must have a diagnosis of dcSSc (with onset ≤60 months since the first dcSSc manifestations, other than Raynaud's phenomenon, at Screening), have skin thickening on the forearm and have an mRSS unit ≥10 and ≤45 at Screening.

9.5.7.4 Vital Signs, Weight and Height

Vital signs (heart rate, blood pressure, respiratory rate, temperature) will be measured at all clinic visits. Vital signs will be measured pre- and post-infusion on Day 1 and Week 3 and pre-infusion on all other dosing days. In addition, if immediate infusion-associated events are noted during the infusion, vital signs will be monitored every 5 minutes until stable and then every 15 minutes for 2 additional determinations. Also, vital signs will be monitored every 15 minutes from the start of the infusion through 60 minutes after infusion completion for any subsequent infusions after the previous occurrence of immediate or delayed infusion-associated events.

Blood pressure and pulse measurements will be obtained with the subject's arm unconstrained by clothing or other material and while the subject is sitting up. When possible, the same arm will be used for measurements in all study visits.

Weight will be measured at Screening and on Day 1, Weeks 3, 6, 9, 12, 15, 18, 21, 24, 36 and 48. To limit the potential for variability in weight collection, the subject should wear lightweight

clothing and no shoes during weighing. Dosing on Day 1 and at Weeks 3, 6 and 9 during the double-blind Treatment Period will be based on the weight measured on Day 1. Dosing at Weeks 12, 15, 18 and 21 during the double-blind Treatment Period will be based on the weight measured at Week 9.

Height will be measured at Screening only.

9.5.7.5 Physical Examination

A physical examination will be performed at Screening, Day 1 and Weeks 3, 12, 24 and 48.

9.5.7.6 Electrocardiograms

A 12-lead ECG will be performed at Screening. Additional ECGs will be performed, as needed. The results will be recorded as normal or abnormal on the eCRF and all abnormal results will be evaluated by the Investigator as clinically significant or not clinically significant. A copy of the ECG tracing will remain with the source documents.

9.5.7.7 Clinical Laboratory Safety Tests

A central study laboratory will be used for all protocol-specified clinical laboratory parameters, with the exception of urine pregnancy tests that will be performed locally (see Section 9.5.7.2 for details). Details concerning the collection of these samples are presented in Table 9.2.

Table 9.2 Schedule of Clinical Laboratory Safety Tests

		Treatment Period									Follow-up Period				
Visit	**SCR**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**EOT 9/PW**	**10**	**11**	**12**	**13**	**EOS 14/PW**
Analysis Panel		**BL**	**W3**	**W6**	**W9**	**W12 M3**	**W15**	**W18**	**W21**	**W24 M6**	**W28 M7**	**W32 M8**	**W36 M9**	**W42**	**W48 M12**
Chemistry (including glucose) [1]	X [2]	X	X	X	X	X	X	X	X	X	X		X		X
CCI		X					X			X					X
CCI		X					X			X					X
Hematology [3]	X	X	X	X	X	X	X	X	X	X	X		X		X
Coagulation [4]	X														
HbA1c [5]	X					X				X					
Urinalysis	X	X	X	X	X	X	X	X	X	X	X		X		X
Serum pregnancy [6]	X											X [7]		X [7]	X
Urine pregnancy [6]		X	X	X	X	X	X	X	X	X	X		X		X

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BL=Baseline; EOS=End of Study; EOT=End of Treatment; CCI, HbA1c=glycated hemoglobin; CCI, M=Month; PW=premature withdrawal; SCR=Screening; ULN=upper limit of normal; W=Week

1. Includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, total bilirubin, ALT, AST, gamma glutamyl transferase, alkaline phosphatase, lactate dehydrogenase, glucose-random, calcium, phosphate, magnesium.
2. ALT/AST must be ≤2.5×ULN and estimated glomerular filtration rate must be ≥30 mL/min/1.73^2 at Screening.
3. Includes hemoglobin; hematocrit; mean cell hemoglobin; mean cell hemoglobin concentration; mean cell volume; mean platelet volume; red blood cell count; white blood cell count; absolute and percent neutrophils, total lymphocytes, monocytes, eosinophils and basophils; large unstained cells; platelet count.
4. CCI
5. HbA1c must be ≤8.0% for randomization. If the HbA1c is elevated and considered clinically significant at any time point after Screening, it will be repeated approximately every 90 days until it returns to normal or Baseline value.
6. Perform for female subjects of childbearing potential (including those with an onset of menopause <2 years prior to Screening, non-therapy-induced amenorrhea for <12 months prior to Screening or not surgically sterile [absence of ovaries and/or uterus]).
7. Perform for female subjects of childbearing potential who report having missed a menstrual cycle at the Week 32 or Week 42 contact (or 6 months after the last infusion if withdrawn early from treatment). The test may be performed by a local laboratory with the result provided to the Investigator or a subject may return to the clinic for testing by the central laboratory.

Instructions for the collection, handling and analysis of clinical laboratory samples will be provided to the site prior to study site initiation.

9.5.8 Appropriateness of Measurements

All safety and efficacy variables, as well as the methods to measure them, are standard variables/ methods in clinical studies and/ or clinical practice. They are widely used and generally recognized as reliable, accurate and relevant.

CCI [redacted]

9.5.9 Study Procedures

Subjects who provide informed consent and who meet all the entry criteria for participation in this study will be randomized to treatment.

9.5.9.1 Screening

Due to the large number of Screening assessments, the Screening Visit may be completed in more than 1 day. During the Screening Visit, potential study subjects will be informed fully regarding the nature of the study and possible AEs and will receive a copy of the ICF for review. Potential study subjects must read the ICF and sign the document after the Investigator has answered all questions to the study candidate's satisfaction. Further procedures can begin only after the ICF has been signed. The original signed ICF will be retained by the Investigator and a copy will be given to the study subject.

Study candidates will be evaluated for study entry according to the stated inclusion and exclusion criteria (Section 9.3). The Investigator will evaluate the results of all examinations, including clinical laboratory tests and will determine each candidate's suitability for the study. The Investigator must review the results of all Screening tests before determining that a candidate is eligible for study drug treatment. The serum pregnancy test performed at Screening on all female candidates of childbearing potential must be negative for those subjects to be eligible for initiation of treatment. All Screening procedures must be completed within 28 days prior to Day 1 (i.e., the first day of administration of study drug). The following procedures will be performed during Screening to establish each candidate's general health and eligibility for enrollment into the study:

- Obtain signed, written informed consent and permission to use Protected Health Information (in accordance with the Health Insurance Portability and Accountability Act). Refusal to provide this permission excludes an individual from eligibility for study participation. Record date and time informed consent was given and who conducted the process on the appropriate source documentation.
- Determine study eligibility through review of the inclusion/exclusion criteria (see Section 9.3)
- Obtain demographics.
- Obtain medical history, including dcSSc history and treatment, as well as substance use history.
- Inquire about prior medications (see Table 9.1 for restrictions regarding medications).
- Query subjects regarding signs and symptoms.

- Measure weight and height.
- Perform physical examination.
- Measure vital signs (blood pressure, heart rate, respiratory rate and temperature). These measurements will be performed according to standardized instructions.
- Perform 12-lead ECG.
- Collect blood samples for hematology, coagulation and chemistry (including glucose and HbA1c) analysis for all subjects (see Section 9.5.7.7 for details concerning test results and study participation) and pregnancy testing for females of childbearing potential.
- Collect urine sample for urinalysis.
- CCI [redacted]
- Enter Screening Visit data in the EDC system.

9.5.9.2 Treatment Period

9.5.9.2.1 Day 1/Baseline

On Day 1, subjects will return to the clinic for Baseline assessments, randomization and the first dose of study drug.

- Perform review of inclusion/exclusion criteria.
- Review medical history.
- Query subjects regarding signs and symptoms and concomitant medications within previous 2 weeks.
- Measure pre-infusion weight.
- Perform pre-infusion physical examination.
- Collect pre-infusion blood samples for hematology and chemistry (including CCI [redacted] and glucose, but not HbA1c) analysis (see Section 9.5.7.7 for details concerning test results and study participation).
- Collect pre-infusion blood samples for ADA/NAb immunogenicity testing.
- CCI [redacted]

- Collect pre-infusion urine sample for urinalysis and also for pregnancy testing for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug.
- CCI [redacted]
- [redacted]
- [redacted]
- Enter visit data in the EDC system in order for unblinded personnel to obtain randomization assignment and study drug dosing information.
- Measure vital signs pre- and post-infusion. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see Section 9.5.7.4 for details).
- Collect pre- and post-infusion blood samples for PK analyses.
- Administer the first dose of study drug and monitor subject for 60 minutes after the end of the infusion.

Subjects will be discharged from the study center after all of the Day 1 procedures have been completed and will be contacted the following day to inquire about AEs and concomitant medication use.

9.5.9.2.2 Week 3

- Perform pre-infusion physical examination, including measuring of weight.
- Query subjects regarding AEs and concomitant medications.
- Collect pre-infusion blood samples for hematology and chemistry (including glucose, but not HbA1c) analysis (see Section 9.5.7.7 for details concerning test results and study participation).
- Collect pre-infusion blood samples for ADA/NAb immunogenicity testing.
- CCI [redacted]
- [redacted]
- Collect pre-infusion urine sample for urinalysis and also for pregnancy testing for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug.

- Measure vital signs pre- and post-infusion. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see Section 9.5.7.4 for details).
- Collect pre- and post-infusion blood samples for PK analyses.
- Complete Step 1 events.
- Enter visit data in the EDC system in order for unblinded personnel to obtain study drug dosing information.
- Administer study drug and monitor subject for 60 minutes after the end of the infusion.

Subjects will be discharged from the study center after all of the Week 3 procedures have been completed and will be contacted the following day to inquire about AEs and concomitant medication use.

9.5.9.2.3 Week 6

- Measure weight.
- Query subjects regarding AEs and concomitant medications.
- Collect pre-infusion blood samples for hematology and chemistry analysis (see Section 9.5.7.7 for details concerning test results and study participation).
- Collect pre-infusion urine sample for urinalysis and also for pregnancy testing for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug.
- Measure pre-infusion vital signs. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see Section 9.5.7.4 for details).
- CCI [redacted]
- Enter visit data in the EDC system in order for unblinded personnel to obtain study drug dosing information.
- Administer study drug and monitor subject for 60 minutes after the end of the infusion.

Subjects will be discharged from the study center after all of the Week 6 procedures have been completed and instructed to return for a clinic visit at Week 9.

9.5.9.2.4 Week 9

- Measure weight.
- Query subjects regarding AEs and concomitant medications.
- Collect pre-infusion blood samples for hematology and chemistry analysis (see Section 9.5.7.7 for details concerning test results and study participation).
- Collect pre-infusion urine sample for urinalysis and also for pregnancy testing for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug.
- Measure pre-infusion vital signs. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see Section 9.5.7.4 for details).
- Complete Step 1 events.
- Enter visit data in the EDC system in order for unblinded personnel to obtain study drug dosing information.
- Administer study drug and monitor subject for at least 30 minutes after the end of the infusion.

Subjects will be discharged from the study center after all of the Week 9 procedures have been completed and instructed to return for a clinic visit at Week 12.

9.5.9.2.5 Week 12

- Measure weight.
- Perform pre-infusion physical examination.
- Query subjects regarding AEs and concomitant medications.
- Collect pre-infusion blood samples for hematology and chemistry (including glucose and HbA1c) analysis (see Section 9.5.7.7 for details concerning test results and study participation).
- Collect pre-infusion blood samples for ADA/NAb immunogenicity testing.
- CCI [redacted]
- Collect pre-infusion urine sample for urinalysis and also for pregnancy testing for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug.

- Measure pre-infusion vital signs. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see Section 9.5.7.4 for details).
- Collect pre- and post-infusion blood samples for PK analyses.
- CCI [redacted]
- Enter visit data in the EDC system in order for unblinded personnel to obtain study drug dosing information.
- Administer study drug and monitor subject for at least 30 minutes after the end of the infusion.

Subjects will be discharged from the study center after all of the Week 12 procedures have been completed and will be instructed to return to the clinic at Week 15.

9.5.9.2.6 Week 15

- Measure weight.
- Query subjects regarding AEs and concomitant medications.
- Collect blood samples for hematology and chemistry (including glucose, CCI [redacted]) analysis (see Section 9.5.7.7 for details concerning test results and study participation).
- Collect pre-infusion urine sample for urinalysis and also for pregnancy testing for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug.
- Measure vital signs.
- Complete Step 1 events.
- Enter visit data in the EDC system in order for unblinded personnel to obtain study drug dosing information.
- Administer study drug and monitor subject for at least 30 minutes after the end of the infusion.

Subjects will be discharged from the study center after all of the Week 15 procedures have been completed and will be instructed to return to the clinic at Week 18.

9.5.9.2.7 Week 18

- Measure weight.
- Query subjects regarding AEs and concomitant medications.
- Collect pre-infusion blood samples for hematology and chemistry analysis (see Section 9.5.7.7 for details concerning test results and study participation).
- Collect pre-infusion urine sample for urinalysis and also for pregnancy testing for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug.
- Measure pre-infusion vital signs. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see Section 9.5.7.4 for details).
- Collect pre-infusion blood samples for ADA/NAb immunogenicity testing.
- CCI [redacted]
- Collect pre- and post-infusion blood samples for PK analyses.
- Complete Step 1 events.
- Enter visit data in the EDC system in order for unblinded personnel to obtain study drug dosing information.
- Administer study drug and monitor subject for at least 30 minutes after the end of the infusion.

Subjects will be discharged from the study center after all of the Week 18 procedures have been completed and instructed to return for a clinic visit at Week 21.

9.5.9.2.8 Week 21

- Measure weight.
- Query subjects regarding AEs and concomitant medications.
- Collect pre-infusion blood samples for hematology and chemistry analysis (see Section 9.5.7.7 for details concerning test results and study participation).
- Collect pre-infusion urine sample for urinalysis and also for pregnancy testing for females of childbearing potential; the pregnancy test must be negative for the subject to receive study drug.

- Measure pre-infusion vital signs. Additional vital sign monitoring may be performed in the event of infusion-associated AEs (see Section 9.5.7.4 for details).
- Complete Step 1 events.
- Enter visit data in the EDC system in order for unblinded personnel to obtain study drug dosing information.
- Administer study drug and monitor subject for at least 30 minutes after the end of the infusion.

Subjects will be discharged from the study center after all of the Week 21 procedures have been completed and instructed to return for a clinic visit at Week 24.

9.5.9.2.9 Week 24 (End of Treatment)

Week 24 is the final visit of the Treatment Period. Study drug is not administered.

- Perform physical examination, including measuring of weight.
- Query subjects regarding AEs and concomitant medications.
- Collect blood samples for hematology and chemistry (including glucose, CCI and HbA1c) analysis.
- Collect blood samples for ADA/NAb immunogenicity testing.
- CCI
- Collect blood samples for PK analyses.
- CCI
- Collect urine sample for urinalysis and also for pregnancy testing for females of childbearing potential.
- Measure vital signs.
- CCI
- Enter visit data in the EDC system.

Subjects will be discharged from the study center after all of the Week 24 procedures have been completed and will enter the Follow-up Period. Subjects will be instructed to return for a clinic visit at Week 28.

If a subject prematurely discontinues from the study during the Treatment Period, he/she will be instructed to return for a clinic visit and undergo the Week 24 assessments.

9.5.9.3 Follow-up Period

9.5.9.3.1 Week 28

- Query subjects regarding AEs and concomitant medications.
- Collect blood samples for hematology and chemistry (including glucose but not HbA1c) analysis.
- Collect urine sample for urinalysis and also for pregnancy testing for females of childbearing potential.
- Measure vital signs.
- Enter visit data in the EDC system.

Subjects will be discharged from the study center after all of the Week 28 procedures have been completed. Subjects will be contacted via phone or email at Week 32.

9.5.9.3.2 Week 32

All subjects will be contacted via phone or email at Week 32 to inquire about signs and symptoms, concomitant medications and if women of childbearing potential have missed a menstrual cycle. If a menstrual cycle has been missed, the subject will have a serum pregnancy test performed, if required.

Subjects will be instructed to return to the clinic at Week 36.

9.5.9.3.3 Week 36

- Measure weight.
- Query subjects regarding AEs and concomitant medications.
- Collect blood samples for hematology and chemistry (including glucose but not HbA1c) analysis.
- Collect blood samples for ADA/NAb immunogenicity testing.

- Collect urine sample for urinalysis and also for pregnancy testing for females of childbearing potential.
- Measure vital signs.
- CCI [redacted]
- [redacted]
- Enter visit data in the EDC system.

Subjects will be discharged from the study center after all of the Week 36 procedures have been completed. Subjects will be contacted via phone or email at Week 42.

9.5.9.3.4 Week 42

All subjects will be contacted via phone or email at Week 42 to inquire about AEs, concomitant medications and if women of childbearing potential have missed a menstrual cycle. If a menstrual cycle has been missed, the subject will have a serum pregnancy test performed, if required.

Subjects will be instructed to return to the clinic at Week 48.

9.5.9.3.5 Week 48 (End of Study)

- Perform physical examination, including measuring of weight.
- Query subjects regarding AEs and concomitant medications.
- Collect blood samples for hematology and chemistry (including glucose, CCI [redacted]) analysis (see Section 9.5.7.7 for details concerning test results and study participation) and pregnancy testing for females of childbearing potential.
- Collect blood samples for ADA/NAb immunogenicity testing.
- Collect urine sample for urinalysis.
- Measure vital signs.
- CCI [redacted]
- [redacted]
- Enter visit data in the EDC system.

Subjects will be discharged from the study after all of the Week 48 procedures have been completed.

If a subject prematurely discontinues from the study during the Follow-up Period, he/she will be instructed to return for a clinic visit and undergo the Week 48 assessments.

9.6 Statistical Methods and Determination of Sample Size

9.6.1 Endpoints

9.6.1.1 Primary Endpoint

The proportion of subjects who experience a TEAE (as defined by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI-CTCAE]) through Week 24 in subjects with dcSSc.

9.6.1.2 Efficacy Endpoints

CCI

CCI

9.6.1.3 Quality-of-Life Endpoints

CCI

9.6.1.4 Pharmacokinetic and Anti-drug Antibody Endpoints

1. PK of teprotumumab.
2. The incidence of ADA and titer levels.

9.6.1.5 Safety and Tolerability Endpoints

1. Incidence of TEAEs and AESIs (hyperglycemia, hearing impairment, infusion reaction, new onset or exacerbation of IBD).
2. Vital signs: change from Baseline at each scheduled visit.
3. Clinical safety laboratory tests: change from Baseline at each scheduled visit.

9.6.2 Analysis Sets

The following analysis sets will be defined for this study:

- CCI [redacted]
- [redacted]
- [redacted]
- [redacted]

9.6.3 Safety, Efficacy and Quality-of-Life Endpoint Analyses

9.6.3.1 Primary Endpoint Analysis

The primary analysis will be conducted using the safety analysis set. The number and percentage of subjects who experience a TEAE will be summarized by treatment group.

9.6.3.2 Efficacy Endpoint Analyses

The efficacy analysis will be conducted using the full analysis set, with select endpoints also summarized for the per protocol analysis set.

CCI [redacted]

[redacted]

CCI

A subject with predicted probability of at least 0.6 will be considered improved. The proportion of subjects who have improved based on CCI values at Week 24 will be provided with an exact 95% confidence interval around the difference in the proportion between the 2 groups (TEPEZZA minus placebo). In addition, the descriptive statistics (n, mean, standard deviation, median, maximum and minimum) of the predicted probabilities will also be provided by treatment group at each scheduled assessment visit. Descriptive summaries of the individual components of CCI for observed and change from Baseline will also be provided.

Using CCI data, the number and percentage of subjects with flares will be summarized by treatment group. Flare is defined as any (one or more) of the following:

1. Worsening of skin disease, defined by an increase of CCI by >3 units *and* new symptoms such as pruritus, redness, allodynia or new areas of skin involvement reported by the subject.
2. Worsening of CCI y ≥0.500 units or CCI by ≥3 (0-10 scale).
3. Worsening of lung function, defined as a decline in CCI change) *and* symptoms of increased dyspnea.
4. New organ involvement such as CCI

Descriptive summaries for observed and change from Baseline values in IGF-1R pathway, inflammatory and fibrotic biomarkers will be summarized by treatment group at each scheduled visit.

Descriptive summaries for observed and change from Baseline values in transcriptomics associated with IGF-1R inhibition will be summarized by treatment group at each scheduled visit.

9.6.3.3 Quality-of-Life Analyses

CCI

CCI [redacted]

[redacted]

9.6.3.4 Safety and Tolerability Analyses

Safety analyses will be performed using the safety analysis set.

The number and percentage of subjects in each treatment group reporting at least one occurrence of a TEAE, a TEAE of grade 3 or higher, a serious TEAE, a TEAE related to study drug, an AESI and a TEAE resulting in discontinuation of treatment will be summarized by treatment group. TEAEs and SAEs will additionally be summarized by system organ class and preferred term.

Concomitant medications will be summarized by Anatomical Therapeutic Chemical Level 4 term and preferred term using counts and percentage of subjects for each treatment group.

Descriptive summaries of observed and change from Baseline values will be presented for each vital sign parameter by treatment group and visit. A shift table for weight gain and weight loss as well as hypertension by NCI-CTCAE grade and visit will be presented by treatment group.

Safety laboratory parameters (chemistry [including HbA1c], hematology, inflammatory evaluations [CCI [redacted]] and urinalysis)) and change from Baseline (if applicable) will be summarized by visit and treatment group using descriptive statistics. The laboratory values will be categorized as low, normal and high based on normal ranges. Shift tables using categories of low, normal and high from Baseline to each visit will be summarized by treatment group. Additionally, a shift table for glucose by NCI-CTCAE grade and visit will be summarized by treatment group. Summaries will be provided separately for hyperglycemia.

9.6.4 Pharmacokinetic and Anti-drug Antibody Analyses

PK data will be analyzed using the PK analysis set. Serum concentrations of teprotumumab will be summarized descriptively, including arithmetic means, standard deviations, geometric means, coefficients of variation, medians and ranges, by time point. The relationship between clinical endpoints and the serum concentrations of teprotumumab may be explored in a descriptive manner.

Immunogenicity data will be analyzed using the safety analysis set. Immunogenicity endpoints include the incidence of ADA and NAb (of positive ADA samples) by visit and treatment group. Overall positive ADA result for a subject will be defined as at least 1 positive ADA measurement at any assayed time point. Cumulative negative result will be defined as negative ADA results at all time points for a subject.

9.6.5 Interim Analyses

No interim analyses are planned.

The primary analysis time point for this study is Week 24. Therefore, the database will be locked after all subjects complete Week 24 assessments or withdraw from study prematurely prior to Week 24 for primary analyses. Select Sponsor personnel/designees may be unblinded after the database lock for the Week 24 analyses.

9.6.6 Multiple Comparisons

While p-values will be calculated for many endpoints, decision-making will not be based on formal testing procedures. Nominal p-values, whether or not they are less than 0.05, will be considered in conjunction with estimates of magnitude of treatment effect and consistency of direction in planning future studies. As such, no adjustment for multiple comparisons will be made.

9.6.7 Sample Size and Power Considerations

For a TEAE that occurs in 20% of TEPEZZA-treated subjects in the dcSSc population, a sample size of 15 subjects provides approximately 95% probability that the TEAE will be observed at least once.

This study is not powered to detect a statistically significant difference in the proportion of CCI responders unless the difference is very large. For example, if 10% of all placebo subjects were responders and 75% of all TEPEZZA subjects were responders, this study would have 87% power to detect that difference (α=0.05, 2-tailed).

9.7 Changes in the Conduct of the Study

If any modifications in the experimental design, dosages, parameters, subject selection or any other sections of the protocol are indicated or required, the Investigator will consult with the Sponsor before any such changes are instituted. Modifications will be accomplished through formal amendments to this protocol by the Sponsor and approved from the appropriate IRB/IEC.

The Sponsor's Medical Monitor will consider any requests for exceptions to protocol entry criteria on a case-by-case basis. The Investigator or other health professional in attendance must contact the Sponsor as soon as possible. All protocol deviations and the reasons for such deviations **must** be documented into the electronic database. In the event of a protocol deviation, the Investigator and Sponsor's Medical Monitor will determine whether the subject should continue to participate in the study.

The Sponsor has a legal responsibility to report fully to regulatory authorities all results of administration of investigational drugs to humans. No investigational procedures other than those described in this protocol will be undertaken on the enrolled subjects without the agreement of the IRB/IEC and Sponsor.

10 SOURCE DOCUMENTATION AND INVESTIGATOR FILES

The Investigator must maintain adequate and accurate records to document fully the conduct of the study and to ensure that study data can be subsequently verified. These documents should be classified in 2 separate categories: (1) Investigator study file and (2) subject clinical source documents that corroborate data collected in the eCRFs. Subject clinical source documents would include, as applicable, original hospital/clinic subject records; physicians' and nurses' notes; appointment book; original laboratory, ECG, electroencephalogram, radiology, pathology and special assessment reports; dispensing records; signed ICFs; consultant letters; and subject Screening and enrollment logs.

In order to comply with regulatory requirements, it is the policy of the Sponsor that, at a minimum, the following be documented in source documents at the study center:

- Medical history/physical condition and diagnosis of the subject before involvement in the study sufficient to verify that the subject meets protocol entry criteria.
- Study number, assigned subject number and verification that written informed consent was obtained (each recorded in dated and signed progress notes).
- Progress notes for each subject visit (each dated and signed).
- Records of each study visit including each study assessment and the identity of the staff member performing the assessment.
- Study drug dispensing and return.
- Review by the Investigator or qualified personnel on the 1572 of laboratory test results.
- AEs (start and stop date, description, action taken and resolution).
- Investigator or Sub-Investigator's signed assessment of each AE.
- Concomitant medications (start and stop dates, reason for use).
- Condition of subject upon completion of, or premature withdrawal from, the study.

11 CASE REPORT FORMS

An eCRF is required for every subject who signs the ICF. Required data must be entered on the eCRF within the required time period, which will be outlined within each site agreement, after data collection or the availability of test results. Separate source records are required to support all eCRF entries.

The Investigator will ensure that the eCRFs are accurate, complete, legible and timely and will review and provide an electronic signature for the eCRF according to the standard operating procedure of the Data Management System. Final eCRFs will be provided to the Investigator and Sponsor by Data Management.

12 STUDY MONITORING

The Investigator will ensure that the study is conducted in accordance with all regulations governing the protection of human subjects. The Investigator will adhere to the basic principles of GCP as outlined in Title 21 of the CFR, Part 312, Subpart D, "Responsibilities of Sponsors and Investigators"; 21 CFR, Part 50, "Protection of Human Subjects"; 21 CFR, Part 56, "Institutional Review Boards"; 21 CFR, Part 54 "Financial Disclosure by Clinical Investigators"; and the ICH guideline entitled "Good Clinical Practice: Consolidated Guidance." Additionally, this study will be conducted in compliance with the Declaration of Helsinki and with all local laws and regulations.

The Investigator will ensure that all work and services described in, or associated with, this protocol are conducted in accordance with the investigational plan, applicable regulations and the highest standards of medical and clinical research practice. The Investigator will provide copies of the study protocol and Investigator's Brochure to all Sub-Investigators, pharmacists and other staff responsible for study conduct.

All aspects of the study will be monitored by qualified individuals designated by the Sponsor. The Sponsor will ensure that the study is monitored adequately in accordance with GCP guidelines.

Prior to initiation of the study, the Sponsor's representatives will review with study center personnel information regarding the investigational drug, protocol requirements, monitoring requirements and reporting of SAEs.

At intervals during the study, as well as after the completion of subject enrollment, the study center will be monitored by the Sponsor or designee for compliance. During these visits, the blinded monitor will discuss study progress, verify adherence to the protocol and verify the completeness, consistency and accuracy of the data being entered on the eCRF (source data verification); oversee the resolution of outstanding data discrepancies; and check on various aspects of study conduct (e.g., sample storage). The Investigator agrees to allow unblinded monitors access to the clinical supplies, dispensing and storage areas and clinical records of the study subjects and, if requested, agrees to assist the monitors. The Investigator must cooperate

with the monitors to ensure that any problems detected in the course of these monitoring visits are resolved.

A secondary audit may be conducted by Quality Assurance designated by the Sponsor. The Investigator will be informed if this is to take place and advised as to the nature of the audit. Representatives of the US FDA and/or representatives of other regulatory authorities may also conduct an inspection of the study at the investigative site. If informed of such an inspection, the Investigator should notify the Sponsor immediately.

Every effort will be made to maintain the anonymity and confidentiality of subjects participating in this clinical study. However, because of the investigational nature of this treatment, the Investigator agrees to allow representatives of the Sponsor, its designated agents and authorized employees of the appropriate regulatory agencies to inspect the facilities used in this study and to have direct access to inspect, for purposes of verification, the hospital or clinical records of all subjects enrolled in this study. A statement to this effect should be included in the ICF.

13 DATA MANAGEMENT

Data will be entered into a clinical database as specified in the Data Management Plan. Quality control and data validation procedures will be applied to ensure the validity and accuracy of the clinical database. Data will be reviewed and checked for omissions, apparent errors and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification will be communicated to the investigational site for resolution. Only authorized personnel will make corrections to the clinical database and all corrections will be documented in an audit trail.

The coding of an AE, medical history and concomitant medication terms will be performed by a qualified medical coder and reviewed and approved by the Sponsor. Concomitant medications will be coded using the World Health Organization Drug Dictionary and AE/medical history/surgery/non-drug therapy terms will be coded using the Medical Dictionary for Regulatory Activities.

14 RETENTION OF RECORDS

No study documents at the study site should be destroyed without prior written agreement between the Sponsor and the Investigator. All subjects' medical records, the Investigator's copy of the eCRF, other supporting data, records of drug dispensing and accountability, signed ICFs, IRB/IEC correspondence and correspondence with the Sponsor must be kept by the Investigator for at least 2 years and as required by the local law following the date of the last approval of a marketing application in an ICH region (including the US) and until there are no pending or contemplated marketing applications in any other ICH region. If an application is not filed or not approved for the indication under study, all study-related files must be retained for at least 2 years following the date of discontinuation of the clinical development program for TEPEZZA and for a period in compliance with all federal, state and local regulations. The Sponsor must be notified prior to the disposal of any study-related files. If the Investigator leaves the practice or

institution during the required retention period, it is important that arrangements be made for continued record retention. In that event, the records generally will be retained at the institution at which the study was conducted.

15 PUBLICATION

To avoid disclosures that could jeopardize proprietary rights, the institution and/or the Investigator agree to certain restrictions on publications (e.g., abstracts, speeches, posters, manuscripts and electronic communications) as detailed in the Clinical Trial Agreement.

16 REFERENCES

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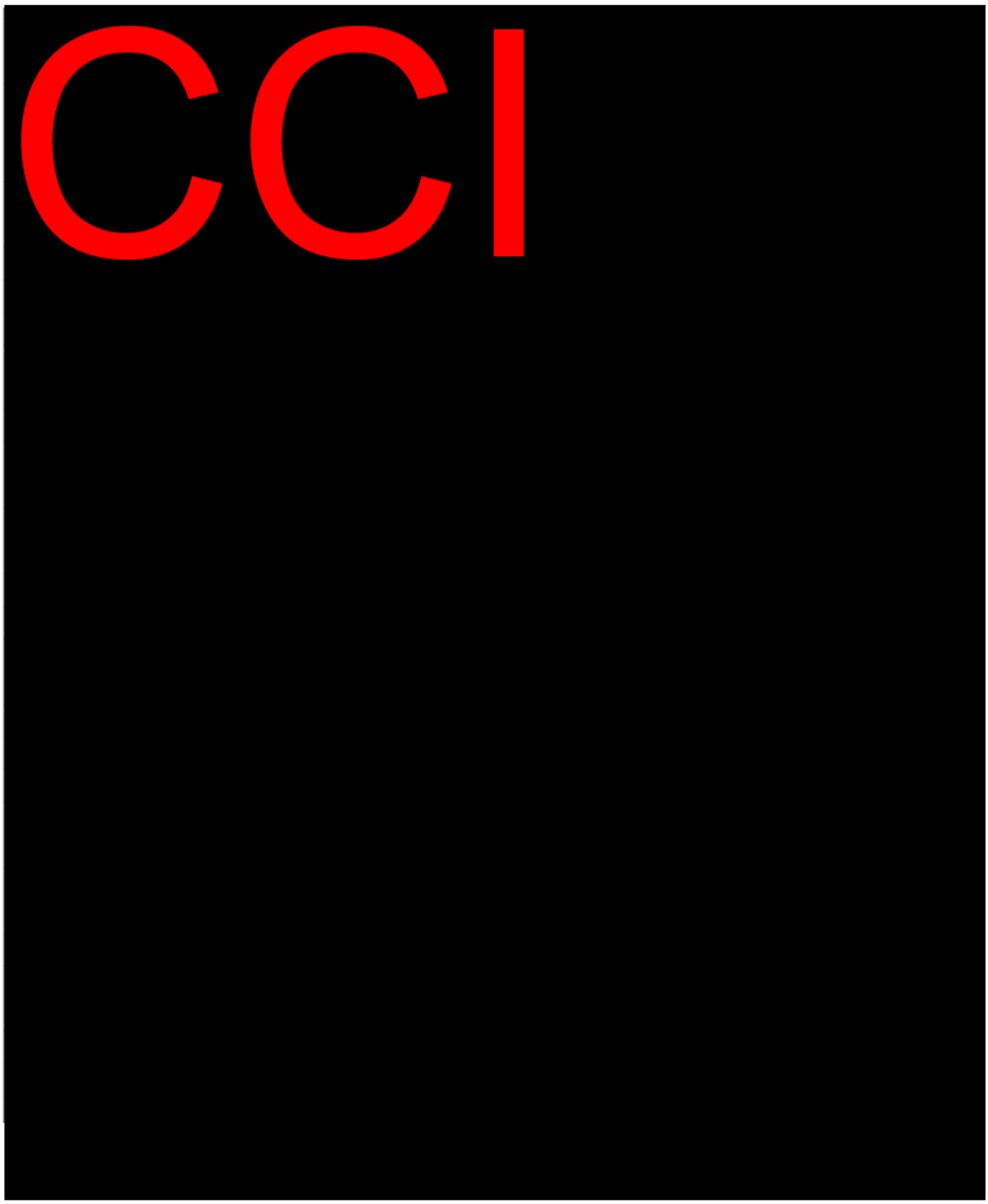
17 APPENDICES

17.1 Administrative Appendix

This appendix provides names and contact information for the study administrative structure. The IRB/IEC must be notified of changes that are made to this section, but IRB/IEC review or approval of these changes is not required. Changes made in this section will be dated but will not be assigned a protocol amendment number.

Medical Monitor	PPD Horizon Therapeutics U.S.A., Inc. 1 Horizon Way Deerfield, IL 60015 Mobile telephone number: PPD Business telephone number: PPD Email: PPD
Sponsor Representative	PPD PPD Horizon Therapeutics U.S.A., Inc. 1 Horizon Way Deerfield, IL 60015 Mobile telephone number: PPD Business telephone number: PPD Email: PPD
Sponsor Contact for Serious Adverse Event Reporting	Horizon Therapeutics U.S.A., Inc. Fax: PPD Email: clinicalsafety@horizontherapeutics.com

17.2 CCI



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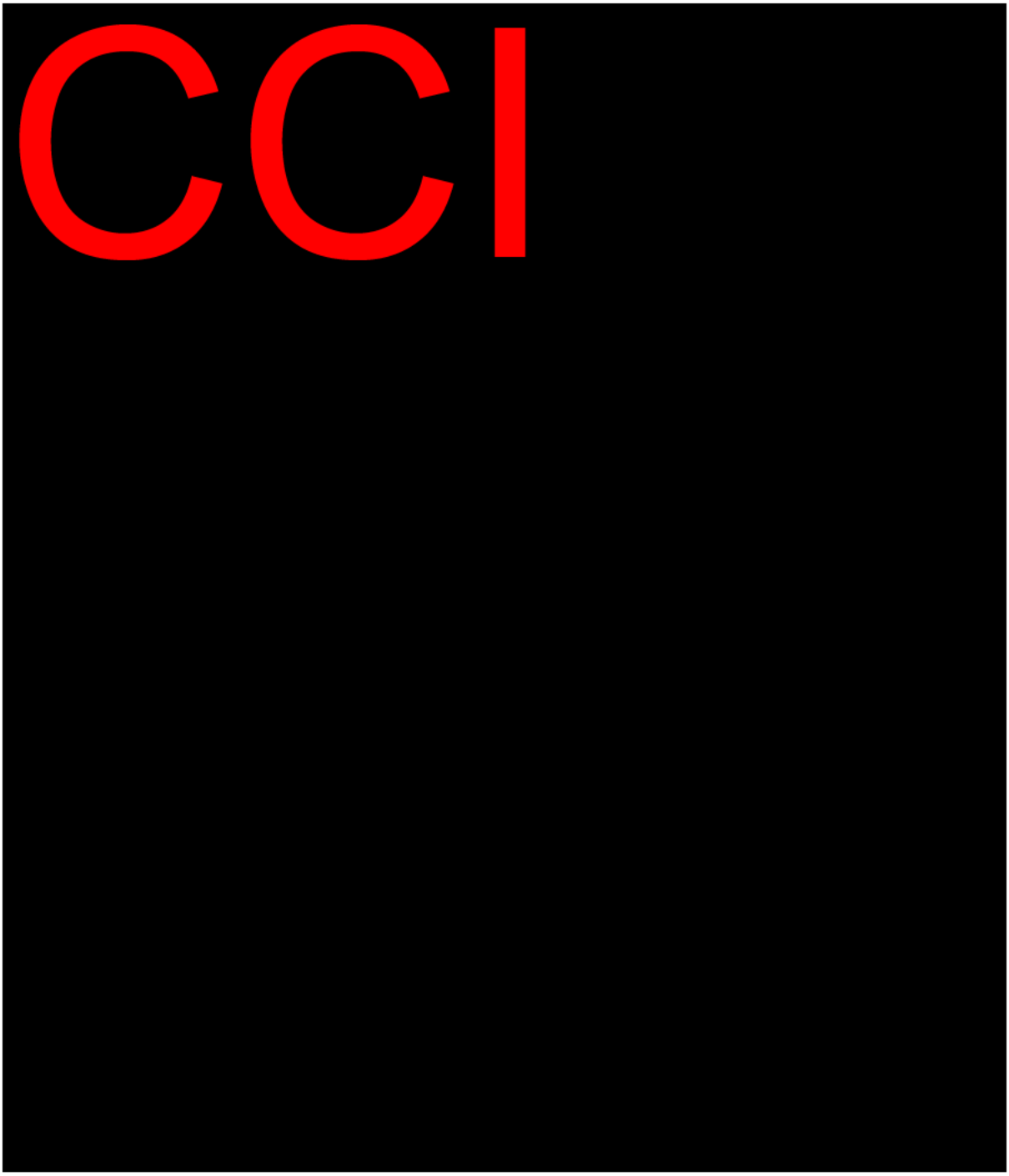

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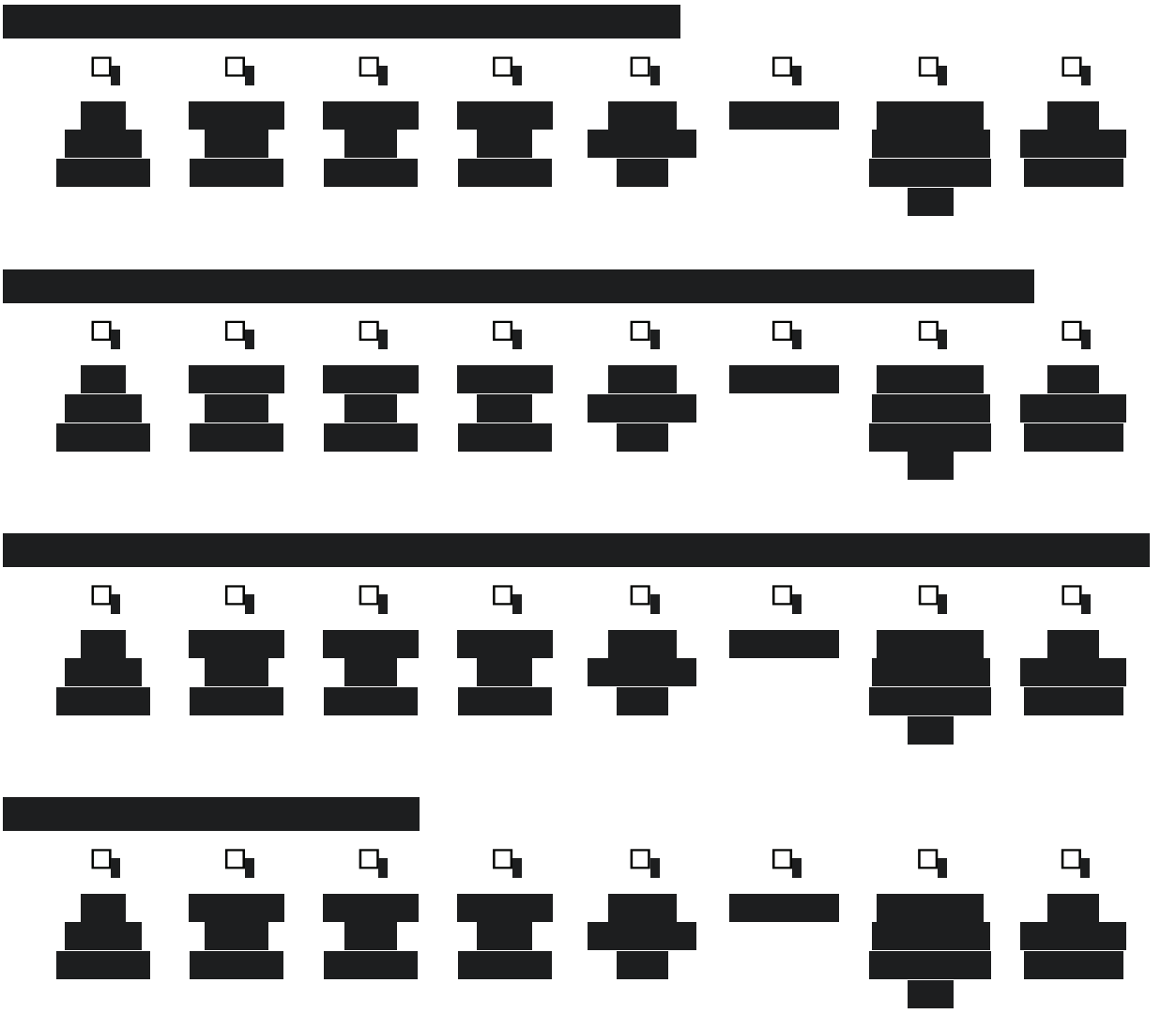

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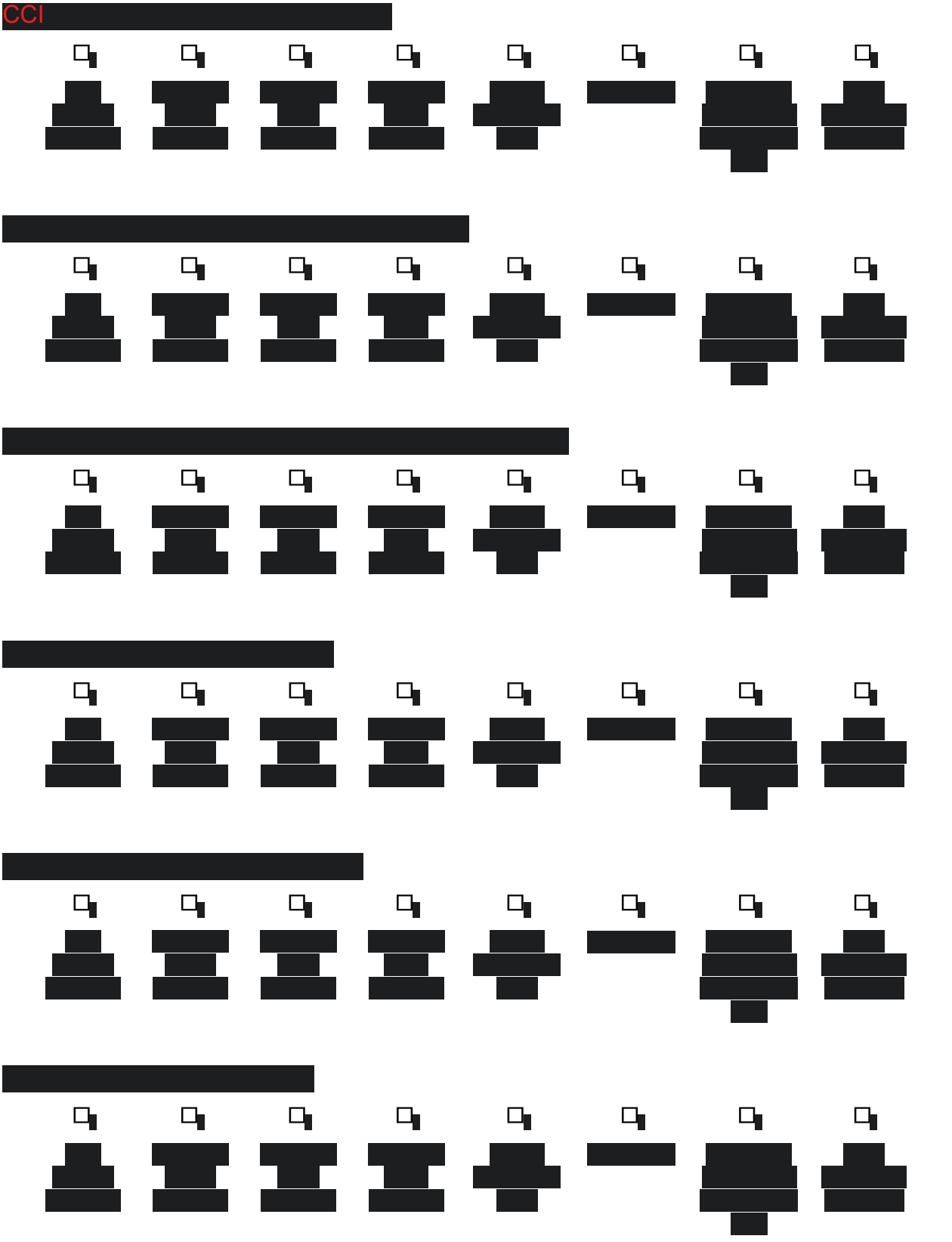

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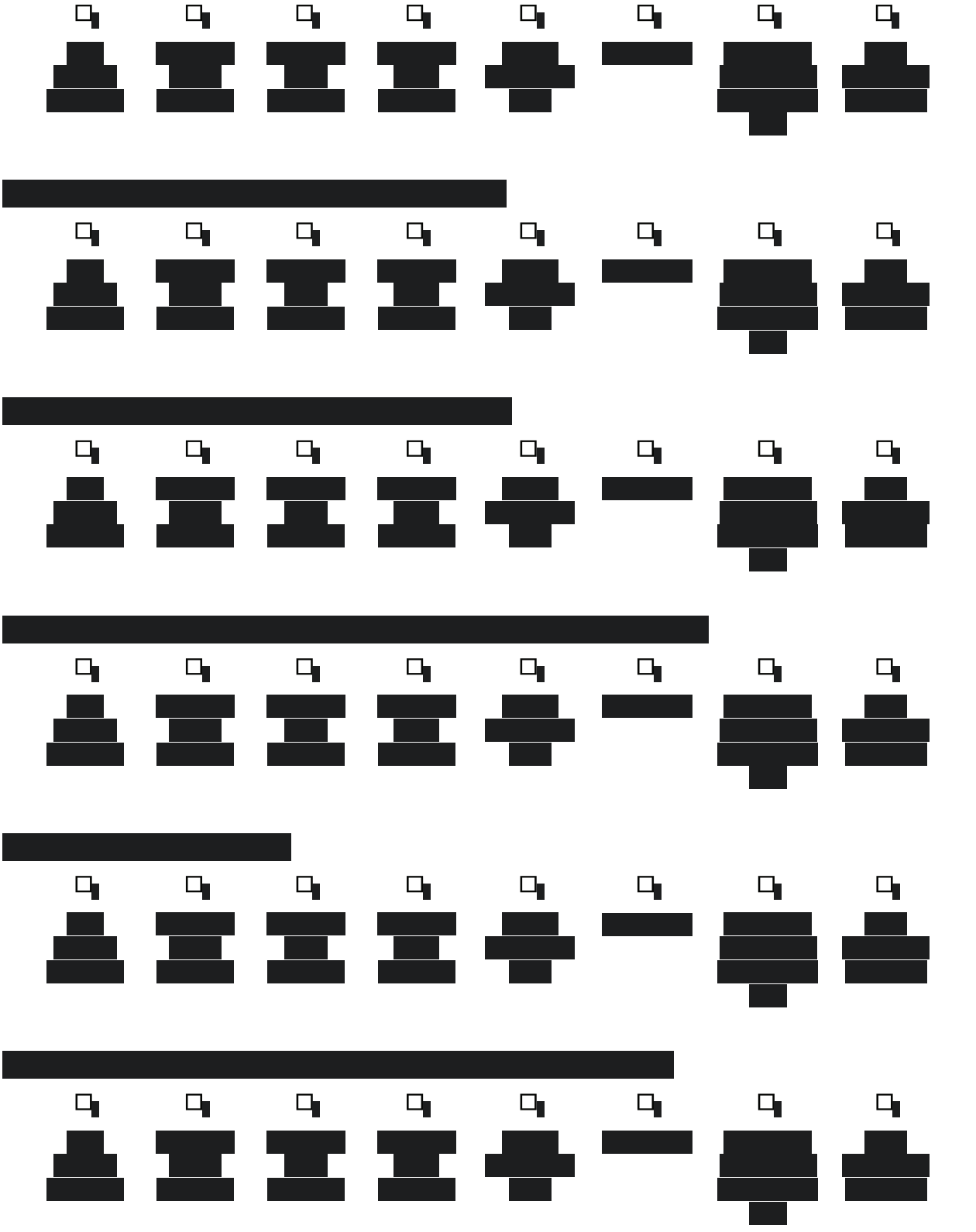

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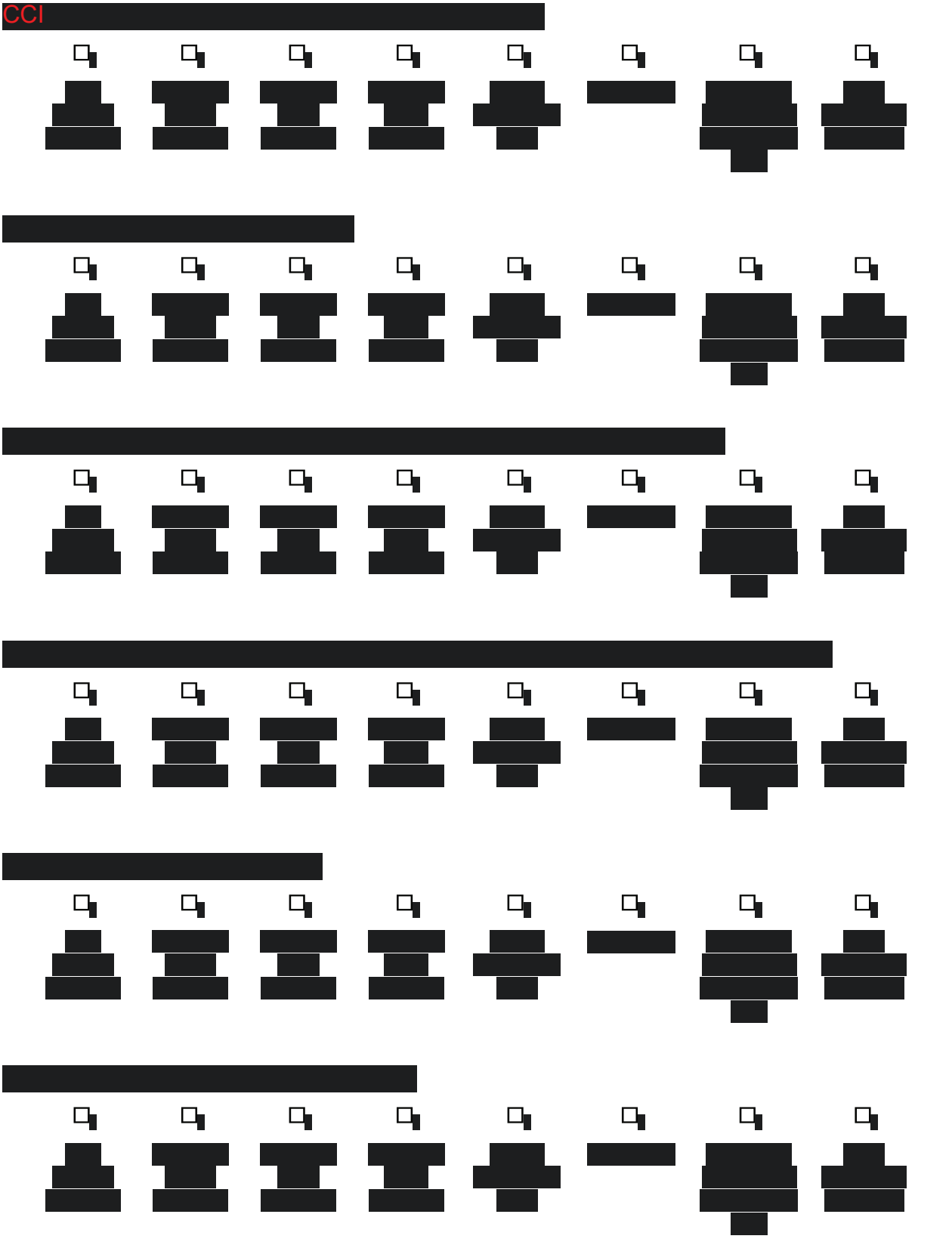

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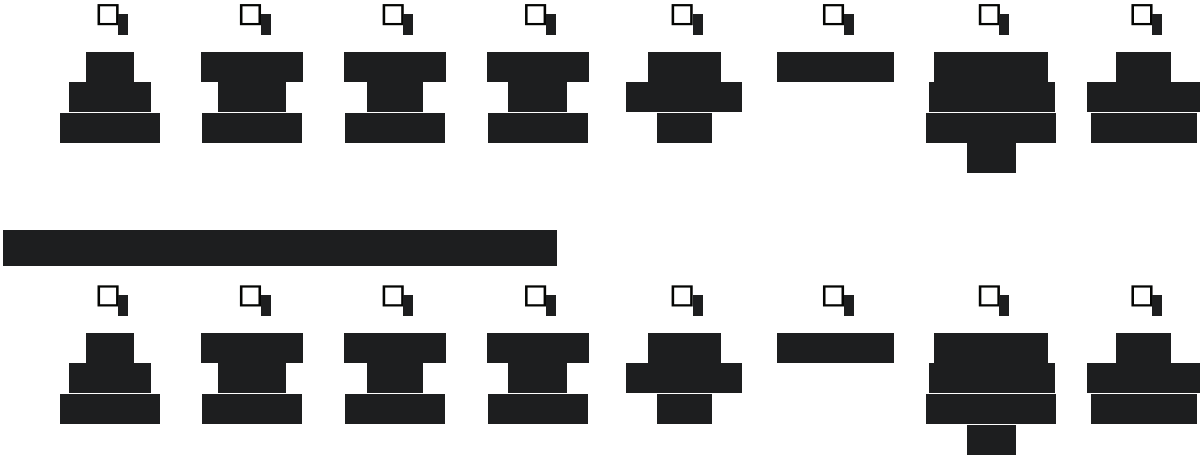

17.7 CCI


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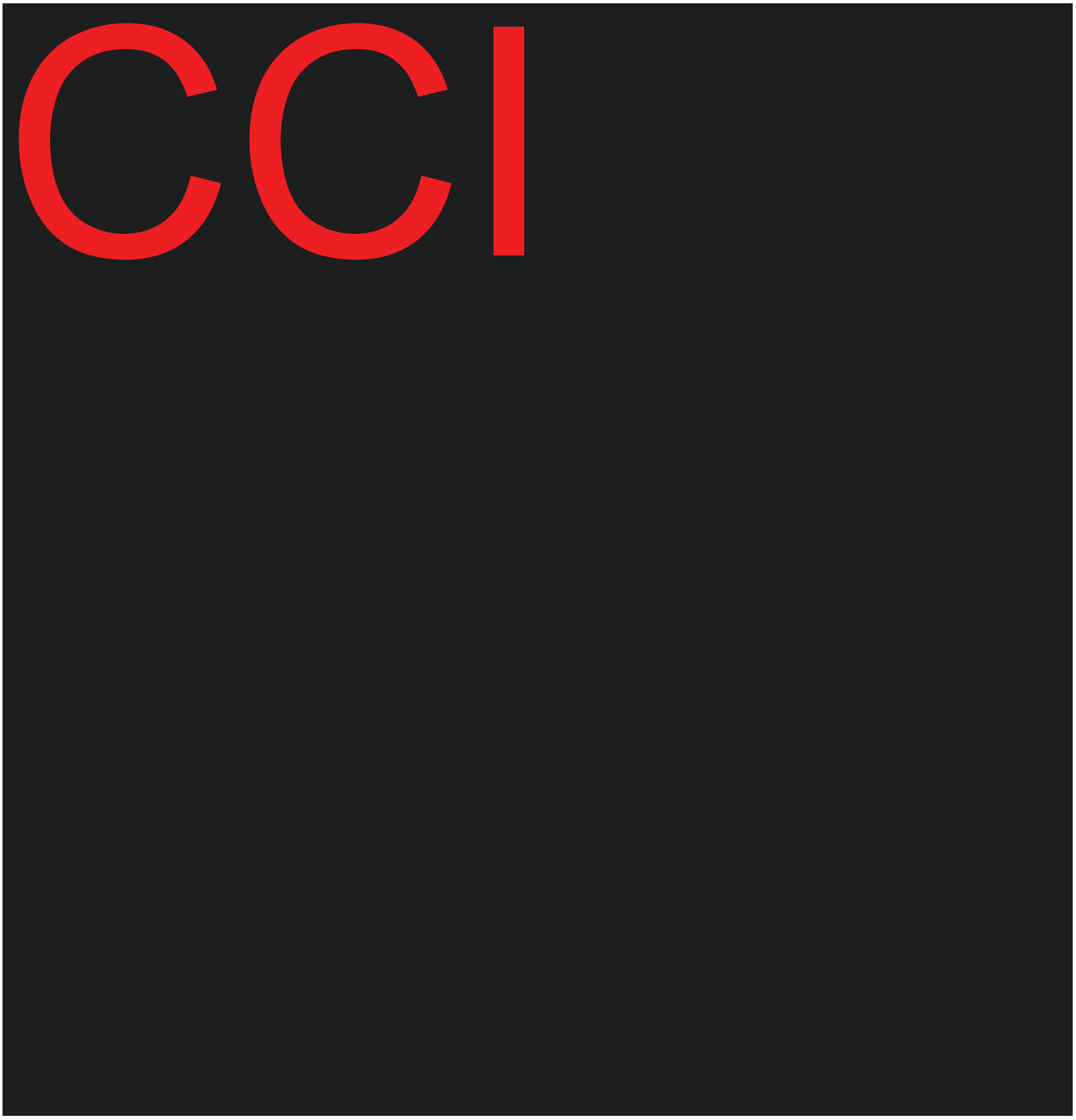
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