A Phase 4 Safety Study Assessing the Adverse Events Occurring Within One Day of TEGSEDI Administration in Patients With Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis (hATTR-PN)

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Protocol Number: TEG4004

Version: Final v2.0
Protocol Date: 08 May 2020

Compound: TEGSEDI® (inotersen)
(for injection, for subcutaneous use)

Sponsor

Akcea Therapeutics, Inc.

[redacted]

United States

Title	A phase 4 safety study assessing the adverse events occurring within one day of TEGSEDI administration in patients with polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN)
Protocol version identifier	v2.0
Date of last version of protocol	20-September-2019
Active substance	Inotersen
Medicinal product	TEGSEDI
Product reference	Not applicable
Sponsor & license holders	**United States (US) and Canada** Akcea Therapeutics, Inc. [redacted] United States
Research question and objectives	The objective of the study is to characterize adverse events (AEs) occurring within one day of TEGSEDI administration to adult patients with hATTR-PN overall and in individual patients with respect to time course of AE onset, vital sign changes, preventive measures, treatment required, risk factors, and subsequent adverse outcomes.
Regions and countries of study	US and Canada
Author	Akcea Therapeutics, Inc.

Sponsor/License Holder

Sponsor & License holders	Akcea Therapeutics, Inc. [redacted] United States
Key contact person	[redacted] Akcea Therapeutics, Inc. [redacted]

1. Table of Contents

List of Tables

2. List of Abbreviations and Definitions of Terms

Abbreviation	Definition
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
AE	Adverse event
AESI	Adverse events of special interest
ADR	Adverse drug reaction
ASO	Antisense oligonucleotide
CNS	Central nervous system
CPM	Canadian Product Monograph
CRO	Contract research organization
CRP	C-reactive Protein
eCRF	Electronic case report form
EDC	Electronic data capture
ESR	Erythrocyte sedimentation rate
ET	Early termination
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GM-CSF	Granulocyte-macrophage colony stimulating factor
hATTR-PN	Polyneuropathy of hereditary transthyretin-mediated amyloidosis
HEENT	Head, eyes, ears, nose and throat
HLT	High level term
ICF	Informed consent form
ICH	International Council For Harmonization
IEC	Independent ethics committee
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IRB	Institutional review board
MCP	Membrane cofactor protein
MedDRA™	Medical Dictionary for Regulatory Activities
MIP	Macrophage inflammatory protein
NCS	Not clinically significant
NK	Natural killer
PT	Preferred term
REMS	Risk Evaluation and Mitigation Strategies
SAE	Serious adverse event
SMQ	Standardized MedDRA query
SOC	System organ class
TNF-α	Tumor necrosis factor-alpha
TRIM21	Tripartite motif containing 21

TTR	Transthyretin
US	United States
USPI	United States Prescribing Information

3. Responsible Parties

Sponsor	Akcea Therapeutics, Inc. [redacted] United States
Contract research organization (CRO)	UBC [redacted] United States

4. Abstract

Title

A Phase 4 Safety Study Assessing the Adverse Events Occurring Within One Day of TEGSEDI Administration in Patients with Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis (hATTR-PN).

Rationale and Background

Polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN) is an inherited, progressive, fatal disease caused by misfolded transthyretin (TTR) proteins that accumulate as amyloid fibrils predominantly in the peripheral nerves, heart, gastrointestinal tract, and other organs. hATTR-PN is a rare disease and there are no large epidemiological studies that reliably provide an indication of its prevalence. The worldwide distribution is unequal, with higher rates in Portugal, Japan, Brazil, Northern Sweden, and the US. Current estimates suggest there may be 10,000 afflicted patients worldwide (Plante-Bordeneuve, V. 2014).

TEGSEDI (inotersen) is an antisense oligonucleotide (ASO) inhibitor of human TTR protein synthesis. In the US, TEGSEDI is indicated for treatment of the polyneuropathy of hATTR in adults. Efficacy has been demonstrated in patients with polyneuropathy of hATTR, as reflected by a slowing or reversal of disease progression.

Research Question and Endpoints

The objective of the study is to characterize adverse events (AEs) occurring within one day of TEGSEDI administration to adult patients with hATTR-PN overall and in individual patients with respect to time course of AE onset, vital sign changes, preventive measures, treatment required, risk factors, and subsequent adverse outcomes.

The endpoints of the study are the AEs, changes in vital signs and cytokines and inflammatory markers 24-hour post-injection with additional assessments of:

- Preventive measures used prior to the injection
- Treatment of AEs post 24-hour injection
- Identification of risk factors for AEs
- Correlation of subsequent adverse outcomes

Study Design

An open-label, phase 4, multicenter safety study in at least 75 patients with hATTR-PN prescribed 284 mg of TEGSEDI in US and Canada.

Duration patient participation

For patients with hATTR-PN prescribed TEGSEDI who stay on drug for the duration of the study and who do not have any hypersensitivity reactions, participation will be a minimum of 12 months and a maximum of 24 months with visits every 4 months. After the first 12 months, visits will continue every 4 months for a maximum of a further 12 months or until one of the Milestones for Study End is triggered.

For patients with hATTR-PN prescribed TEGSEDI who have a hypersensitivity reaction while in the study, participation will be a minimum of 12 months and a maximum of 36 months depending upon when in their study participation the hypersensitivity reaction occurred. This additional duration is due to the additional Post-Treatment Follow-up visits required in response to the hypersensitivity reaction which are a minimum of an additional 4 months and maximum of an additional 12 months based upon when one of the Milestones for Study End is triggered (see definition of Milestones for Study End and anti-drug antibody (ADA) testing and hypersensitivity below).

Study visits for all patients while being treated with TEGSEDI

TEGSEDI (inotersen 284 mg/1.5ml) will be injected subcutaneously once weekly according to product label. The dose and dosing regimen of TEGSEDI will follow the approved United States Prescribing Information (USPI) (TEGSEDI USPI) or Canadian Product Monograph (CPM) (TEGSEDI CPM).

During the clinic visits, a scheduled dose of TEGSEDI will be injected and the patients will be monitored at 1, 2, 4, and 8 hours post injection for AE assessments, changes in vital signs, and laboratory testing. The patient will return to the clinic 20-30 hours post injection for a further assessment of AEs, vital signs, and laboratory testing. In addition to these visits, the patient will be monitored according to the USPI (TEGSEDI USPI) or CPM (TEGSEDI CPM). Additional blood samples will be drawn and stored for possible non-genetic testing in this study.

Anti-Drug Antibody testing and hypersensitivity

All patients will have a minimum of 2 ADA samples taken. One sample will be taken at the first on-study visit (Month 0) prior to the scheduled dose of TEGSEDI, and the other sample will be taken at the end of the patient's participation in the study, prior to the scheduled dose of TEGSEDI if the patient is still on treatment.

Patients who develop a hypersensitivity reaction during the study will have additional blood samples taken for ADA testing on the day of the hypersensitivity reaction at the 20-30 hour time point and again at their Post-Treatment Follow-up visits for 12 months or when one of the Milestones for Study End has been met, whichever is earliest. All patients who have a hypersensitivity reaction will be followed for a minimum of 4 months.

Discontinuation of TEGSEDI

If a patient discontinues TEGSEDI for a reason other than a hypersensitivity reaction, the patient will have an Early Termination (ET) visit as soon as possible after the decision to end treatment and will be followed for 8 weeks after treatment discontinuation for AEs assessments, changes in vital signs and laboratory sampling.

If a patient discontinues TEGSEDI due to hypersensitivity, the patient will undergo an ET visit and an 8-week follow-up visit. He/she will also return for additional ADA testing at 4 months after the hypersensitivity reaction, and then again at 8 months and 12 months after the hypersensitivity reaction, if the study is still ongoing (see definition of Milestones for Study End).

Withdrawal from study

Patients who withdraw from the study but continue on treatment with TEGSEDI should return for an ET visit as soon as possible after the decision to withdraw from the study. After the ET visit, no further follow-up is required for patients who continue treatment on TEGSEDI.

Patients continuing TEGSEDI after completing the study

Patients who complete the study and plan to continue TEGSEDI treatment will have the ADA testing prior to the scheduled dose of TEGSEDI at their End of Study visit. US patients who complete the study will continue on the Risk Evaluation and Mitigation Strategies (REMS) program.

Population

Eligibility Criteria:

1. Satisfy one of the following:
   a. US Patients: Adult patients (≥ 18 years old) diagnosed with hATTR-PN and prescribed TEGSEDI according to the USPI (TEGSEDI USPI).
   b. Canadian Patients: Adult patients (≥ 18 years old) diagnosed with stage 1 or stage 2 hATTR-PN and prescribed TEGSEDI according to the CPM (TEGSEDI CPM).
2. Must have given written informed consent for participation in this study.
3. Must provide access to their previous medical records.
4. Are about to initiate or have recently initiated treatment with TEGSEDI and have not received more than 9 doses in total.
5. Be willing to complete required testing and report any AEs and/or changes in medications.
6. Satisfy one of the following:
   a. Females: Non-pregnant and non-lactating; abstinent, or if engaged in sexual relations of childbearing potential, patient is using an acceptable contraceptive method from time of signing the informed consent form (ICF) until 13 weeks after the last dose of TEGSEDI administration.
   b. Males: Abstinent or if engaged in sexual relations with a female of childbearing potential, patient is utilizing an acceptable contraceptive method from the time of signing the ICF until 13 weeks after the last dose of TEGSEDI administration.

Data Sources

Source of the data will be an electronic case report form (eCRF), which will be created for prospective data collection. Data will be collected in the eCRF following on-site clinic visits every 4 months.

Study Size

A sample size of 75 patients will allow 95% probability to detect an AE occurring as infrequently as 4% of patients.

Data Analysis

Incidence (95% confidence interval), onset, and duration of each AE occurring within 1 day of TEGSEDI administration will be summarized by visit and overall in any visits. The rates of AEs

occurring after preventive measures will also be summarized. Resolution time with and without treatment administered for these AEs will be summarized.

For each study visit while on treatment, the results and changes from pre dose baseline in vital signs and cytokines and inflammatory markers will be summarized using descriptive statistics for patients with and without AEs within 1 day of TEGSEDI administration.

Milestones for Study End

The last visit of the study will be determined by the last visit date of one of the following scenarios:

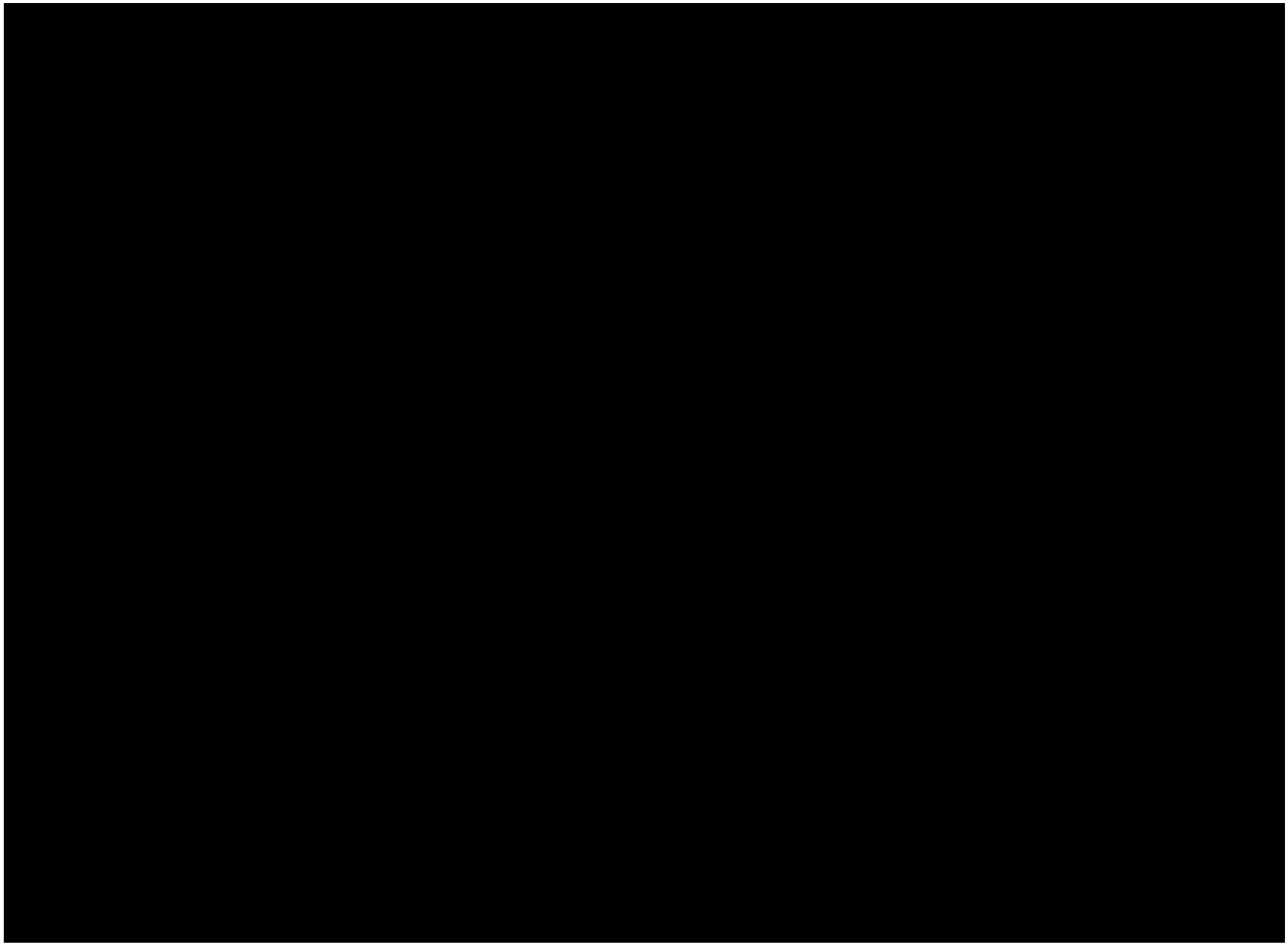
- The date of the last 12 month clinic visit
- The last 4 month follow up visit of a patient who had a hypersensitivity reaction
- The last 8-week follow-up visit of a patient who has discontinued TEGSEDI

[redacted]

4. Abstract/ 7. Background/ 9.2.4 Treatment of Patients	US only References to USPI	US and Canada References to USPI and CPM	Study may also be performed in Canada
4. Abstract- Study Design/ 9.1 Study Design	An open-label, phase 4, multicenter safety study in at least 75 patients with hATTR-PN prescribed 284 mg of TEGSEDI who will be followed in the protocol for a minimum of 1 year and a maximum of 2 years with visits every 4 months. Patients who have a hypersensitivity reaction while participating on the study may be followed for up to 1 year following the initial event. This may increase their participation beyond 2 years.	An open-label, phase 4, multicenter safety study in at least 75 patients with hATTR-PN prescribed 284 mg of TEGSEDI. *Duration patient participation* For patients with hATTR-PN prescribed TEGSEDI who stay on drug for the duration of the study and who do not have any hypersensitivity reactions, participation will be a minimum of 12 months and a maximum of 24 months with visits every 4 months. After the first 12 months, visits will continue every 4 months for a maximum of a further	To improve clarity regarding duration of study and follow up for patients who do and do not experience hypersensitivity

Section	Version 1.0	Version 2.0	Reason for change
		12 months or until one of the Milestones for Study End is triggered. For patients with hATTR-PN prescribed TEGSEDI who have a hypersensitivity reaction while in the study, participation will be a minimum of 12 months and a maximum of 36 months depending upon when in their study participation the hypersensitivity reaction occurred. This additional duration is due to the additional Post-Treatment Follow-up visits required in response to the hypersensitivity reaction which are a minimum of an additional 4 months and maximum of an additional 12 months based upon when one of the Milestones for Study End is triggered	
4. Abstract- Study design/9.1 Study Design	NA	Additional multiple edits reflecting above changes	To improve clarity regarding duration of study and follow up for patients who do and do not experience hypersensitivity
4. Abstract: Eligibility Criteria/9.2.1 Eligibility Criteria	7. Adult patients (≥ 18 years old) diagnosed with polyneuropathy of hereditary transthyretin-mediated amyloidosis and prescribed TEGSEDI according to the USPI.	1. Satisfy one of the following: a. US Patients: Adult patients (≥ 18 years old) diagnosed with hATTR-PN and prescribed TEGSEDI according to the TEGSEDI USPI b. Canadian Patients: Adult patients (≥ 18 years old) diagnosed with stage 1 or stage 2 hATTR-PN and prescribed TEGSEDI according to the TEGSEDI CPM	To allow for potential inclusion of Canadian patients
4. Abstract/ 9.1 Study Design	**Milestones**	**Milestones for Study End**	To improve clarity regarding Study End

Section	Version 1.0	Version 2.0	Reason for change
9.2.2.1 Study Schedule	Table 1 Schedule of Assessments included schedule for patients who did and did not experience a hypersensitivity reaction	Two separate tables Table 1 Schedule of Assessments for Patients Who do not Develop a Hypersensitivity Reaction Table 2 Schedule of Assessments for Patients Who Develop a Hypersensitivity Reaction	To improve clarity with respect to differing schedules between those who do and do not experience a hypersensitivity reaction
9.2.2.1 Study Schedule	Post injection assessment at the following intervals 1-hour ± 15 mins 2-hour ± 30 mins 4-hour ± 60 mins 8-hour ± 120 mins 20-30 hours	Post injection assessment at the following intervals 1-hour ± 15 mins 2-hour ± 15 mins 4-hour ± 30 mins 8-hour ± 30 mins 20-30 hours	Correction
9.2 Study procedures	The following subsections were in existence • Screening • On Treatment • Contraceptive requirements • Post Treatment Period	Amended to the following subsections • Screening • Initial Treatment Visit (Month 0) and Every 4 Months Including End of Study Visit • End of Study Visit • Early Termination Visit • ADA Testing • Contraception Requirements Addition of definition of Full Physical Examination and Abbreviated Physical Examination	To improve clarity
9.2.3.1 Physical Examinations and Vital Signs	Weight will be measured at each visit.	The physical examination and weight do not need to be completed at the Month 0 study visit if they occurred prior during Screening.	To clarify that a duplication is not required at Month 0 if performed at screening
9.2.3.1 Physical Examinations and Vital Signs	NA	Post injection assessments will be made at 1 hour ± 15 minutes; 2 hour ± 15 minutes; 4 hour ± 30 minutes; 8 hour ± 30 minutes and 20-30 hours following injection of TEGSEDI	To improve clarity
9.3 Variables	Full list of variables	Removal due to availability in 9.2.2.1	To improve clarity



Section	Version 1.0	Version 2.0	Reason for change
	• Central nervous system (CNS) vasculitis		
11.4.3.6 Follow up of Adverse Event	The investigator should follow up or support the Sponsor's effort to follow up with all pregnancies reported during the study from either the study patient or the female partner of male study patient until pregnancy outcome is available.	The investigator should follow up or support the Sponsor's effort to follow up with all pregnancies reported during the study from either the study patient or the female partner of male study patient until pregnancy outcome is available. If the pregnancy results in the birth of a child, the mother and infant may continue to be followed for up to 8 weeks after birth.	Clarification of follow-up period consistent with Akcea's pharmacovigilance processes
Annex 1 Laboratory Analytes	NA	Addition of ADA and rationale for ADA	To improve clarity
Annex 1 List of MedDRA terms	Outdated table	Revised table	To reflect current Akcea's pharmacovigilance practices

6. Milestones

Not applicable.

7. Rationale and Background

Polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR-PN) is an inherited, progressive, fatal disease caused by misfolded TTR proteins that accumulate as amyloid fibrils predominantly in the peripheral nerves, heart, gastrointestinal tract, and other organs. hATTR-PN is a rare disease and there are no large epidemiological studies that reliably provide an indication of its prevalence. The worldwide distribution is unequal, with higher rates in Portugal, Japan, Brazil, Northern Sweden, and the US. Current estimates suggest there may be 10,000 afflicted patients worldwide (Plante-Bordeneuve, V. 2014).

TEGSEDI is an ASO inhibitor of human TTR protein synthesis. In the US, TEGSEDI is indicated for treatment of the polyneuropathy of hATTR in adults. Efficacy has been demonstrated in patients with polyneuropathy of hATTR, as reflected by a slowing or reversal of disease progression. For information on TEGSEDI please refer to the product label (TEGSEDI USPI - US; TEGSEDI CPM-Canada) as follows:

Information	**USPI Section**	**CPM Section**
Preclinical Experience	8.1 Pregnancy-Animal Data 13. Nonclinical Toxicology	7 Warnings and Precautions. Sexual Health 16 Non-Clinical Toxicology
Clinical Experience	6.1 Clinical Trial Experience 8.5 Geriatric Use 12.2 Pharmacodynamics 12.3 Pharmacokinetics 14 Clinical Studies	7.1.4 Geriatric Use 10.2 Pharmacodynamics 10.3 Pharmacokinetics 14 Clinical Trials
Rationale for Dose and Schedule of Administration	2 Dosage and Administration	4 Dosage and Administration
Benefit-risk Assessment	1 Indications and usage 5 Warnings and Precautions	1 Indication 7 Warnings and Precautions
TEGSEDI Description	11 Description 16 How Supplied/Storage and Handling	11 Storage, Stability and Disposal 12 Special Handling Instructions 13 Pharmaceutical Information

8. Research Question and Endpoints

The objective of the study is to characterize AEs occurring within one day of TEGSEDI administration to adult patients with hATTR-PN overall and in individual patients with respect to time course of AE onset, vital sign changes, preventive measures, treatment required, risk factors, and subsequent adverse outcomes.

The endpoints of the study are the AEs, changes in vital signs and cytokines and inflammatory markers 24-hour post-injection with additional assessments of:

- Preventive measures used prior to the injection
- Treatment of AEs post 24-hour injection
- Identification of risk factors for AEs
- Correlation of subsequent adverse outcomes

9. Research Methods

9.1. Study Design

This open-label Phase 4, multicenter safety study will enroll at least 75 patients with hATTR-PN in the US and Canada.

9.1.1. Duration of Patient Participation

For patients with hATTR-PN prescribed TEGSEDI who stay on drug for the duration of the study and do not have any hypersensitivity reactions, participation will be a minimum of 12 months and a maximum of 24 months with visits every 4 months. After the first 12 months, visits will continue every 4 months for a maximum of a further 12 months or until one of the Milestones for Study End is triggered (see definition of Milestones for Study End below).

For patients with hATTR-PN prescribed TEGSEDI who have a hypersensitivity reaction while in the study, participation will be a minimum of 12 months and a maximum of 36 months depending upon when in their study participation the hypersensitivity reaction occurred. This additional duration is due to the additional Post-Treatment Follow-up visits required in response to the hypersensitivity reaction which are a minimum of an additional 4 months and maximum of an additional 12 months based upon when one of the Milestones for Study End is triggered (see definition of Milestones for Study End and ADA Testing and Hypersensitivity below).

9.1.2. Study Visits for all Patients While Being Treated With TEGSEDI

During the study visits, a scheduled dose of TEGSEDI will be injected and the patients will be monitored at 1, 2, 4, and 8 hours post injection for AEs assessments, changes in vital signs and laboratory testing. The patient will return to the clinic 20-30 hours post injection for a further assessment of AEs, vital signs and laboratory testing. In addition to these study visits, the patient will be monitored according to the USPI or CPM. Additional blood samples will be drawn and stored for possible non-genetic testing in this study.

9.1.3. ADA Testing and Hypersensitivity

All patients will have a minimum of 2 ADA samples taken. One sample will be taken at the first on-study visit (Month 0) prior to the scheduled dose of TEGSEDI, and the other sample will be taken at the end of the patient's participation in the study prior to the scheduled dose of TEGSEDI if the patient is still on treatment.

Patients who develop a hypersensitivity reaction during the study will have additional blood samples taken for ADA testing on the day of the hypersensitivity reaction at the 20-30 hour time point and again at their Post Treatment Follow-up visits for 12 months or when one of the Milestones for Study End has been met, whichever is earliest. All patients who have a hypersensitivity reaction will be followed for a minimum of 4 months.

9.1.4. Discontinuation of TEGSEDI

If a patient discontinues TEGSEDI for a reason other than a hypersensitivity reaction, the patient will have an ET visit as soon as possible after the decision to end treatment and will be followed for 8 weeks after treatment discontinuation for AEs assessments, changes in vital signs and laboratory sampling.

If a patient discontinues TEGSEDI due to hypersensitivity, the patient will undergo an ET visit and an 8-week follow-up visit. He/she will also return for additional ADA testing at 4 months after the hypersensitivity reaction, and then again at 8 months and 12 months after the hypersensitivity reaction, if the study is still ongoing (see definition of Milestones for Study End).

9.1.5. Withdrawal From Study

Patients who withdraw from the study but continue on treatment with TEGSEDI should return for an ET visit as soon as possible after the decision to withdraw from the study. After the ET visit no further follow-up is required for patients who continue treatment on TEGSEDI. US patients will continue on the REMS program.

9.1.6. Patients Continuing TEGSEDI After Completing the Study

Patients who complete the study and plan to continue TEGSEDI treatment will have the ADA testing prior to the scheduled dose of TEGSEDI at their End of Study visit. US patients who complete the study will continue on the REMS program.

9.1.7. Milestones for Study End

The last visit of the study will be determined by the last visit date of one of the following scenarios:

- The date of the last 12 month study visit
- The last 4-month follow-up visit of a patient who had a hypersensitivity reaction
- The last 8-week follow-up-visit of a patient who has discontinued TEGSEDI

9.2. Setting

This study will be conducted at multiple study centers in the US and Canada. TEGSEDI will be prescribed to the patient by their healthcare provider prior to enrolling in this study. TEGSEDI will be administered from approved packaged and labeled packs. Used syringes will be disposed of per the product's instructions for use.

9.2.1. Selection of Study Population

To be eligible to enroll in this study, patients must meet the following eligibility criteria:

1. Satisfy one of the following:
    a. US Patients: Adult patients (≥ 18 years old) diagnosed with hATTR-PN and prescribed TEGSEDI according to the USPI (TEGSEDI USPI)
    b. Canadian Patients: Adult patients (≥ 18 years old) diagnosed with stage 1 or stage 2 hATTR-PN and prescribed TEGSEDI according to the CPM (TEGSEDI CPM)

2. Must have given written informed consent for participation in this study
3. Must provide access to their previous medical records
4. Are about to initiate or have recently initiated treatment with TEGSEDI and have not received more than 9 doses in total
5. Be willing to complete required testing and report any AEs and/or changes in medications
6. Satisfy one of the following:
    a. Females: Non-pregnant and non-lactating; abstinent, or if engaged in sexual relations of childbearing potential, patient is using an acceptable contraceptive method from time of signing the ICF until 13 weeks after the last dose of TEGSEDI administration
    b. Males: Abstinent or if engaged in sexual relations with a female of childbearing potential, patient is utilizing an acceptable contraceptive method from the time of signing the ICF until 13 weeks after the last dose of TEGSEDI administration

9.2.2. Study Procedures

9.2.2.1. Study Schedule

The study will consist of a Screening/Qualification period, a Treatment period and Post-Treatment Follow-up period as per Table 1 and Table 2.

Table 1. Schedule of Assessments for Patients Who do not Develop a Hypersensitivity Reaction

Study Periods	Screening[1]	Treatment Period					Post-Treatment Follow-up (Patients who discontinued TEGSEDI) 8-weeks[3]
		Initial Treatment Visit (Month 0) and Every 4 months Visit		End of Study Visit			
Procedures and Testing	-2 to 0 weeks prior to first study injection	Pre-injection	Post injection 1-hour ± 15 mins 2-hour ± 15 mins 4-hour ± 30 mins 8-hour ± 30 mins 20-30 hours	Pre-injection	Post injection 1-hour ± 15 mins 2-hour ± 15 mins 4-hour ± 30 mins 8-hour ± 30 mins 20-30 hours	Early Termination Visit[3]	
Informed Consent	X						
Demographics	X						
Medical History	X						
Full Physical Examination	X						
Abbreviated Physical Examination		X[2]		X		X	X
Height	X						
Weight	X	X[2]		X		X	X
Vital Signs	X	X	X	X	X	X	X
Urine Pregnancy Testing	X[4]	X[4]		X[4]		X[4]	
IgE, IgG, IgM		X	X	X	X	X	
Inflammatory Markers		X	X	X	X	X	
Samples for Possible Future Testing		X	X	X	X	X	X
ADA		X[5]		X		X[6]	
Adverse Events Since Last Study Visit		X		X		X	X
Adverse Events Post Injection at Study Visit			X		X		
Concomitant Medications	X	X		X		X	X

1. The Screening visit and the Month 0 visit can occur on the same day.
2. The Physical Examination and Weight does not need to be completed at the Month 0 study visit if they were performed during Screening.
3. If the patient discontinues the study, the patient will return for an Early Termination visit as soon as possible after the decision to early terminate from the study. If the patient also discontinues TEGSEDI, they will also have one follow-up visit 8-weeks after their last dose of TEGSEDI.
4. Urine pregnancy testing is only for women of childbearing potential as defined in the protocol.
5. The baseline ADA sample is only drawn at the Month 0 visit.
6. An ADA sample will only be taken at the Early Termination visit if the patient does not have an End of Study visit.

Table 2. Schedule of Assessments for Patients Who Develop a Hypersensitivity Reaction

Study Periods	Screening[1]	Treatment Period: Initial Treatment Visit (Month 0) and Every 4 months Visit		Treatment Period: Early Termination Visit	Post-Treatment Follow-up (Patients who discontinued TEGSEDI) 8-weeks 4-month 8-month[3] 12-month[3] Post-Treatment visits
Procedures and Testing	**-2 to 0 weeks prior to first study injection**	**Pre-injection**	**Post injection 1-hour ± 15 mins 2-hour ± 15 mins 4-hour ± 30 mins 8-hour ± 30 mins 20-30 hours**		
Informed Consent	X				
Demographics	X				
Medical History	X				
Full Physical Examination	X				
Abbreviated Physical Examination		X[2]		X	X
Height	X				
Weight	X	X[2]		X	X
Vital Signs	X	X	X	X	X
Urine Pregnancy Testing	X[4]	X[4]		X[4]	
IgE, IgG, IgM		X	X	X	
Inflammatory Markers		X	X	X	
Samples for Possible Future Testing		X	X	X	X
ADA		X[5]	X[6]	X	X[6]
Adverse Events Since Last Study Visit		X		X	X
Adverse Events Post Injection at Study Visit			X		
Concomitant Medications	X	X		X	X

1. The Screening visit and the Month 0 visit can occur on the same day.
2. The Physical Examination and Weight does not need to be completed at the Month 0 study visit if they were performed during Screening.
3. The 8 month and 12-month follow-up visits will occur only if a Milestone for Study End has not been triggered.
4. Urine pregnancy testing is only for women of childbearing potential as defined in the protocol.
5. The baseline ADA sample is only drawn at the Month 0 visit. The ADA sample is only drawn post injection, at the 20-30 hour time point, in the event of a hypersensitivity reaction
6. A patient who develops a hypersensitivity reaction during the study will have additional blood samples taken for ADA testing on the day of the hypersensitivity reaction at the 20-30 hour time point and again at their Post-Treatment Follow-up visits for 12 months or when a Milestone for Study End has been met, whichever is earliest. All patients who have a hypersensitivity reaction will be followed for a minimum of 4 months

9.2.2.1.1. Screening

Written informed consent/assent for the study will be obtained prior to the performance of any study-related procedures including screening procedures. A 2-week period is provided for completing screening assessments and determining patient eligibility for the study. However, it is also possible for the screening visit and the Initial Treatment Visit (Month 0) to occur at the same time.

Patients must meet the required laboratory testing referenced in the applicable product label.

Medical history (including a retrospective chart review for relevant hATTR-PN disease history from the onset of the disease) and concomitant medications used within the past 12 months will be collected for each patient.

In addition, the following will be carried out at screening:

- Full Physical examination including height, weight and vital signs and examination of the following body systems: head, eyes, ear, nose throat (HEENT), cardiovascular, respiratory, lymphatic, gastrointestinal, musculoskeletal, dermatological, and neurological
- Urine pregnancy testing for women of childbearing potential

Demographics, including race & ethnicity, data will be collected for all enrolled patients.

9.2.2.1.2. Initial Treatment Visit (Month 0) and Every 4 Months Including End of Study Visit

Pre-injection assessments will be performed prior to administration of each dose of TEGSEDI at study visits. Pre-injection assessments will include:

- Abbreviated Physical examination, i.e. weight and vital signs, general appearance, dermatological, respiratory, cardiovascular and abdomen. (except Month 0 if they were performed at Screening)
- Concomitant Medications
- Laboratory testing
    - IgE, IgG, IgM (see Annex 1)
    - Inflammatory markers: C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), interferon α (IFN- α), IFN-β, Chemokines (Macrophage inflammatory protein (MIP)-1a and membrane cofactor protein (MCP)-1), Granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin (IL)-1α, IL-1β, IL-6, IL-8, IL-12. Tumor necrosis factor – α (TNF- α) (see Annex 1)
    - ADA sampling at Month 0 visit pre-injection first dose and at End of Study visit, pre-injection
    - Urine pregnancy testing for women of childbearing potential
    - Additional blood samples will be drawn and stored for possible future non-genetic testing in this study.
- Adverse events since last study visit

Post injection assessments will be made at 1 hour ± 15 minutes; 2 hour ± 15 minutes; 4 hour ± 30 minutes; 8 hour ± 30 minutes and 20-30 hours following injection of TEGSEDI. Post-injection assessments will include:

- Vital signs
- Laboratory testing
    - IgE, IgG, IgM (see Annex 1)
    - Inflammatory markers: CRP, ESR, IFN-α, IFN-β, Chemokines (MIP-1a and MCP-1), GM-CSF, IL-1α, IL-1β, IL-6, IL-8, IL-12, TNF- α (see Annex 1)
    - Additional blood samples will be drawn and stored for possible future non-genetic testing in this study
- Adverse events post injection at study visit
- The ADA sample is only drawn post injection, at the 20-30 hour time point, in the event of a hypersensitivity reaction

In addition to these study visits, the patient will be monitored according to the applicable product label.

9.2.2.1.3. End of Study Visit

Patients who plan to continue TEGSEDI treatment at the end of the study will complete an End of Study visit. Assessments as in Section 9.2.2.1.2. will be undertaken and additionally blood for ADA will be taken.

9.2.2.1.4. Early Termination Visit

Patients who discontinue TEGSEDI treatment, for reasons other than hypersensitivity, will have an ET visit as soon as possible after the decision to end treatment and will return to the study center for a Post-Treatment Follow-up visit 8 weeks after their last administration of TEGSEDI. During the visits the following procedures will be completed:

- Abbreviated physical examination including weight, vital signs and an examination of general appearance, dermatological, respiratory, cardiovascular and abdomen.
- Laboratory testing
    - IgE, IgG, IgM (see Annex 1)
    - Inflammatory markers: CRP, ESR, IFN-α, IFN-β, Chemokines (MIP-1a and MCP-1), GM-CSF, IL-1α, IL-1β, IL-6, IL-8, IL-12, TNF- α (see Annex 1)
    - Additional blood samples will be drawn and stored for possible future non-genetic testing in this study
- Adverse events since last study visit
- Concomitant medication
- Urine pregnancy testing for women of childbearing potential
- ADA if not taken at End of Study visit

9.2.2.1.5. ADA Testing

All patients will have a minimum of 2 ADA samples taken. One sample will be taken at the first on-study (Month 0) clinic visit prior to the scheduled dose of TEGSEDI, and the other sample will be taken at the end of patient's participation in the study prior to the scheduled dose of TEGSEDI if the patient is still on treatment. Patients who develop a hypersensitivity reaction during the study will have additional blood samples taken for ADA testing on the day of the hypersensitivity reaction at the 20-30 hour time point and again at their Post-Treatment Follow-up visits for 12 months or when one of the Milestones for Study End is triggered, whichever is earliest. All patients who have a hypersensitivity reaction will be followed for a minimum of 4 months.

9.2.2.1.6. Contraception Requirements

For the purposes of this study, women of childbearing potential are defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Post-menopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the post-menopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post hysterectomy

All male patients and women of childbearing potential must refrain from sperm/egg donation and either be abstinent* or, if engaged in sexual relations, practice effective contraception from the time of signing the ICF until at least 13 weeks after their last dose of TEGSEDI administration. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the patient's last dose of TEGSEDI administration.

For the purposes of the study, effective contraception is defined as follows:

- For male patients: effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the use of condoms together with spermicidal foam/gel/film/ cream/suppository. Male patients must also encourage their female partner to use effective contraception from the time of signing the informed consent until 13 weeks after the patient's last dose of study treatment.
- For a female partner of a male patient: effective contraception includes surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or barrier methods (female condom**, diaphragm, sponge, cervical cap) together with spermicidal foam/gel/film/cream/suppository. Male patients with partners that are pregnant must use condoms to ensure that the fetus is not exposed to TEGSEDI.
- For female patients: effective contraception is using one or more of the following acceptable methods of contraception: surgical sterilization (e.g., bilateral tubal ligation), hormonal contraception, intrauterine contraception/device, or any two barrier methods (a combination of male or female condom** with diaphragm, sponge, or cervical cap) together with spermicidal foam/gel/film/cream/suppository.

Note:

*Abstinence is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial and withdrawal are not acceptable methods of contraception.

**A female condom and a male condom should not be used together as friction between the two can result in either product failing.

9.2.3. Schedule of Assessments

9.2.3.1. Physical Examinations and Vital Signs

Physical examinations and vital signs will be performed as indicated in the Study Schedule. A full physical examination will be performed at the screening visit and an abbreviated physical examination will be performed at each subsequent study visit, prior to the TEGSEDI injection.

The full physical examination comprises a routine medical examination and a neurological exam. The following body systems will be examined: HEENT, cardiovascular, respiratory, lymphatic, gastrointestinal, musculoskeletal, dermatological, and neurological.

An abbreviated physical examination consists of an examination of general appearance, dermatological, respiratory, cardiovascular and abdomen.

The physical examination and weight do not need to be completed at the Month 0 study visit if they were performed at Screening.

Vital signs will include blood pressure, pulse rate, respiratory rate and body temperature. Blood pressure and pulse rate will be recorded after the patient has been in a sitting position for at least 5 minutes. Semi-supine systolic and diastolic blood pressure should always be measured on the same arm (preferentially on the left arm). Height will be measured at Screening only.

9.2.3.2. Laboratory Assessments

Laboratory analyte samples will be collected and processed throughout the study at the central laboratory. ESR will be processed at the local laboratory. During their study visit, IgE, IgG, IgM, and inflammatory marker testing will occur at the time points noted in Table 1 and Table 2.

Samples for ADA will be taken at the Month 0 visit prior to TEGSEDI injection and at the last visit in all patients. If the patient experiences a hypersensitivity reaction within 24 hours of any dose of TEGSEDI administration during a study visit, the patient will have a further ADA test at the 20-30 hour time point and at their Post-Treatment Follow-up visits for 12 months or when one of the Milestones for Study End is triggered, whichever is earliest. Additional blood samples will be drawn and stored for possible future non-genetic testing in this study. For example, future tests may measure biomarkers or other safety parameters. These blood samples will be stored during the study and destroyed upon completion of the final study report.

9.2.4. Treatment of Patients

9.2.4.1. TEGSEDI Administration

US

Please reference the USPI Section 2 – Dosage and Administration, Medication Guide and Instructions for Use (TEGSEDI USPI).

Canada

Please reference the CPM Section 2- Dosage and Administration (TEGSEDI USPI).

9.2.4.2. Treatment Precautions

US

Please reference the USPI Section 4 - Contraindication, Section 5 -Warnings and Precautions, Section 6 - Adverse Reactions, Section 7 - Drug Interactions, and Section 8 - Use in Specific Populations. Investigator and patients should refer to the USPI medication guide (TEGSEDI USPI).

Canada

Please refer to the CPM Section 2- Contraindications, Section 7- Warnings and Precautions, Section 8- Adverse Reactions, Section 9- Drug Interactions and Section 7.1- Use in Special Populations (TEGSEDI CPM).

9.2.4.3. Safety Monitoring Rules

US

Please refer to the USPI for safety monitoring (TEGSEDI USPI).

Canada

Please refer to the CPM for safety monitoring (TEGSEDI CPM).

9.2.4.4. Discontinuation of Treatment

A patient may discontinue treatment for any of the following:

- The patient withdraws consent to continue treatment.
- The patient experiences an AE that in the opinion of the investigator necessitates discontinuation of TEGSEDI.
- In the opinion of the investigator, it is in the best interest of the patient that the patient is withdrawn from treatment.
- The patient develops laboratory test abnormalities that meet any of the treatment discontinuation requirements listed in USPI Section 2.4 (TEGSEDI USPI) and CPM Section 4.2 (TEGSEDI CPM).

The reason for discontinuation from treatment must be recorded in the eCRF and source documentation.

9.2.4.5. Withdrawal of Patients From the Study

Patients must be withdrawn from the study for any of the following:

- Patient withdraws consent
- Patient is unwilling or unable to comply with the required testing outlined in the USPI (TEGSEDI USPI) or CPM (TEGSEDI CPM) or the study visits

Other reasons for withdrawal of patients from the study might include:

- At the discretion of the investigator for medical reasons
- At the discretion of the Sponsor for medical reasons or noncompliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the eCRF.

Any patient who withdraws consent to participate in the study will be removed from further study data collection immediately upon the date of request. These patients should be encouraged to complete the ET study procedures and observations at the time of withdrawal.

For patients withdrawn for reasons other than withdrawal of consent, every effort should be made to complete the ET visit and observations at the time of withdrawal and ideally within 2 weeks from the last dose of TEGSEDI.

9.2.4.6. Concomitant Therapy

The use of concomitant therapies defined below must be recorded on the patient's eCRF. AEs related to administration of these therapies must also be documented on the appropriate eCRF.

A concomitant therapy is any non-protocol specified drug or substance (including over-the-counter medications, herbal medications, and vitamin supplements) administered from the time of consent until the End of Study visit.

9.2.4.7. Treatment Adherence

Compliance with treatment administration during the study visits will be monitored and recorded in the eCRF by study center staff. Compliance with treatment administration between study visits will be reported by the patients and recorded in the eCRF.

9.2.4.8. Study Termination

The Sponsor or designee reserves the right to terminate the study. The investigator reserves the right to terminate their participation in the study, according to the terms of the site contract. The investigator/Sponsor or designee should notify the independent ethics committee (IEC)/institutional review board (IRB) in writing of the trial's completion or ET.

9.3. Data Sources

Data will be collected prospectively into the eCRF at study visits.

9.4. Study Size

The study will enroll at least 75 patients.

A sample size of 75 patients will allow 95% probability to detect an AE occurring as infrequently as 4% of patients.

9.5. Data Management

9.5.1. Study Documentation and Storage

An eCRF utilizing an electronic data capture (EDC) application will be used for this study.

The investigator should ensure that all appropriately qualified persons to whom he/she has delegated trial duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, imaging, and correspondence.

The investigator and study center staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with International Council For Harmonization (ICH) Good Clinical Practice (GCP), suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable regulatory authorities. Elements should include:

- Patient files containing, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor or designee

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or designee and the investigator. Should the investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor or designee.

9.6. Data Analysis

9.6.1. Analysis Populations

Evaluable Set: All patients who have at least one post-dose assessment.

9.6.2. Definition of Baseline

The overall baseline is defined as the last non-missing assessment prior to the Month 0 dose of TEGSEDI.

On days when serial assessments of vital signs and cytokines/inflammatory markers are performed, the pre-dose values will be used as baseline for the analysis of these parameters.

9.6.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics for all patients who receive TEGSEDI. All patients enrolled will be included in a summary of patient disposition.

9.6.4. Safety Analysis

Patient incidence rates of all AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC), and by MedDRA preferred term (PT). Narratives of deaths, all discontinuations, serious AEs, pregnancies and AEs of special interest (AESI) will also be provided.

All treatment emergent AEs, all treatment emergent AEs potentially related to TEGSEDI, all treatment emergent serious AEs, and all treatment emergent serious AEs potentially related to TEGSEDI will be summarized.

Incidence (95% confidence interval) of AEs occurring within 1 day of TEGSEDI administration, and time to onset from TEGSEDI injection and duration of these AEs will be summarized by visit and overall in any visit. The rates of AEs during the 1-day visit occurring after preventive measures will also be summarized. Resolution time with and without treatment administered for the AEs will be summarized.

For each study visit on treatment, the result and change from pre-dose baseline in vital signs (body temperature, heart rate, respiratory rate, and systolic, diastolic blood pressure) and cytokines/inflammatory markers will be summarized using descriptive statistics for all patients in the Evaluable Set and by presence/absence of AEs within 1 day of TEGSEDI administration.

9.6.5. Interim Analyses and Early Stopping Guidelines

No formal interim analysis is planned; although data related to disposition, exposure, and safety considerations will be reported on an annual basis.

9.7. Quality Control

9.7.1. Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the trial (e.g., eCRFs and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor or designee is responsible for inspecting the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the eCRFs.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor or designee. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or study center notifications will be sent to the study center for completion and return to Sponsor or designee.

The investigator will sign and date the indicated places on the case report form. These signatures will indicate that the investigator inspected or reviewed the data on the case report form, the data queries, and the study center notifications, and agrees with the content.

9.7.2. Language

E-CRFs must be completed in English. Generic names and trade names are acceptable for concomitant medications. Combination medications should be recorded using their trade name.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

9.7.3. Inspection and Auditing Procedures

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department (or designees). Inspection of study center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the trial conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

9.7.4. Source Document Maintenance

Source documents contain the results of original observations and activities of a clinical investigation. Source documents include, but are not limited to, medical records (progress notes), computer printouts, screening logs, and recorded data from automated instruments.

All source documents from this study will be maintained by the site and made available for inspection by authorized persons. The original signed ICF for each patient shall be filed with records kept by the site and a copy shall be given to the patient.

9.7.5. Record Maintenance

Records will be retained in accordance with the applicable local regulations. All essential study documents, including records of patients, source documents, signed ICFs, and eCRFs, must be kept by the investigator for at least 15 years from study termination/completion or until instructed in writing by the Sponsor that records may be destroyed or forwarded to the Sponsor . The Investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations

and data generated during this study. Such documentation is subject to inspection by the Sponsor, its representatives, and regulatory authorities.

If an investigator moves, withdraws from the study, or retires, the responsibility for maintaining the records must be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the Sponsor.

9.8. Limitations of the Research Methods

Patient-selection bias is a consideration, as motivation to consent to join the study can vary between patients for different reasons. If prescribers and patients are not willing to participate, selection bias may occur, resulting in limited generalizability of the results. However, as TEGSEDI ordering and dispensing data will be available to the Sponsor, all patients who will receive TEGSEDI treatment will be known at the sites selected to participate in this study. All eligible patients at the study sites who have received less than 9 doses will be invited to participate minimizing the selection bias.

Patients may be enrolled in the study if they have initiated treatment with commercial TEGSEDI prior to study enrollment and received less than 9 doses. This approach allows patients who began treatment prior to the launch of the study to be included in order to evaluate as large an exposure population as possible. The limitation of this approach is that patients who initiate TEGSEDI and discontinue shortly thereafter may not be included and could differ in demographic characteristics from those who become enrolled, i.e., survivor bias. Also, any AESI that occur shortly after treatment initiation may be underrepresented in the study population. Another limitation of this approach is that patients will have had TEGSEDI treatment prior to their baseline testing; therefore, it will not be possible to evaluate the change in test results from one study visit compared to prior to receiving the patient's initial dose of TEGSEDI.

9.9. Other Aspects

9.9.1. Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor or designee. Agreement from the investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the trial. The investigators **must** send a copy of the approval letter from the IEC/IRB to the Sponsor or designee.

9.9.2. Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the Informed Consent document.

10. Protection of Human Patients

10.1. Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor or designee.

Before a patient's participation in the trial, the investigator is responsible for obtaining written informed consent from the patient or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study before any data are collected for the study. The patient or legally acceptable representative must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the ICF should be signed and personally dated by the patient or a legally acceptable representative and by the person who conducted the informed consent discussion (not necessarily the investigator). The original signed ICF should be retained in the Investigator Site File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient or legally acceptable representative.

10.2. Ethical Conduct of the Study

All applicable regulations and guidelines of current GCP as well as the demands of national drug and data protection laws and other applicable regulatory requirements must be followed.

10.3. Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed ICFs, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and ICF must be received by the Sponsor or designee before recruitment of patients into the study. A copy of the written approval of any other items/materials that must be approved by the study center or IEC/IRB must also be received by the Sponsor or designee before recruitment of patients into the study.

The investigator must submit to and, where necessary, obtain approval from the IEC/IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP. The investigator should also notify the IEC/IRB of Serious Adverse Events (SAEs) occurring at the study center and other AE reports received from the Sponsor or designee, in accordance with local procedures.

The investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study.

10.4. Patient Confidentiality

The investigator must ensure that the patient's confidentiality is maintained. On the eCRFs or other documents submitted to the Sponsor or designee, patients should be identified by initials (if permitted by local law) and a patient identification number only. Documents that are not for submission to the Sponsor or designee (e.g., signed ICFs) should be kept in strict confidence by the investigator.

In compliance with Federal and local regulations/ICH GCP Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

11. Management and Reporting of Adverse Events/Serious Adverse Events/Adverse Events of Special Interest

11.1. Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor or designee.

11.2. Regulatory Requirements

The Sponsor or designee is responsible for regulatory submissions and reporting of AEs, SAEs, AESIs per the ICH guidelines E2A and ICH GCP. Country specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards (IRBs)/IECs will be notified of any SAE according to applicable regulations.

In addition to the investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of all reported SAEs, AESIs, and determine if there is a reasonable possibility that TEGSEDI is causally related to a reported SAE. While the Sponsor may upgrade an investigator's decision, it is not permissible to downgrade the investigator's opinion for the purposes of determining whether the SAE meets the criteria of an Expedited Report.

The Reference Safety Information for this study will be the USPI, CPM or the respective country label as applicable.

11.3. Definitions

11.3.1. Adverse Event

An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of medicinal product, whether or not the AE is considered related to the medicinal product.

An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., electrocardiogram, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from TEGSEDI
- AEs that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

11.3.2. Adverse Drug Reaction and Unexpected Suspected Adverse Drug Reaction

Adverse Drug Reaction (ADR)

In the clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not have been established, ADR is defined as follows:

All noxious and unintended responses to a medicinal product related to any dose should be considered ADRs.

The phrase "responses to a medicinal product" means that a causal relationship between the medicinal product and the AE has been determined by the Sponsor as at least a reasonable possibility, i.e., the relationship cannot be ruled out.

11.3.3. Serious Adverse Event

A SAE is any AE that in the view of either the investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life threatening: that is, poses an immediate risk of death at the time of the event
  An AE or suspected adverse reaction is considered “life-threatening” if, in the view of either the investigator or Sponsor, its occurrence places the patient 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
- Requires inpatient hospitalization or prolongation of existing hospitalization
  Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

11.4. Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition has worsened during study treatment. The investigator should always group signs and symptoms into a single term that constitutes a single unifying diagnosis if possible. Before a diagnosis is confirmed, all symptoms should be reported as separate AEs.

11.4.1. Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements, all SAEs, AESIs, (regardless of their relationship to TEGSEDI) should be reported to the Sponsor or designee within 24 hours of the study center's first knowledge of the event. The collection of SAEs, AESIs, will begin after the patient signs the ICF and stop at the end of the patient's End of Study visit. When the investigator is reporting by telephone, it is important to speak to someone in person versus leaving a message. SAEs should be reported using an electronic SAE submission form whenever possible. In situations where the electronic SAE submission is unavailable, an Initial SAE Form should be completed, and a copy should be faxed or emailed to the Sponsor or designee. The SAE reporting instruction, including the fax number and email address can be found in the study safety form completion guidelines.

Detailed information should be actively sought and included on Follow-Up SAE Forms as soon as additional information becomes available. All SAEs will be followed until resolution. SAEs that remain ongoing past the patient's last protocol-specified visit will be evaluated by the investigator and Sponsor. If the investigator and Sponsor agree the patient's condition is unlikely to resolve, the investigator and Sponsor will determine the follow-up requirement.

11.4.2. Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the ICF and will stop at the end of the patient's end-of-study visit. The investigator will monitor each patient closely and record all observed or volunteered AEs (Serious and Non-Serious) on the AE eCRF within 24 hours.

11.4.3. Evaluation of Adverse Events (Serious and Non-Serious)

The investigator's opinion of the following should be documented on the AE eCRF:

11.4.3.1. Relationship to TEGSEDI

The event's relationship to TEGSEDI is characterized by one of the following:

- **Related:** There is clear evidence that the event is related to the use of TEGSEDI, e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and TEGSEDI administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to TEGSEDI administration and/or exposure suggests that a causal relationship is unlikely (For reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the investigator believes no relationship exists between the event and TEGSEDI

11.4.3.2. Severity

The severity of AEs and SAEs will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

11.4.3.3. Action Taken with TEGSEDI

Action taken with TEGSEDI due to the event is characterized by one of the following.

- **None:** No changes were made to TEGSEDI administration
- **Not Applicable:** SAE/AE was reported prior to TEGSEDI administration
- **Permanently Discontinued:** TEGSEDI was discontinued and not restarted
- **Temporarily Interrupted, Restarted – Same Dose:** Dosing and/or dosing frequency was temporarily interrupted/changed or delayed due to the AE and restarted at the same dose

11.4.3.4. Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the AE eCRF. Treatment should also be recorded on the concomitant treatment or ancillary procedures eCRF, as appropriate.

11.4.3.5. Outcome of the Adverse Event

If the event is a non-serious AE, then the event's outcome is characterized by one of the following:

- **AE Persists:** Patient terminates from the trial and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity (if applicable):** AE severity changed

If the event is an SAE, then the event's outcome is characterized by one of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Recovered with Sequelae:** The signs/symptoms of the reported SAE have improved but not completely resolved, and a new baseline for the patient is established since full recovery is not expected
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)
- **Unknown:** The outcome of the reported SAE is not available, e.g., patient is lost to follow-up

11.4.3.6. Follow-up of Adverse Event

Investigator Follow-Up

During the study period, the investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs, AESIs, considered to be related to TEGSEDI or related to study procedures until a final outcome can be reported.

Resolution of AE (with dates) should be documented on the AE eCRF and in the patient's medical record.

The investigator should follow up or support the Sponsor's effort to follow up with all pregnancies reported during the study from either the study patient or the female partner of male study patient until pregnancy outcome is available. If the pregnancy results in the birth of a child, the mother and infant may continue to be followed for up to 8 weeks after birth.

Sponsor Follow-Up

For SAEs, AESI and pregnancy cases in any patient who has completed or terminated study, the Sponsor or a designee should follow-up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports, pregnancy status/outcome, new born status, etc.) in order to perform an independent medical assessment of the reported case.

11.5. Procedures for Handling Special Situations

11.5.1. Abnormalities of Laboratory Tests

Clinically significant abnormal laboratory test results may, in the opinion of the investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically significant abnormalities will be monitored by the investigator until the parameter returns to its baseline value or until agreement is reached between the investigator and Sponsor. Laboratory abnormalities deemed not clinically significant (NCS) by the investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the investigator should not be deemed NCS.

The investigator is responsible for reviewing all laboratory reports. The clinical laboratory reports will serve as source documents and should include the investigator's assessment of clinical significance of out of range/abnormal laboratory values. If the lab results are electronically received, the investigator should assess clinical significance and document the assessment in the patient medical record.

11.5.2. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the study center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

11.5.3. Dosing Errors

TEGSEDI treatment errors occurring during the study visit (including overdose, underdose, and administration error) should be documented as Protocol Deviations. A brief description should be

provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing eCRF. If the patient takes a dose of TEGSEDI that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 11.4.

Dosing errors occurring between study visits will be reported by the patient and recorded in the eCRF; however, these dosing errors will not be considered a protocol deviation.

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of TEGSEDI should be recorded on the AE eCRF. If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

Should an overdose occur, the investigator or designee should contact the Sponsor or designee within 24 hours.

11.5.4. Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners or refrain from sexual activity.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the study center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee within 24 hours of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported on Follow-up Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including follow-up), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with TEGSEDI. However, the patient will be encouraged to complete the post-treatment follow-up period of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the study center and Sponsor may require access to the mother's and infant's medical records for an additional 8 weeks after birth.

Male patients: The progress of the pregnancy in a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, additional follow-up information may be requested for the mother and infant. Follow-up will be performed to the extent permitted by applicable regulations and privacy considerations.

12. Plans for Disseminating and Communicating Study Results

The results of this study will be summarized in a study report that, after review and approval by the sponsor, will be communicated to the US Food and Drug Administration (FDA) and Health Canada within the agreed timeframe.

13. References

Plante-Bordeneuve, V. (2014). Update in the diagnosis and management of transthyretin familial amyloid polyneuropathy. J Neurol, 261(6), 1227-1233. doi: 10.1007/s00415-014-7373-0

Tegsedi (inotersen) [US Prescribing Information]. Boston, MA. Akcea Therapeutics, Inc. 2018. Available from:
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https://www.cadth.ca/sites/default/files/cdr/monograph/Tegsedi-product-monograph.pdf

14. Investigator Protocol Signature Page

Protocol Signature Page

Protocol Number:	TEG4004
Protocol Title:	A Phase 4 Safety Study Assessing the Adverse Events Occurring Within One Day of TEGSEDI Administration in Patients with Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis (hATTR-PN)
Version:	Final Protocol (v2.0)
Date:	8 May 2020

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "*A Phase 4 Safety Study Assessing the Adverse Events Occurring Within One Day of TEGSEDI Administration in Patients with Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis (hATTR-PN)"*, dated 8 May 2020, and agree to conduct the study as described herein.

I agree to comply with the International Council For Harmonization Guideline on Good Clinical Practice.
I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Akcea Therapeutics, Inc.

Investigator's Signature

Investigator's Name *(please print)* Date (DD Month YYYY)

STATISTICAL ANALYSIS PLAN

Protocol Number: TEG4004
TEGSEDI Phase 4 AE Assessment

Sponsor: Akcea Therapeutics, Inc.

[redacted]

[redacted]

Statistical Analysis Plan (SAP) Version 2.0/ Date: 06 October 2023

[redacted]

[redacted]

[redacted]

Table of Contents

1 List Of Abbreviations And Definitions Of Terms

Term	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
ATTR	Transthyretin-mediated amyloidosis
CI	Confidence interval
CPM	Canadian Product Monograph
CRP	C-reactive Protein
eCRF	Electronic case report form
EDC	Electronic data capture
ESR	Erythrocyte sedimentation rate
ET	Early termination
GM-CSF	Granulocyte-macrophage colony stimulating factor
hATTR-PN	Polyneuropathy of hereditary transthyretin-mediated amyloidosis
ICF	Informed consent form
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
MCP	Membrane cofactor protein
MedDRA	Medical Dictionary for Regulatory Activities
MIP	Macrophage inflammatory protein
PT	Preferred term
SAE	Serious adverse event

Term	Definition
SD	Standard deviation
SE	Standard error
SOC	System organ class
TEAE	Treatment emergent adverse event
TNF-α	Tumor necrosis factor-alpha
TTR	Transthyretin
US	United States
USPI	United States Prescribing Information

2 Introduction

This document outlines the statistical methods to be implemented within the scope of Protocol TEG4004: A Phase 4 Safety Study Assessing the Adverse Events Occurring Within 24 hours of TEGSEDI Administration in Patients with Polyneuropathy of Hereditary Transthyretin-mediated Amyloidosis (hATTR-PN) version 3.0, 23 May 2023.

3 Study Objectives

The objective of the study is to characterize adverse events (AEs) occurring within 24 hours of TEGSEDI administration in adult patients with hATTR-PN and in individual patients with respect to time course of AE onset, vital sign changes, preventive measures, treatment required, risk factors, and subsequent adverse outcomes.

The endpoints of the study are AEs occurring within the first 24 hours of TEGSEDI administration at study visits, changes in vital signs and cytokines and inflammatory markers 24-hour post-injection with additional assessments of:

- Preventive measures used prior to the injection
- Treatment of AEs post 24 hour injection of TEGSEDI at study visits
- Identification of risk factors for AEs occurring within the first 24 hours of TEGSEDI administration at study visits
- Correlation of subsequent adverse outcomes

4 Overall Study Design

An open-label, phase 4, multicenter safety study in at least 75 patients with hATTR-PN prescribed 284 mg of TEGSEDI in the US (United States) and Canada.

5 Selection of Study Population

This study will be conducted at multiple study centers in the US and Canada. TEGSEDI will be prescribed to the patient by the healthcare provider prior to enrolling in this study. TEGSEDI will be administered from approved packaged and labeled packs. Used syringes will be disposed of per the product's instructions for use.

5.1 Patient Inclusion Criteria

To be eligible to enroll in this study, patients must meet the following eligibility criteria:

1. Satisfy one of the following:

    a. US Patients: Adult patients (≥ 18 years old) diagnosed with hATTR-PN and prescribed TEGSEDI according to the USPI (United States Prescribing Information)

    b. Canadian Patients: Adult patients (≥ 18 years old) diagnosed with stage 1 or stage 2 hATTR-PN and prescribed TEGSEDI according to the CPM (Canadian Product Monograph) (TEGSEDI CPM)

2. Must have given written informed consent for participation in this study

3. Must provide access to their previous medical records

4. Are about to initiate or have initiated treatment with TEGSEDI

5. Be willing to complete required testing and report any AEs and/or changes in medications

6. Satisfy one of the following:

    a. Females: Non-pregnant and non-lactating; abstinent, or if engaged in sexual relations and of childbearing potential, patient is using an acceptable contraceptive method from time of signing the ICF (Informed consent form) until 13 weeks after the last dose of TEGSEDI administration

    b. Males: Abstinent or if engaged in sexual relations with a female of childbearing potential, patient is utilizing an acceptable contraceptive method from the time of signing the ICF until 13 weeks after the last dose of TEGSEDI administration

Notes:

a) If a patient has started TEGSEDI and then stops and restarts at a later date, they can be enrolled in the study upon re-starting if they meet the inclusion criteria above

b) Patients may participate in both studies TEG4004 and TEG4001

c) Patients with any stage of disease can be enrolled provided they meet the inclusion criteria specified above

d) Patients with a history of prior liver transplant may be enrolled

e) Patients with transplanted liver with amyloidogenic mutation (associated with amyloid formation) are considered to have ATTR (Transthyretin-mediated amyloidosis) and therefore these patients can enter the study

5.2 Patient Exclusion Criteria

None

6 Schedule of Assessments

The study will consist of a Screening/Qualification period, a Treatment period and Post-Treatment Follow-up period as per Table 1 and Table 2.

The Screening/Qualification period is defined as the interval of time from the signing of informed consent until the first on-study dose of TEGSEDI.

The treatment period begins at the time of the first on study TEGSEDI administration and the end of treatment period is defined as follows:

- For patients who complete treatment with TEGSEDI on study, the last observation in the treatment period will be the 20-30 hour post-injection visit of the last administered TEGSEDI dose on study. If the time of the last TEGSEDI dose is missing, or the time of the assessment in question is missing, the assessment will be included in the treatment period if it occurred on the same day or one day subsequent to the last dose of TEGSEDI

- For patients who discontinue TEGSEDI or withdraw from the study and continue with TEGSEDI outside the study, the early termination (ET) visit will serve as the end of the treatment period

For patients who discontinue TEGSEDI, the post treatment follow-up period begins after the end of the treatment period, as defined above, and ends with the last available data collected per the clinical trial protocol. Data for the post-treatment follow-up period will be analyzed and summarized separately for patients who develop a hypersensitivity reaction.

Table 1. Schedule of Assessments for Patients Who do not Develop a Hypersensitivity Reaction

Study Periods	Screening[1]	Treatment Period					Post-Treatment Follow-up (Patients who discontinued TEGSEDI) 8-weeks (+/- 1 week)[3]
		Initial Treatment Visit (Month 0) and Every 4 months Visit (+/- 2 weeks) for 12 months		End of Study Visit		Early Termination Visit[3]	
Procedures and Testing	-2 to 0 weeks prior to first study injection	Pre-injection	Post injection 1-hour ± 15 mins 2-hour ± 15 mins 4-hour ± 30 mins 8-hour ± 30 mins 20-30 hours	Pre-injection	Post injection 1-hour ± 15 mins 2-hour ± 15 mins 4-hour ± 30 mins 8-hour ± 30 mins 20-30 hours		
Informed Consent	X						
Demographics	X						
Medical History	X						
Full Physical Examination[7]	X						
Abbreviated Physical Examination[7]		X[2]		X		X	X
Height	X						
Weight	X	X[2]		X		X	X
Vital Signs	X	X	X	X	X	X	X
Urine Pregnancy Testing	X[4]	X[4]		X[4]		X[4]	
IgE, IgG, IgM		X	X	X	X	X	

Inflammatory Markers		X	X	X	X	X	
Samples for Possible Future Testing		X	X	X	X	X	X
ADA		X[5]		X		X[6]	
Adverse Events Post Injection at Study Visit			X		X		
Concomitant Medications	X	X		X		X	X

1. The Screening visit and the Month 0 visit can occur on the same day.

2. The Physical Examination and Weight does not need to be completed at the Month 0 study visit if they were performed during Screening.

3. If the patient withdraws from the study, the patient should return for an ET visit within 2 weeks after the decision to withdraw from the study. If the patient discontinues TEGSEDI, they should have an ET visit within 2 weeks of the decision to end treatment and one follow-up visit 8-weeks (± 1 week) after their last dose of TEGSEDI. If the ET and the 8 week follow up visit are within 2 weeks of each other, the assessments can be combined

4. Urine pregnancy testing is only for women of childbearing potential as defined in the protocol.

5. The baseline ADA sample is only drawn at the Month 0 visit.

6. An ADA sample will only be taken at the Early Termination visit if the patient does not have an End of Study visit.

7. Full physical examination to be undertaken at screening and abbreviated physical examination to be undertaken at initial treatment visit, end of study visit, early termination visit and post-treatment follow-up as indicated to assess changes from screening.

Table 2. Schedule of Assessments for Patients Who Develop a Hypersensitivity Reaction

Study Periods	Screening[1]	Treatment Period			Post-Treatment Follow-up (Patients who discontinued TEGSEDI) 8-weeks (+/- 1 week) 4-month (+/- 2 weeks) 8-month[3] (+/- 2 weeks) 12-month[3] (+/- 2 weeks) Post-Treatment visits
		Initial Treatment Visit (Month 0) and Every 4 months Visit (+/- 2 weeks)		Early Termination Visit	
Procedures and Testing	-2 to 0 weeks prior to first study injection	Pre-injection	Post injection 1-hour ± 15 mins 2-hour ± 15 mins 4-hour ± 30 mins 8-hour ± 30 mins 20-30 hours		
Informed Consent	X				
Demographics	X				
Medical History	X				
Full Physical Examination[7]	X				
Abbreviated Physical Examination[7]		X[2]		X	X
Height	X				
Weight	X	X[2]		X	X
Vital Signs	X	X	X	X	X
Urine Pregnancy Testing	X[4]	X[4]		X[4]	
IgE, IgG, IgM		X	X	X	
Inflammatory Markers		X	X	X	

Samples for Possible Future Testing		X	X	X	X
ADA		X[5]	X[6]	X	X[6]
Adverse Events Post Injection at Study Visit			X		
Concomitant Medications	X	X		X	X

1. The Screening visit and the Month 0 visit can occur on the same day.

2. The Physical Examination and Weight does not need to be completed at the Month 0 study visit if they were performed during Screening.

3. The 8 month and 12 month follow-up visits will occur only if a Milestone for Study End has not been triggered.

4. Urine pregnancy testing is only for women of childbearing potential as defined in the protocol.

5. The baseline ADA sample is only drawn at the Month 0 visit. The ADA sample is only drawn post injection, at the 20-30 hour time point, in the event of a hypersensitivity reaction.

6. A patient who develops a hypersensitivity reaction during the study will have additional blood samples taken for ADA testing on the day of the hypersensitivity reaction at the 20-30 hour time point and again at their Post-Treatment Follow-up visits for 12 months or when a Milestone for Study End has been met, whichever is earliest. All patients who have a hypersensitivity reaction will be followed for a minimum of 4 months.

7. Full physical examination to be undertaken at screening and abbreviated physical examination to be undertaken at initial treatment visit, end of study visit, early termination visit and post-treatment follow-up as indicated to assess changes from screening.

7 Outcome Variables

Outcomes are measured by reported AEs, changes in vital signs and cytokines/inflammatory markers over a 24 hour interval post-injection of TEGSEDI.

8 Statistical Methods

For this phase IV study, only descriptive analyses will be provided. No hypothesis testing will be done. However, 95% confidence intervals will be provided where indicated using the Clopper-Pearson method. Descriptive statistics will comprise the number of observations (n), mean, standard deviation (SD), standard error (SE) of mean, median, minimum, and maximum for continuous variables, and n and percent for categorical variables.

The overall study baseline is defined as the last available observation prior to the first on study TEGSEDI administration.

For each study visit on treatment, changes in vital signs and cytokines/inflammatory markers post-injection of TEGSEDI are calculated relative to the pre-injection values, not relative to the overall baseline values. For visit level summarization, analyses will be performed by the study visit using data as collected in the electronic case report form (eCRF).

8.1 Analysis Populations

The safety set includes all patients who received at least one dose of TEGSEDI while enrolled in this study protocol. The safety set will be used in the summary of demographics, medical history, patient disposition, AEs, concomitant medications and ADA (Anti-drug antibody).

The evaluable set includes patients in the safety set having at least one post-dose assessment. The evaluable set will be used in the summaries of AEs by study visit and vital signs and cytokines/inflammatory markers recorded over a 24-hour period.

Listings will be run on the safety set.

8.2 Description of Statistical Analyses

8.2.1 Enrollment Disposition and Baseline Information

Summaries using descriptive statistics using the safety set will be provided for:

- Patient disposition

- Demographics and other baseline characteristics
- Medical history

Patient disposition will be presented by counts and percentages for the completion and discontinuation of the study treatment and for completion of the post-treatment follow-up phase. Medical history will be coded starting with MedDRA (Medical Dictionary for Regulatory Activities) version 22.1 or higher and coding will be re-run periodically using the most recent version of MedDRA. Medical history will be summarized by System Organ Class (SOC) and Preferred Term (PT).

8.2.2 Adverse Events

8.2.2.1 Treatment-emergent Adverse Events (TEAEs)

TEAEs are defined as AEs with an onset date/time on or after the date/time of the first on study administration of TEGSEDI. Related TEAEs are TEAEs with a reported relationship of "Possible" or "Related". TEAEs with a missing relationship will also be counted as Related. Serious Adverse Events (SAEs) will be indicated as such in the eCRF and can be defined as treatment emergent, based on when the SAE initiated. AEs will be summarized using the safety set for the treatment period among both patients who develop a hypersensitivity reaction and those patients who do not develop a hypersensitivity reaction.

TEAEs will be summarized as follows:

- Overview of Treatment-emergent AEs
- Treatment-emergent AEs by System Organ Class and Preferred Term
- Treatment-emergent AEs by System Organ Class, Preferred Term and Severity
- Treatment-emergent AEs Related to TEGSEDI by System Organ Class and Preferred Term
- Treatment-emergent AEs Related to TEGSEDI by System Organ Class, Preferred Term and Severity
- Treatment-emergent Adverse Events of Special Interest (AESI) by System Organ Class and Preferred Term

- Treatment-emergent AESIs by System Organ Class, Preferred Term and Severity
- Treatment-emergent Serious AEs by System Organ Class and Preferred Term
- Treatment-emergent Serious AEs Related to TEGSEDI by System Organ Class and Preferred Term
- Treatment-emergent AEs leading to discontinuation of TEGSEDI by System Organ Class and Preferred Term

AEs will also be presented in data listings as follows:

- Listing of All Adverse Events
- Listing of Adverse Events Leading to Discontinuation
- Listing of Serious Adverse Events
- Listing of Adverse Events of Special Interest

8.2.2.2 Adverse Events Occurring Within 24 hours of TEGSEDI Administration

AEs occurring within 24 hours of administration of TEGSEDI are defined as all AEs with an onset date/time no longer than the 24-hour planned timepoint using a window interval from 20 to 30 hours after the date/time of the injection. For AEs with missing time of onset, AEs occurring within 24 hours of TEGSEDI administration are defined as AEs with an onset date of the same day as the TEGSEDI administration or the subsequent day. This rule will also be applied for missing time of administration of TEGSEDI.

The incidence of AEs occurring within 24 hours post TEGSEDI administration will be summarized at each visit and overall using counts and percentages in the evaluable set. The incidence will be reported with 95% confidence intervals (CIs). Additionally, a summary of AEs occurring within 24 hours post TEGSEDI administration will be displayed by SOC and PT and will be summarized at each visit and overall.

The denominator for the calculation of the percentages by visit will be the number of patients who received a TEGSEDI administration for the specific visit. The denominator for the calculation of the percentages for the overall occurrence of AEs in any visit will be the number of patients in the evaluable set. These denominators will also be presented in the table.

The time from the injection of TEGSEDI until the occurrence of the first AE will be summarized by each visit and overall using descriptive statistics for continuous variables. The time (hours) will be calculated as:

(Onset date/time of the AE – injection date/time of TEGSEDI)/3600

Time from injection of TEGSEDI until the onset of the AE will only be summarized for the AEs with available time for the onset of the AE and available time of TEGSEDI injection. Where time is not available, the AE will be included in the incidence count but will not be included in the summary of time to onset.

The duration of AEs occurring within 24 hours of TEGSEDI administration (in hours) will be calculated as:

- (Date/time of resolution – date/time of onset)/3600

Duration of the AEs will only be calculated for AEs with an outcome of "Recovered" or "Recovered with sequelae" for which date/time for onset and resolution is available.

Preventive Measures Used Prior to the TEGSEDI Injection

The incidence of AEs occurring within 24 hours will also be calculated for injections with preventive measures as reported by the eCRF question "Did the patient take any preventive measures prior to the administration of the dose". The incidence of AEs will be calculated for TEGSEDI administrations with and without preventive measures by visit and overall for any visit. The denominator for the calculation of the percentages by visit will be the number of patients who received a TEGSEDI administration with or without preventive measures, respectively. For the calculation of the overall occurrence of AEs with or without preventive measures, the patients will be included in the denominator if the patient received at least one TEGSEDI administration with or without preventive measures, respectively.

The preventive measures as reported on the Dosing at Visit eCRF will be provided as listings.

Treatment and Duration of AEs within 24 hours

Duration of the AEs will be calculated separately for AEs where treatment was given to mitigate and where treatment was not given. Whether or not treatment was given will be taken from the AE page in the eCRF (Question Treatment given Yes/No).

Identification of Risk Factors for AEs

For AEs observed within the 24 hour drug administration window, patient's medical history, baseline characteristics and concomitant medications will be reviewed and potential risk factors will be explored.

In addition, the impact of ADA formation on development of hypersensitivity reactions will be evaluated by summarizing the hypersensitivity reactions by ADA status.

8.2.3 Vital Signs

Vital signs include body temperature, heart rate, respiratory rate, and systolic/diastolic blood pressure, and will be summarized using the evaluable set. Observed values and changes from the pre-injection assessment will be calculated for all assessments. Observed values and changes from the pre-injection value will also be calculated by presence/absence of AEs occurring within 24 hours of TEGSEDI administration. For the treatment period, changes will be calculated based on the pre-treatment value of the specific visit. For the post-treatment follow-up period and the early termination visit, changes will be calculated relative to the pre-treatment assessment at Month 0.

8.2.4 Cytokines and Inflammatory Markers

Cytokines and inflammatory markers include the following parameters: Immunoglobulin (Ig) E, IgG, IgM, C-reactive protein (CRP), Erythrocyte sedimentation rate (ESR), interferon α (IFN- α), IFN-β, Chemokines (Macrophage inflammatory protein (MIP)-1a and membrane cofactor protein (MCP)-1), Granulocyte-macrophage colony stimulating factor (GM-CSF), interleukin (IL)-1α, IL-1β, IL-6, IL-8, IL-12, and Tumor necrosis factor – α (TNF- α). Cytokines and inflammatory markers will be analyzed in the same way as the vital signs using the evaluable set.

8.2.5 TEGSEDI Administration and Exposure

TEGSEDI administration will be summarized using the safety set by both individual study visit and an overall study drug administration using a derived algorithm. Each visit will summarize the injection location, dose (mg), volume, number of patients having any hypersensitivity and

the number of patients taking any preventive measures prior to administration as recorded on the Dosing at Visit eCRF. For the overall analysis, the first on-site visit injection will initiate the start of TEGSEDI for this protocol. It will be assumed that the dose at a specific visit will be applied weekly from each specific visit until the subsequent visit, unless captured in the injection dosing log. Total exposure will be estimated using the number of doses, duration of exposure and dose intensity as mg/week and will use both the visit date as recorded for the on-site injection in combination with the dosing log form to calculate any changes.

8.2.6 Concomitant Medications

Concomitant medications will be coded using the most recent World Health Organization Drug Dictionary Version and will be updated on re-runs on an ongoing basis. Concomitant medications will be summarized using the safety set by therapeutic/pharmacological subgroup (ATC level 3) and preferred term (ATC Level 5). Concomitant medications given as a preventive measure will be summarized by therapeutic/pharmacological subgroup, preferred term, by treatment month and overall.

8.2.7 Procedures

Procedures will be listed but not summarized.

8.2.8 Anti-drug Antibody (ADA) Data

The hypersensitivity reactions will be summarized by ADA status (Yes/No).

9 Annual Progress Reports

No formal interim analysis is planned. Data related to disposition, exposure and safety considerations will be reported on an annual basis. Specifically, the following information will be presented separately in table format as described below.

- Recruitment status
- Subject disposition
- Demographics and Baseline Characteristics
- Exposure
- Number of Patients with Any Treatment-emergent Adverse Events occurring within 24 hours of TEGSEDI Administration by Study Visit
- Treatment-emergent Adverse Events occurring within 24 hours of TEGSEDI Administration by System Organ Class, Preferred Term and Study Visit

- Treatment-emergent Adverse Events Related to TEGSEDI by System Organ Class, and Preferred Term
- Treatment-emergent Serious Adverse Events by System Organ Class, and Preferred Term
- Treatment-emergent Adverse Events of Special Interest by System Organ Class, and Preferred Term
- Listing of Pregnancies

10 Appendices

Appendix A – TEG4004 Annual Progress Report Template

Appendix B – Mock TLFs