NOVARTIS

Ophthalmology Global Drug Development

Non-Interventional Study Protocol (PASS)

CLTW888A12401

REDACTED PROTOCOL

Title	A Post-Authorization, Multicenter, Multinational, Longitudinal, Observational Safety Registry Study for Patients Treated with Voretigene Neparvovec
Protocol version identifier	v02, 11 March 2022 (Clean)
Date of last version of protocol	v01, 11 July 2019 (Original Protocol v01)
EU PAS register number	EUPAS31153
Active substance	Voretigene neparvovec
Medicinal product	Luxturna®
Product reference	EU/1/18/1331/001
Procedure number	EMEA/H/C/004451

Name of marketing authorization holder(s)	Novartis Pharmaceuticals Corporation
Joint PASS	No
Research question and objectives	The objective of this post-authorization observational study is to collect long-term safety information (i.e., for 5 years after treatment) associated with voretigene neparvovec (vector and/or transgene), its subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.
Country (-ies) of study	European Union and United Kingdom. Additional countries may be added upon market approval.
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List of abbreviations

AAV	adeno-associated virus vector
AAV2	adeno-associated virus vector serotype 2
ADR	adverse drug reactions
AE	adverse event
AESI	adverse events of special interest
BCVA	best corrected visual acuity
BIC	Burden Index of Caregivers
cDNA	complementary deoxyribonucleic acid
CRF	case report form
CRO	contract research organization
DHP	data handling plan
eCRF	electronic case report form
EC	ethics committee
ETDRS	Early Treatment Diabetic Retinopathy Study
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS	European Union Post-Authorization Study
FAS	full analysis set
FST	full-field light sensitivity threshold testing
GDPR	General Data Protection Regulation
GMO	genetically modified organisms
GPP	Guidelines for Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HCP	health care provider
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
IRD	inherited retinal dystrophy
LCA	Leber congenital amaurosis
MedDRA	Medical Dictionary for Regulatory Activities
mVFQ-25	Modified Visual Function Questionnaire-25
OCT	optical coherence tomography
OD	oculus dexter (right eye)
OS	oculus sinister (left eye)
OU	oculus uterque (both eyes)
PAS	post-authorization study
PASS	post-authorization safety study
PHI	protected health information
PSUR	periodic safety update reports
PT	preferred term
RMP	risk management plan
RP	retinitis pigmentosa
RPE	retinal pigment epithelium

RPE65	retinal pigment epithelium 65 kDa protein
RPE65	retinal pigment epithelium 65 kDa protein gene
SAE	serious adverse event
SmPC	summary of product characteristics
SOC	system organ class
VA	visual acuity
VF	visual field
[redacted]	[redacted]
[redacted]	[redacted]
vg	vector genome

1 Responsible parties

Table 1-1 Responsible parties

Role	Person
Main protocol author(s)	[redacted], MD, [redacted] [redacted], PhD, [redacted] [redacted], PhD, [redacted] [redacted], PhD, [redacted] [redacted], MD, [redacted] [redacted], PhD, [redacted] Novartis Pharma AG, CH-4002 Basel, Switzerland
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2 Abstract

Title

A Post-Authorization, Multicenter, Multinational, Longitudinal, Observational Safety Registry Study for Patients Treated with Voretigene Neparvovec

Version and date

v02, 11 March 2022

Name and affiliation of main author

[redacted]

Rationale and background

Voretigene neparvovec is a gene therapy developed to restore functional vision in adult and paediatric patients with confirmed biallelic *RPE65* mutation-associated retinal dystrophy. It was approved in the United States and European Union (EU) under the brand name Luxturna®. Inherited retinal dystrophy caused by biallelic *RPE65* mutations is a rare genetic condition. Mutations in the *RPE65* gene are associated with several clinical manifestations including nyctalopia, decreased visual field and decreased visual acuity. The individuals carrying these mutations exhibit vision loss that substantially limits major life activities, often during childhood or adolescence, and ultimately progresses to total blindness. Voretigene neparvovec uses a non-pathogenic recombinant adeno-associated virus vector serotype 2 (AAV2) to deliver cDNA encoding RPE65 protein to target cells in the retina, allowing for restoration of the visual cycle. Voretigene neparvovec is a one-time treatment. It is administered by subretinal injection in a dose of $1.5x10^{11}$ vector genomes in each eye separately, in a total volume of 0.3 mL.

Gene therapies, like voretigene neparvovec, are a novel class of therapy containing genetically modified organisms (GMO). Post authorisation follow-up of patients administered with gene therapy medicinal products is of interest due to limited data availability and is a post-approval requirement in the EU, agreed as part of the Risk Management Plan.

This post approval observational study will focus on further characterizing the long-term safety profile of voretigene neparvovec using an observational, longitudinal, and multinational design. Since product use will expand beyond the limited investigative clinical sites to multiple Luxturna treatment centers, a broader patient population and experience are expected to be captured.

Research question and objectives

The objective of this registry-based study is to collect long-term safety information (i.e., for 5 years after treatment) associated with voretigene neparvovec (vector and/or transgene), its subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products.

Study design

This study is a post-authorization, multicenter, multinational, longitudinal, observational safety registry study.

As the safety registry study seeks to evaluate the safety of voretigene neparvovec over time, the longitudinal events following administration are the focus of this study.

Safety will be assessed through collection of all adverse events (AEs) and serious adverse events (SAEs) as well as adverse events of special interest (AESIs) queried through a standardized safety questionnaire (Section 12.1). In addition visual function will be assessed over time by means of visual acuity (VA), visual field (VF), full-field light sensitivity threshold testing (FST), optical coherence tomography (OCT), and by patient-reported outcome questionnaires.

Setting and study population

Every effort will be made to enroll all patients treated with voretigene neparvovec, and it is expected that a minimum of 40 adult or pediatric, male or female patients can be enrolled over a five year enrollment period. Patients will be followed until five years following administration of voretigene neparvovec. Patients will be enrolled based on selection criteria described below. Participation in the study is voluntary but strongly encouraged.

Patients who are scheduled to receive treatment with voretigene neparvovec or patients who were treated prior to the start of the registry study will be encouraged to enroll.

Variables

The safety profile of voretigene neparvovec, administered to patients who enroll in this study, will be evaluated based on the examination of general demographic and safety variables, including specific clinical measures as well as patient reported outcomes and caregiver burden.

Safety assessments will primarily be evaluated through pre-defined AESIs. At each visit the patient should be specifically questioned on each of these AESIs. Additionally the patient should also be asked whether they have had any other AEs, SAEs or whether they or their partner have been pregnant during the period since the last visit.

Data sources

Data sources for the collection of safety variables, demographics/baseline characteristics, and surgical details will include but not be limited to medical notes, electronic medical records, and hospital discharge files documented during routine care or may be derived from ocular assessments, including VA, VF, FST, and OCT. AESIs will be collected using a standardized safety questionnaire. Patient- and caregiver-reported outcomes will be collected through questionnaires from patients and caregiver, respectively.

Sites enrolling patients in this study will record data on CRFs provided by Novartis (or designee) which will capture and store the data.

Study size

This study is intended to collect long-term safety follow-up information and the sample size estimate is not based on statistical measures. Every effort will be made to enroll all patients treated with voretigene neparvovec, and it is expected that a minimum of 40 adult or pediatric patients can be enrolled over a five year enrollment period.

Data analysis

This study is intended to present the frequency and severity of adverse events of interest in a patient population receiving voretigene neparvovec (vector and/or transgene). Additionally the study will assess the AEs associated with the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products. The Full Analysis Set (FAS), defined as all patients for whom an informed consent/assent was signed and who were enrolled in the study and received at least one injection of voretigene neparvovec, will be used to summarize all data.

A complete description of the statistical analyses and methods will be available in the Statistical Analysis Plan.

Study progress reports will occur, at a minimum, on an annual basis and will be presented within the PSUR. A standalone study report will be provided if a PSUR is not due for submission.

Milestones

Planned dates of study milestones:

Study Active	Dec 2019
End of data collection	Dec 2029
Study progress reports*	Annually starting April 2020
Final report of study results	June 2030
Registration in the EU PAS register	Aug 2019

* Study progress reports will be provided annually in within the PSUR. A standalone study report will be provided if a PSUR is not due for submission.

3 Amendments and updates

Table 3-1 Study protocol amendments and updates

Numbers	Date	Section of study protocol	Amendment or update	Reason
v02	11 Mar 2022	Section 1, Table 1-1	Updates	Update sponsor contacts
		Section 5 Section 7.2	Amendment	Added risk of vision loss due to progressive chorioretinal atrophy
		Section 7.2 Other Variables	Amendment	Inclusion and clarification of new PRO questionnaires,
		Section 7.3 Table 7-1	Updates	Added ocular characteristics and PRO collection to Table 7-1
		Section 7.6	Amendment Update	Added retinal atrophy sub-group analysis Updated FAS definition
		Section 9.1 & 9.2	Update	Updated AE reporting instructions
		Section 12.1	Amendment	Added Chorioretinal atrophy (e.g. injection site atrophy/treatment emergent progressive atrophy) to list of AESIs (Safety Questionnaire)
		Section 12.2	Amendment	Modified VFQ-25 Questionnaire Clarified completion instructions
		[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]
		Section 12.5	Update	Relocation of BIC (previously was Annex 3)
		Section 12.6	Update	Relocation of ENCePP annex (previously was Annex 4)

4 Milestones

Table 4-1 Planned dates of study milestones

Study Active	Dec 2019
End of data collection	Dec 2029
Study progress reports*	Annually starting April 2020
Final report of study results	June 2030
Registration in the EU PAS register	Aug 2019

* Study progress reports will be provided annually within the PSUR. A standalone study report will be provided if a PSUR is not due for submission.

5 Rationale and background

Voretigene neparvovec is a gene therapy developed to restore functional vision in adult and paediatric patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. It was approved in the United States and European Union (EU) under the brand name Luxturna®. Inherited retinal dystrophy caused by biallelic *RPE65* mutations is a rare genetic condition. Mutations in the *RPE65* gene are associated with several clinical manifestations including nyctalopia, decreased visual field and decreased visual acuity. The individuals carrying these mutations exhibit vision loss that substantially limits major life activities, often during childhood or adolescence, and ultimately progresses to total blindness. Voretigene neparvovec uses a non-pathogenic recombinant adeno-associated virus vector serotype 2 (AAV2) to deliver cDNA encoding RPE65 protein to target cells in the retina, allowing for restoration of the visual cycle.

Gene therapies, like voretigene neparvovec, are a novel class of therapy containing or consisting of a genetically modified organism (GMO). Post authorisation follow-up of patients administered with gene therapy medicinal products is of interest due to limited data availability and is a post-approval requirement in the EU, as agreed in the RMP. A comparable registry study is being conducted by Spark Therapeutics, the marketing authorization holder for Luxturna® in the US.

This post authorizational observational study (originally termed SPKRPE-EUPASS) will focus on further characterizing the long-term safety profile of voretigene neparvovec using an observational, longitudinal, and multinational design. Since product use will expand beyond the limited investigative clinical sites to multiple Luxturna® treatment centers, a broader patient population and experience are expected to be captured.

The *RPE65* gene is involved in the production of the RPE65 enzyme made in the retinal pigment epithelium (RPE) that is essential for normal vision. The biochemical blockade of the visual cycle resulting from RPE65 enzyme deficiency causes a profound impairment in visual function and functional vision with eventual (but delayed) degeneration of retinal (foveal) cone cells (Jacobson et al 2005). The inability to regenerate 11-*cis* retinal, via 11-*cis* retinol, in the RPE cells impairs the ability to respond to light, and the accumulation of toxic precursors proximal to the block (caused by lack of functioning RPE65 enzyme) leads eventually to death of RPE

cells. This in turn leads to death of photoreceptors (Redmond et al 1998, Katz and Redmond 2001).

The RPE65 enzyme is encoded by the *RPE65* gene, and autosomal recessive mutations in this gene lead to inherited retinal degenerative disease (Redmond et al 1998, Redmond et al 2005). The disease process that results from mutations in the *RPE65* gene affects mainly rod photoreceptors that mediate peripheral vision and ability to detect low luminance light; cone photoreceptors may also be regulated by a different biochemical pathway (Tang et al 2013) and are secondarily affected in individuals with biallelic *RPE65* mutation-associated retinal dystrophy. As a result of initial rod degeneration, affected individuals have such decreased light sensitivity that they are night blind and, in addition, have great difficulty performing activities of daily living, even under normal daytime lighting conditions. Due to continued retinal degeneration, affected individuals suffer from an inexorable progression to complete blindness (Ferrari et al 2011). Biallelic mutations in the *RPE65* gene are associated with several clinical manifestations of inherited retinal disease including subtypes of Leber congenital amaurosis (LCA) and retinitis pigmentosa (RP).

Voretigene neparvovec

Voretigene neparvovec is an adeno-associated virus vector-based gene therapy indicated for the treatment of adult and pediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells. The presumed mechanism of action is recovery of the biochemical activity of the RPE65 isomerohydrolase enzyme, and thus the retinoid cycle, by gene augmentation.

Voretigene neparvovec uses a non-pathogenic adeno-associated virus vector serotype 2 (AAV2) to deliver the *RPE65* genetic material to target cells in the retina.

Voretigene neparvovec is a one-time treatment. It is administered in a dose of 1.5×10^{11} vector genomes (vg) to each eye, delivered in a total subretinal volume of 0.3 mL. Prior to voretigene neparvovec administration, biallelic *RPE65* mutations must be confirmed by genetic testing in a certified laboratory, and patients must have viable retinal cells. Please refer to the locally approved product information for full product and prescribing information.

Important identified risks of voretigene neparvovec identified from the clinical development program include increased intraocular pressure, retinal tear, macular disorders (e.g., macular hole, foveal dehiscence, maculopathy [epiretinal membrane, macular pucker], foveal thinning or loss of foveal function), cataract, intraocular inflammation and/or infection related to the procedure and retinal detachment. Important potential risks for voretigene neparvovec include tumorigenicity, host immune response, and third-party transmission. Vision loss due to progressive chorioretinal atrophy is added as an important potential risk based on post-marketing experience.

This medicinal product contains genetically modified organisms (GMOs) i.e. viral vector. Based on the characteristics of voretigene neparvovec, the intended use after placing it on the market and the receiving environment, the inherent risk of third-party transmission associated with voretigene neparvovec are considered to be very low.

In clinical studies of voretigene neparvovec, only low levels and transient shedding of infective virus from treated individuals were detected. Additionally, any potential consequence of transmission of voretigene neparvovec is negligible due to the non-pathogenic nature of the

parental virus. Voretigene neparvovec is indicated for an ultra-rare disease, and will only be distributed through a limited number of treatment centers, where qualified staff (i.e. vitreoretinal surgeons and pharmacists) have participated in the mandatory educational program about use of the product. The manufacture, supply, and traceability of voretigene neparvovec is tightly controlled and monitored in accordance with pharmaceutical legislation.

Appropriate instructions to ensure correct handling, dilution and administration of the product are provided in the Product Information. It is important that instructions on the use of personal protective equipment (e.g. laboratory coat, safety glasses and gloves) while preparing or administering voretigene neparvovec are followed and that patients/caregivers are advised to handle waste material generated from dressings, tears and nasal secretion appropriately, which may include storage of waste material in sealed bags prior to disposal, as described in the Product Information. Local biosafety guidelines applicable for GMOs should be followed.

The capacity for widespread dissemination from commercial use of voretigene neparvovec is expected to be severely limited. This safety registry study is part of the proposed safety monitoring and risk management plan for voretigene neparvovec.

The voretigene neparvovec clinical program has been shown to be safe and efficacious in 43 patients including the phase III study consisting of 31 patients (Russell et al 2017). These clinical study patients continue to be monitored in a 15-year long-term follow-up study. However, it is important to further characterize the benefit-risk of this novel gene augmentation therapy in more patients in a real-world setting after marketing authorization.

6 Research question and objectives

This study is a non-interventional registry-based study to evaluate the long-term safety profile of voretigene neparvovec for 5 years post-administration in a real-world setting. Following marketing approval, administration of voretigene neparvovec will expand beyond the limited investigative clinical sites to multiple Luxturna® treatment centers and will allow characterization of product safety in a larger population. The study will collect all AEs and SAEs including AEs of special interest (AESIs) (through the standardized safety questionnaire), information about pregnancy occurrence and outcomes, and ophthalmic examination results.

6.1 Primary objective

The primary objective for this safety registry study for voretigene neparvovec is to collect all AESIs, as well as any other AEs and SAEs.

6.2 Secondary objectives

The secondary objectives of this safety registry study are:

- To follow pregnancy outcomes in patients (and female partners of patient) who received voretigene neparvovec
- To assess visual function over time (e.g., as measured by visual acuity (VA), visual field (VF), full-field light sensitivity threshold testing (FST)), and optical coherence tomography (OCT))

7 Research methods

7.1 Study design

This study is a post-authorization, multicenter, multinational, longitudinal, observational safety registry study.

As the safety registry study seeks to evaluate the safety of voretigene neparvovec over time, the longitudinal events following administration are the focus of this study.

Safety will be assessed through collection of all AESIs, as well as any other AEs and SAEs. In addition visual function will be assessed over time by means of VA, VF, FST, and OCT. Patient reported outcomes (PRO) and caregiver questionnaire information will also be collected.

The main aim of this registry study is to collect prospective data. Therefore, it is expected that patients who are scheduled to receive treatment with voretigene neparvovec will be informed of this registry study and are encouraged to participate. However, in order to maximize data collection, this study will also allow inclusion of patients who were treated with voretigene neparvovec before the study is started.

7.2 Setting

This is a non-interventional study and does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be treated according to the local prescribing information and routine medical practice in terms of visit frequency and types of assessments performed and only these data will be collected as part of the study.

Every effort will be made to enroll all patients treated with voretigene neparvovec, and it is expected that a minimum of 40 adult or pediatric, male or female patients can be enrolled over a five year enrollment period. Patients will be followed for five years following administration of voretigene neparvovec.

Patients will be enrolled based on the selection criteria described below. Participation in the study is voluntary but strongly encouraged to enroll all patients treated with voretigene neparvovec.

Selection criteria:

1. Is planning to receive or has received voretigene neparvovec in at least one eye.
2. Provided informed consent/assent to participate in this study.
3. Has not previously participated and is not currently participating in an interventional clinical trial with voretigene neparvovec.

Patients who planned to be treated or have been treated with voretigene neparvovec will be informed of this study by qualified study sites. After informed consent/assent is provided, data (including any relevant pre-existing data collected prior to informed consent) will be collected in this registry-based study.

Qualified study sites will be primarily Luxturna® treatment centers where qualified staff (i.e., vitreoretinal surgeons and pharmacists) have participated in the mandatory educational program about use of the product, and inherited retinal dystrophy (IRD) referral centers. Preferably, patients are followed up at the same Luxturna® treatment center or IRD referral center where they were enrolled, for consistency of data collection. If more than one center is involved in the

treatment and follow-up of a patient (e.g. a treatment center and a referral center), then enrollment into the study should take place at the site where the patient will be seen most frequently and data from all other centers will be collected at this study site.

The recommended data collection schedule is outlined in Table 7-1. Regardless of whether a patient is enrolled prior to or after treatment with Luxturna®, the same data collection points apply. At a minimum, the site should attempt to collect pre-treatment/baseline data, post-treatment data, and annual follow-up data.

For patients enrolled prior to treatment, any pre-treatment/baseline data listed in Table 7-1 including patient demographics, medical and surgical history, relevant concomitant medication and procedures performed, baseline ocular characteristics (viable cells) as well as genetic and clinical diagnoses related to the inherited retinal dystrophy will be collected. When collecting pre-existing data, the most recent ophthalmic examinations performed within 3 months prior to treatment with voretigene neparvovec will be considered pre-treatment/baseline assessments for each eye. In addition, any patient reported-outcome and patient caregiver questionnaires completed prior to receiving treatment with voretigene neparvovec will also be collected.

After the patient has received voretigene neparvovec in at least one eye, patient visits for surgical follow up will be scheduled at the discretion of the surgeon/physician as part of routine clinical care. All post-administration information as outlined in Table 7-1 including information on the subretinal administration of voretigene neparvovec, concomitant medications and procedures, safety information, as well as all AEs, and perioperative steroid use from the time of voretigene neparvovec administration will be collected.

For patients enrolled after treatment, any available baseline and post-treatment information as outlined in Table 7-1 has to be collected retrospectively. This includes all AESIs, AEs, SAEs, and pregnancy information, and ophthalmic assessment information since the time of treatment until enrollment which should be captured on the respective CRFs. Please also see Section 9 for AE/SAE and pregnancy reporting for events which occurred prior to ICF.

For all patients, additional data should be collected in the study at a minimum on an annual basis after treatment, including AESI/AE/SAEs, pregnancy occurrence and outcomes (in patient and female partners of patient), concomitant medications and procedures, patient-reported outcome questionnaires, caregiver questionnaires, and post-administration ophthalmic examinations. Study sites will be provided with a list of questions regarding AESIs to standardize safety data collection as much as possible (refer to Safety Questionnaire in Section 12.1). At each visit the patient should be specifically questioned and evaluated on each of these AESIs. Additionally the patient should also be asked whether they have had any other AEs, SAEs or whether they or their partner has been pregnant during the period since the last visit. Any findings will be entered on the AE eCRF.

Data may be collected in the study more frequently, as safety events become known for an individual patient. Qualified site personnel may obtain data from the patient at any time via other forms of contact such as telephone, e-mail or postal mail. Patients should be encouraged to return to the same study site for their follow-up. Data may be sourced from the study site, other treating physicians (e.g. primary physicians, local/primary ophthalmologists, and ophthalmic surgeons), patient, or patient caregivers (e.g. family members, home nursing).

In addition, patients and their physicians will be instructed to contact the study site any time an AESI/AE/SAE, pregnancy occurrence or pregnancy outcome (in patient and female partners of patient) becomes known. Each enrolled patient will be given a patient/care provider card noting s/he has been treated with voretigene neparvovec and is participating in this study. The patient/care provider card should be shown to any health care practitioner treating the patient in order to facilitate the reporting of safety events and pregnancy occurrence (in patient and female partners of patient).

If the study site staff becomes aware of an adverse event in a study patient at any time, or a pregnancy in a patient or female partner of a patient, those data are to be reported as per the study reporting timelines (Section 9.1).

Patients may withdraw from the study at any time without prejudice to their care. For patients who discontinue prematurely, the reason for discontinuation should be determined.

A patient will be considered potentially lost to follow-up if they do not return to the study site for the annual follow-up visits and no information can be obtained via telephone contact or other sources. The site is encouraged to make every effort (phone, email, certified mail) and document those efforts to regain contact to resume data collection. A patient cannot be considered as lost to follow-up until the time point of their scheduled End of Study visit has passed.

Variables

The safety profile of voretigene neparvovec, administered to patients who enroll in this study, should be evaluated based on the examination of general demographic and safety variables, including specific clinical measures.

Pre-treatment and Baseline characteristics

- Demographics (e.g. age, gender, race, ethnicity, and country of residence)
- Medical and surgical history (including prior gene and cell therapy)
- Ocular characteristics (including information on viable cells and ophthalmic exam results)
- Genetic diagnosis related to the inherited retinal dystrophy
- Clinical diagnoses related to the inherited retinal dystrophy
- Concomitant medications and procedures
- PRO and caregiver questionnaires

Voretigene neparvovec administration information

- Surgical center location
- Date of injection(s) (right eye, left eye)
- Lot number and volume administered (right eye, left eye)
- Details of perioperative corticosteroids use
- Surgical details including number and location of retinotomies (right eye, left eye)

Safety Variables

- The following events are designated as AESIs and will be queried through the standardized safety questionnaire (Section 12.1) and entered into the AE CRF:
  - Ocular AEs
  - Lack of efficacy and/or decline in efficacy over time*
  - Third-party transmission
  - Host immune response
  - Development or exacerbation of oncologic, hematologic, neurologic, or auto-immune diseases

  ***Note**: Signs and symptoms resulting from “lack of efficacy” or “decline of efficacy over time” or "failure of expected pharmacological action" should be provided in the AE or SAE description.
- Follow-up information on reported chorioretinal atrophy
- Any other AEs and SAEs
- Information on pregnancy occurrence, outcomes, and lactation (from patients and female partners of patient)
- Ophthalmic examination results for VA, VF, FST, and OCT:
  - VA: best-corrected visual acuity (BCVA) should be measured according to the method used by the site in the course of routine care and recorded in the CRF. For consistency and analyses, it is recommended that the same method of assessment be used throughout the study wherever possible. Use of the ETDRS-like chart is suggested.
  - VF: visual field or perimetry should be measured according to the method used by the site in the course of routine care and recorded in the CRF. For consistency and analyses, it is recommended that the same method of assessment be used throughout the study wherever possible. Kinetic perimetry with Goldmann stimuli III4e and V4e is suggested.
  - FST: full-field light sensitivity threshold testing should be measured according to the method used by the site in the course of routine care and recorded in the CRF. For consistency and analyses, it is recommended that the same method of assessment be used throughout the study wherever possible. It is suggested that white light as well as blue and red light testing is performed.
  - OCT: optical coherence tomography should be measured according to the method used by the site in the course of routine care and recorded in the CRF. For consistency and analyses, it is recommended that the same method of assessment be used throughout the study wherever possible.

Other variables (where allowed by local regulations)

- Questionnaires for patients/guardians/caregivers:

  Paper or electronic versions of the questionnaires will be provided by the Sponsor. For detailed instructions and specific completion guidelines, please refer to the respective Section for each questionnaire and Table 7-1.

- Patient-reported outcome questionnaires:
  - The modified Vision Functional Questionnaire-25 (mVFQ-25) (Section 12.2).
  - [redacted]
  - Burden Index of Caregivers (BIC) questionnaire (Section 12.5) (Khan et al 2016).
- Other assessments to follow patients' progress are or may become standard of care in this rapidly evolving field, and may optionally be collected in the context of this registry-based study (including e.g. mobility testing and pupillometry). Respective CRFs for data collection will be provided.
- All new concomitant medications and procedures.

7.3 Data sources

Data sources for the collection of safety variables, demographics, pre-treatment/baseline characteristics, and surgical details will include medical notes, electronic medical records, and hospital discharge files documented during routine care or may be derived from ocular assessments including VA, VF, FST, and OCT. AESIs will be collected using a standardized safety questionnaire. Patient- and caregiver-reported outcomes will be collected through questionnaires from patients and caregiver, respectively.

Safety data will be transferred to Novartis at a frequency as defined in Section 9 of this protocol and/or CRO contract.

Data collection schedule

This is a non-interventional study which does not impose a therapy protocol, diagnostic/therapeutic procedure, or a visit schedule. Patients will be treated according to the local prescribing information, and routine medical practice in terms of visit frequency and types of assessments performed and only these data will be collected as part of the study. The treating physician is asked to complete – if possible – the appropriate CRF at every patient visit.

However, in addition to the questionnaires, below is the minimum recommended data collection schedule that most likely aligns with the patterns of routine clinical care of patients being treated with voretigene neparvovec.

Table 7-1 Data collection

Assessments	Pre-treatment/ baseline data collection point	Post-treatment data collection point	Follow-Up data collection point (Years 1-5)
Signed informed consent/assent	To be completed prior to data collection		
Eligibility assessment	To be completed prior to data collection		
Demographics (age, gender, race, ethnicity, and country of residence)	X		
Medical and surgical history (including prior gene and cell therapy)	X		
Ocular characteristics (including information on viable cells and ophthalmic exam results)	X		X
Genetic diagnosis related to inherited retinal dystrophy	X		
Clinical diagnoses related to inherited retinal dystrophy	X		
Concomitant medications and procedures	X[a]	X	X
Date of injection(s) (right eye, left eye), Treatment center that treated patient, & treatment funding source (country)		X	
Lot number, expiry date, and volume administered (right eye, left eye). Perioperative steroid use.		X	
Surgical details including number and location of retinotomies (right eye, left eye)		X	
For patients enrolled under protocol version 01			
mVFQ-25 (Section 12.2)	X[b]		X
For patients enrolled under protocol version 02			
[redacted]			
For all protocol versions			
BIC (Section 12.5)	X[b]		X
Safety Variables			
Ophthalmic examination: visual acuity (VA), visual field (VF), full-field light sensitivity threshold testing (FST), and optical coherence tomography (OCT)	X[c]		X
All AEs of special interest (AESIs): ocular AEs, lack of efficacy and/or decline of efficacy over time, third-party transmission, host immune response, and development or exacerbation of oncologic, hematologic, neurologic, or auto-immune diseases (NOTE: Collection must be assessed at each visit in accordance with the standardized safety questionnaire)		X	X

Assessments	Pre-treatment/ baseline data collection point	Post-treatment data collection point	Follow-Up data collection point (Years 1-5)
Any other AEs or SAEs		X	X
Pregnancy occurrence and outcomes (from both patient and female partners of patient), including whether any child was breastfed		X	X
End of study visit		X	

a - Concomitant medications taken and procedures performed within 30 days prior to voretigene neparvovec treatment.

b - Baseline questionnaire to be completed prior to voretigene neparvovec treatment.

c - Most recent ophthalmic examinations performed within 3 months prior to voretigene neparvovec treatment.

7.4 Study size

This study is intended to collect long-term safety follow-up information and the sample size estimate is not based on statistical measures. Every effort will be made to enroll all patients treated with voretigene neparvovec, and it is expected that a minimum of 40 adult or pediatric patients can be enrolled over a five-year enrollment period.

7.5 Data management

7.5.1 Data Collection

Data will be entered from patient source documents to case report forms (CRF) that are specifically designed for this study. Data will be retained based on local regulatory requirements or the terms in the clinical trial agreements, whichever is longer.

7.5.2 Data management

Novartis Data Management or a designated CRO will assure database quality processes are followed including review of the data entered into the CRFs by investigational staff for completeness and accuracy, and in accordance with the data validation plan.

7.6 Data analysis

This study is intended to descriptively document the frequency and severity of events of interest related to voretigene neparvovec (vector and/or transgene), the subretinal injection procedure, the concomitant use of corticosteroids, or a combination of these procedures and products. The Full Analysis Set (FAS), defined as all individuals for whom an informed consent/assent was signed and who are enrolled in the study and received at least one injection of voretigene neparvovec, will be used to summarize all data.

Continuous variables will be summarized in terms of mean, standard deviation, median, minimum and maximum. Other descriptive statistics (e.g., quartiles, coefficient of variation) may be reported when appropriate. Categorical variables will be summarized using frequency

counts and percentages. Unless otherwise noted, the denominator for the percentages will include all patients in the FAS population.

The unit of analysis for disposition, demographics and baseline diagnoses will be patient; the unit of analysis for ophthalmic examination findings will be right eye and/or left eye. The unit for non-ocular AEs will be patient; the unit for ocular AEs will be eye(s). The unit for other variables will be patient or eye(s) as appropriate.

Analyses to assess the impact of subgrouping based on selected variables which become of interest during the study will be performed as defined in the Statistical Analysis Plan (SAP).

Interim data assessments will occur at a minimum, on an annual basis and will be included in annual progress reports. A complete description of the statistical analyses and methods will be available in the SAP.

7.6.1 Demographics, baseline disease characteristics, disposition, ophthalmic examination findings, and other variables

Descriptive summary statistics will be provided for demographics and pre-treatment/baseline disease characteristics. Descriptive summary statistics will also be provided for ophthalmic examination results (e.g., VA, VF, FST, and OCT) at pre-treatment/baseline and post-administration. Ophthalmic examination results will be presented by age categories. Patient- and caregiver-reported outcomes will be summarized at pre-treatment/baseline and annually for questionnaire overall and subscale scores presented as percentages. Disposition, including number of patients enrolled in the study at the time of each analysis, will be tabulated; demographic characteristics will also be re-summarized at each analysis point.

The unit of analysis for disposition, demographics and pre-treatment/baseline diagnoses will be patient; the unit of analysis for ophthalmic examination findings will be right eye and/or left eye. The unit for non-ocular AEs will be patient; the unit for ocular AEs will be eye(s). The unit for other variables will be patient or eye(s) as appropriate.

7.6.2 Voretigene neparvovec safety

Adverse events including the AESIs, SAEs, and pregnancy occurrence and outcome information (including information collected in the Novartis Global Safety database) will be summarized in annual progress reports and the final study report. All AEs and SAEs will be provided in patient data listings. Additional listings, summaries, and graphics may be generated, as appropriate.

Adverse events will be coded to system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The incidence (number and percentage of patients with an AE observed one or more times) and number of events for each AE will be presented for AEs and SAEs, and will be tabulated by SOC and PT, both overall and by severity level and relationship to treatment and/or surgical procedure, as appropriate. This will be performed both for the cumulative duration of follow-up through the analysis time point of interest and/or on an annual basis, the latter to assess the potential, if any, for increasing or decreasing trend in reported AEs. Safety results will be presented by age categories.

Administration of voretigene neparvovec includes the surgical procedures of pars plana vitrectomy followed by voretigene neparvovec injection via bleb formation in the subretinal space. AEs associated with the administration procedures include: increased intraocular pressure, retinal tear, retinal detachment, macular disorders, cataract, and intraocular inflammation and/or infection related to the procedure. A comparative analysis of these ocular AEs between treated patients and published literature data on pars plana vitrectomy will be included in the progress reports.

The incidence of these identified AEs will be summarized descriptively for this study.

7.7 Quality control

7.7.1 Data quality management

Novartis data management or a designated CRO will ensure that database quality processes are followed including review of the data entered into the CRFs by site staff for completeness and accuracy, and in accordance with the data validation plan. Once data are entered into the eCRFs and if the site subsequently edits the data, the database contains an audit trail to track the updates. Details may be found in the Data Handling Plan.

7.7.2 Data recording and document retention

In all scenarios, the physician must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, and the results of any other tests or assessments. All information entered in the CRF must be traceable to these source documents in the patient's file.

The physician must give Novartis (or designee) access to all relevant source documents to confirm their consistency with the CRF entries. No information in source documents about the identity of the patients will be disclosed.

7.7.3 Site monitoring

Formal site monitoring will be performed as described in the Monitoring Plan for this study.

Novartis Data Management or a designated CRO will assure compliance monitoring.

7.8 Limitations of the research methods

The absence of randomization and of a control group in this single arm study is not able to account for selection bias. The observational nature of the study, without using standardized assessment procedures, is also not able to account for potential information bias.

Nonetheless, this study design will be able to describe what is observed when voretigene neparvovec is used in the real-world setting, when patients are treated as per the current standard of care.

Observational studies are prone to missing data, particularly when data is collected retrospectively. Therefore, retrospective data collection is limited to patients who were treated prior to the start of the registry study.

No formal statistical evaluations are planned. Output will be limited to data listings and descriptive statistics, where applicable.

7.9 Other aspects

None applicable.

8 Protection of Human Patient

Confidentiality

Medical records with protected health information (PHI) will be kept separately from study records at each study site. Study patients will be assigned unique patient identifiers to protect confidentiality. De-identified patient data will be entered into eCRFs. All data and records generated during this study will be kept confidential and in accordance with local regulations, institutional policies, and European data protection law (e.g., General Data Protection Regulation (GDPR)). The study site personnel will not use such data and records for any purpose other than conducting this study.

Risk assessment

As this is a minimal risk study, the chief risk is loss of confidentiality. All study personnel with access to the patient' medical records/source documents will be trained on the applicable requirements for maintaining a patient's confidentiality. There is also the potential risk of discomfort from ophthalmic examinations.

Regulatory and ethical compliance

Compliance with Novartis and regulatory standards provides assurance that the rights, safety, and well-being of patients participating in non-interventional studies are protected (consistent with the principles that have their origin in the Declaration of Helsinki) and that the study data are credible and responsibly reported.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE 2016), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (Vandenbroucke et al 2007), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' (European Medicines Agency 2010).

Informed consent procedures

The physician must keep the original signed informed consent/assent form signed by the patient or parent/guardian (a copy of the signed form is given to the patient).

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/EC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing

so, he/she should assent by personally signing and dating the written informed consent document or a separate assent form. Because this is a long-term study, the investigator should check the progressing maturation of pediatric patients and their ability for assent. When an adolescent is legally emancipated, i.e. ceases to be a minor as defined in national law, informed consent must be sought directly from the individual and as soon as possible.

Informed consent must be obtained before any data are collected. The process of obtaining informed consent and assent should be documented in the patient source documents.

Novartis will provide to treating physicians or other involved medical professionals in a separate document a proposed informed consent form that complies with the Declaration of Helsinki principle and regulatory requirements and is considered appropriate for this study.

9 Management and Reporting of Adverse Events

All adverse events (AE) will be collected and recorded in the study database, irrespective of seriousness or causal association. All **serious adverse events (SAEs)** and reports of drug exposure during **pregnancy** that occurred in patients exposed to the Novartis drug(s) of interest, irrespective of causality, will be reported to Novartis Patient Safety within 24 hours of becoming aware of the event. All **non-serious AEs** and events describing a special scenario will be recorded in the study database within 10 calendar days of site awareness and reported to Novartis Patient Safety on a periodic basis via batch reports.

Adverse Drug Reactions (ADRs) occurring in patients exposed to a Novartis drug other than the Novartis drug of interest (i.e., voretigene neparvovec), can be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or to Novartis Patient Safety as a spontaneous report. All adverse reactions identified for non-Novartis products should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or the Marketing Authorization Holder as these will not be recorded in the Novartis safety database. All study site staff and physicians who follow patients will be trained on voretigene neparvovec safety reporting procedures and regulations as outlined below.

9.1 Adverse event collection and reporting

Definition of AE

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

A **serious adverse event** (SAE) is defined as an AE which:

- Results in death or is life-threatening
- Results in persistent or significant disability/incapacity
- Constitutes a congenital anomaly/birth defect
- Requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition. This would include when the patient is hospitalized either pre or post-injection for routine monitoring, as per local custom.
- Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of the drug of interest
- Social reasons and respite care in the absence of any deterioration in the patient's general condition

- Is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above e.g. may require treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission

Note: Transmission of infectious disease via medication is considered to be a serious adverse reaction and should be reported and assessed as medically significant in the absence of other seriousness criteria.

An **adverse drug reaction** (ADR) is a response to a medicinal product which is noxious and unintended. An ADR implies at least a reasonable possibility of a causal relationship between a medicinal product and an adverse event.

The **Novartis drug of interest** evaluated in this study is voretigene neparvovec.

AE Collection

All AEs from all patients enrolled in the study must be collected and recorded in the study database, irrespective of seriousness or causal association. For patients who have been dosed prior to the enrollment in the registry, all the AEs from the time of dosing upto the time of entry to the registry should also be collected and recorded in the registry database.

The occurrence of AEs should be sought by non-directive questioning of the patient at each visit during the study. AEs may also be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. Medical conditions/ diseases ongoing before starting treatment with a study drug are only considered AEs if they worsen after receiving the Novartis drug of interest.

All AEs must be recorded on the AE case report form (CRF) with the following information:

1. the severity grade (mild, moderate, severe)
2. the site (right eye, left eye, both eyes, or non-ocular)
3. its relationship to the voretigene neparvovec (vector and/or transgene), the subretinal injection procedure, the concomitant use of corticosteroids that are administered as part of the treatment, a combination of these procedures and products (suspected/not suspected)
4. its duration (start and end dates or if continuing at final exam)
5. whether it constitutes a SAE

In addition, all reports of the following **special scenarios**, whether or not associated with AEs, are also collected and reported in the same manner as AEs:

- Drug-drug or drug-food interaction
- Drug use during lactation
- Lack of efficacy

- Overdose
- Intentional drug abuse and misuse
- Medication errors including drug maladministration
- Dispensing or prescribing errors
- Drug dependence or addiction
- Withdrawal reaction/ syndrome or rebound symptoms
- Unexpected beneficial effect
- Treatment non-compliance (with clinical symptoms)

A standardized safety questionnaire (Section 12.1) will be used, in conjunction with clinical observations and ophthalmic examination results, to solicit **Adverse events of special interest (AESI)** information. At each visit the patient should be specifically questioned on each of these AESIs. The AESI will be captured on the AE case report form (CRF).

The following events are designated AESIs:

- Ocular AEs
- Lack of efficacy and/or decline in efficacy over time
- Third-party transmission
- Host immune response
- Development or exacerbation of oncologic, hematologic, neurologic, or auto-immune diseases

Note: In addition to the reporting laid out above, any occupational or accidental exposure, for example of study personnel or family members of the patient should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or to Novartis Patient Safety as a spontaneous report.

Any action taken with study drug or addition of treatment medication as a result of an AE should be recorded on the AE eCRF. Some examples to be recorded are: no action taken (i.e., further observation only) or not applicable/unknown; study drug dosage increased/reduced/not changed/ interrupted; study drug withdrawn due to this AE.

Once an AE is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common adverse effects already known about the study drug(s) can be found in the locally available labeling document for the approved indication under evaluation in this study.

AE Reporting

Serious adverse events (SAE)

Information about **all treatment-emergent SAEs that occur after enrollment** into the registry study, irrespective of causality, must be recorded in the Novartis safety database. The treating physician or other involved HCP must assess the relationship to the Novartis drug, complete the AE Report Form and send the completed, signed form by fax/ email immediately without

undue delay, but under no circumstances later than **within 24 hours of obtaining knowledge of the events (Note: if more stringent, local regulations regarding reporting timelines prevail)** to the local Novartis Patient Safety department.

The investigator is responsible for reporting any SAEs prior to entry into this registry to their local Health Authority according to local regulations. Therefore, **all treatment-emergent SAEs that have occurred prior to a patient's enrollment** into the registry study should have been reported previously to the local Health Authority by the investigator as per local regulations. These SAEs that occurred before entry to the registry must be recorded as SAEs in the CRF, but are not required to be additionally reported to the local Novartis Patient Safety department.

The email address, telephone and telefax number of the contact persons in the local Patient Safety department, specific to the site, are listed in the treating physician/ HCP folder provided to each site. The original copy of the AE Report Form and the fax confirmation sheet or the email must be kept with the CRF documentation at the study site.

Exposure during pregnancy of study patient and pregnancies in partners of patient treated with voretigene neparvovec

Any occurrence of a pregnancy in a patient exposed to the Novartis drug(s) of interest after enrollment into the registry study must be recorded on the CRF and reported to Novartis **within 24 hours** of learning of its occurrence. The pregnancy should be followed-up to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Standard Novartis Safety follow-ups are conducted for reports of pregnancy and data on health of newborns are collected for one year after delivery.

Information about the pregnancy should be recorded on the respective CRF as well as on the Pregnancy Form and reported by the treating physician or other involved HCP to the local Novartis Patient Safety department. In case of any congenital abnormality, birth defect or maternal and newborn complications, the possible relationship to the Novartis drug should be reported. Information on whether the baby was breast fed should be included where appropriate.

For patients who have been dosed prior to the enrollment in the registry, any pregnancies occurring between the time of dosing and entry to the study should be collected and recorded on the respective CRF. Such pregnancies do not need to be additionally reported to Novartis Patient Safety.

Additionally, any SAE/ non-serious AE experienced during pregnancy must be collected on the respective CRF and reported to Novartis following the respective reporting routes described in this section.

Pregnancy outcomes must be collected for the female partners of any males who took the Novartis drug(s) of interest in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the female partner.

Non-serious AEs and events describing a special scenario (other than drug exposure during pregnancy)

Information on all non-serious AEs and events describing a special scenario must be collected on the individual patient eCRFs **within 10 calendar days** of the site becoming aware of it.

Information on all non-serious AEs that occurred in patients exposed to the Novartis drug(s) of interest is then transferred from the study database to the Novartis Patient Safety department by Novartis data management group on a periodic basis as per the terms defined in the Data Handling Plan (DHP).

Protocol-exempt events

The following events are defined as "exempt" from collection and entry into the clinical and safety database.

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the study site physician to be more severe than expected for the patient's condition.
- All reports of lack of efficacy and/or decline in efficacy over time should be reported as AESIs. However the disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, **unless more severe than expected for the patient's condition** (e.g., expected changes in the fundus appearance consistent with the underlying disease and without any associated visual function changes) is not required to be reported as an AE.

Any protocol-exempted event which is suspected to be related to voretigene neparvovec (i.e., an Adverse Drug Reaction, ADR) should be reported by the investigator to Novartis Patient Safety as a spontaneous report or to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting.

Safety reporting for Novartis drugs other than the Novartis drug(s) of interest and for non-Novartis drugs

Adverse Drug Reactions (ADRs) occurring in patients exposed to a Novartis drug other than the Novartis drug of interest (i.e., voretigene neparvovec), can be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting **or** to Novartis Patient Safety as a spontaneous report.

All adverse reactions identified for non-Novartis drugs should be reported to the local Health Authority in accordance with national regulatory requirements for individual case safety reporting or the Marketing Authorization Holder as these will not be recorded in the Novartis safety database.

9.2 Follow-up Information

Recurrent episodes, complications, or progression of the initial event must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within the same timelines immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: if more stringent, local regulations regarding reporting timelines prevail). Any event that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Follow-up information is sent to the same contact person to whom the initial information was sent, stating, where an AE report form is used, that this is a follow-up to the previously reported event and providing the date of the original report. If known, the information missing from the

initial report should be completed. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, whether the patients continued or withdrew from study participation.

In case an SAE is not previously documented in the product information (EU SmPC or local equivalent), a Novartis Patient Safety associate may urgently require further information from the treating physician or other involved health care professional for Health Authority reporting.

In case an adverse event is considered to be of particular interest, a Novartis Patient Safety associate may seek additional information concerning the event. Corresponding questionnaires will then be provided by Novartis Patient Safety to the treating physician or other involved health care professional on a case-by-case basis.

9.3 Safety reporting period

Every AESI/AE/SAE, exposure during pregnancy, regardless of causality assessment, that occurred in patients exposed to the Novartis drug of interest must be reported to Novartis patient safety:

- after the patient has provided informed consent
- until early discontinuation from the study or the last patient last visit.

Any AESI/AE/SAEs and pregnancies **experienced after the last patient visit** should only be reported to Novartis if the investigator suspects a causal relationship to the Novartis drug of interest.

10 Plans for disseminating and communicating safety registry study results

Upon study completion and finalization of the study report, or at an earlier time point if deemed appropriate by the Sponsor, the results of this non-interventional study should be either submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.

The annual progress reports, which include but are not limited to an update of the enrollment, AEs/SAEs, and ophthalmic examination results, will precede the final study publication and study completion. Study progress reports will be provided annually within the PSUR. A standalone study report will be provided if a PSUR is not due for submission. The final manuscript will be submitted to EMA and the competent authorities of the Member States in which the product is authorized within two weeks after first acceptance for publication.

11 References

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12 Annexes

12.1 Safety Questionnaire

Patient ID:_____ Date of Visit _____

Since the patient's last visit, has s/he experienced:

Ocular Event	**No**	**Yes*, Right Eye (OD)**	**Yes*, Left Eye (OS)**	**Yes*, Both Eyes (OU)**	**Start Date**	**Ongoing/ End Date**
Increased Intraocular Pressure						
Retinal Tear						
Macular Disorders						
• Macular Hole						
• Foveal Dehiscence						
• Maculopathy (e.g., epiretinal membrane, macular pucker)						
• Foveal thinning						
• Loss of foveal function						
Chorioretinal atrophy (e.g. injection site atrophy/treatment emergent progressive atrophy)						
Cataract						
Intraocular Inflammation and/or Infection Related to the Procedure						
Retinal Detachment						
Host Immune Response (Ocular)						
Lack of Efficacy						
Decline in Efficacy over Time						
Other ocular event, specify						

Event	No	Yes*	Start Date	Ongoing/ End Date
New or exacerbated neoplastic event, specify				
Third Party Transmission				
Host Immune Response (Non-ocular)				
New or exacerbated hematologic event, specify				
New or exacerbated neurologic event, specify				

***NOTE**: **If YES to <u>any</u> of the above, the event(s) MUST be reported as an Adverse Event or Serious Adverse Event and documented in eCRFs**

***NOTE: If yes to any of the above, please provide a narrative of the event(s), including relevant information (e.g., presenting signs or symptoms, relevant associated medical or ocular conditions, concomitant medications, tests performed to assess the event and results, treatment given for the event, etc).**

Event:

Narrative:

12.2 Modified VFQ-25 Questionnaire

This questionnaire should be completed for participants who were enrolled under the original protocol version 01.

Adult participants:

- Participants should complete the questionnaire, but due to limited vision, may need assistance.

Minor participants:

1. Parent/guardian should complete one copy of the questionnaire and provide their perspective of the participant's vision.
2. The participant should complete a second copy of the questionnaire to provide his/her perspective in collaboration with the parent/guardian as needed.
    - If the participant is very young, it is expected that the parent/guardian will assist the child as needed to answer the questions and to complete the questionnaire. It is desirable that the parent/guardian will contribute less as the child ages. By the time the child becomes a young teenager, it is assumed that the teenager themselves will provide the questionnaire responses. However, the parent/caregiver may assist as needed.

This questionnaire should be completed by the same parent/guardian throughout the duration of the study, if possible.

Modified VFQ-25 Questionnaire

For the following questions, an answer of "0" means "Never":

1. Can you read lighted dials or lights on electronic equipment (for example, LED lights on clocks, cellular phones, radios, or hand-held video games)?

   Never Sometimes Always Not Answered

   0 1 2 3 4 5 6 7 8 9 10

2. Using your vision alone, can you locate doorknobs and handles without first passing your hand over them?

   Never Sometimes Always Not Answered

   0 1 2 3 4 5 6 7 8 9 10

3. If your things are moved from their normal spots, can you find them quickly using your vision alone?

   Never Sometimes Always Not Answered

   0 1 2 3 4 5 6 7 8 9 10

4. Can you walk in unfamiliar outdoor places by yourself without help (e.g. canes, guides) at dusk?

   Never Sometimes Always Not Answered

   0 1 2 3 4 5 6 7 8 9 10

5. Can you recognize people first by vision alone (rather than by some other means, for example the sound of their voice or the way they walk)?

   Never Sometimes Always Not Answered

   0 1 2 3 4 5 6 7 8 9 10

6. Can you find a new bus stop (e.g. school bus or public transportation) by yourself?

   Never Sometimes Always Not Answered

   0 1 2 3 4 5 6 7 8 9 10

7. Can you read normal print books or see details in pictures without magnifiers or computer/television screens?

Never Sometimes Always Not Answered

0 1 2 3 4 5 6 7 8 9 10

8. Can you see a movie in a theater, or a planetarium show?

Never Sometimes Always Not Answered

0 1 2 3 4 5 6 7 8 9 10

9. Using your vision (only), can you find your plate, fork and spoon in a restaurant that is dimly lit?

Never Sometimes Always Not Answered

0 1 2 3 4 5 6 7 8 9 10

10. Can you read labels on cans/food products/medicine bottles?

Never Sometimes Always Not Answered

0 1 2 3 4 5 6 7 8 9 10

11. Can you read street signs or signage in buildings (such as STOP and EXIT signs)?

Never Sometimes Always Not Answered

0 1 2 3 4 5 6 7 8 9 10

For the following questions, an answer of "0" means "Always":

12. Using your vision (only), do you have difficulty judging whether someone is male or female?

Always Sometimes Never Not Answered

0 1 2 3 4 5 6 7 8 9 10

13. Using your vision (only), do you have trouble determining the expression (happy, sad, neutral) on unfamiliar faces?

Always Sometimes Never Not Answered

0 1 2 3 4 5 6 7 8 9 10

14. Do you have trouble identifying simple shapes (circle, rectangle, square)?

Always Sometimes Never Not Answered

0 1 2 3 4 5 6 7 8 9 10

15. Do you have difficulty seeing which direction hands on a clock (non-digital) are facing?

Always Sometimes Never Not Answered

0 1 2 3 4 5 6 7 8 9 10

16. Do you put things down in specific places so that you can find them by feel/touch?

Always Sometimes Never Not Answered

0 1 2 3 4 5 6 7 8 9 10

17. When using your vision alone and in good light, do you make mistakes when dressing (e.g. mismatched socks, wrong outfit, confusing left vs. right shoe)?

Always Sometimes Never Not Answered

0 1 2 3 4 5 6 7 8 9 10

18. When using your vision alone, do you make mistakes when using the bathroom or bathing (e.g. unable to locate bottles, bathroom fixtures)?

Always Sometimes Never Not Answered

0 1 2 3 4 5 6 7 8 9 10

19. In your home or school environment, if someone accidentally leaves a cabinet door, a gate, a locker door, or some other moveable object in a new position, are you likely to bump into it?

Always Sometimes Never Not Answered

0 1 2 3 4 5 6 7 8 9 10

20. Do you need assistance such as a guide or a cane to walk confidently in new places?

Always Sometimes Never Not Answered

0 1 2 3 4 5 6 7 8 9 10

21. In unfamiliar surroundings, how often do you run into things by mistake (e.g. stub your toe, hit your shoulder, trip)?

Always Sometimes Never Not Answered

0 1 2 3 4 5 6 7 8 9 10

22. In familiar surroundings, how often do you get lost or disoriented, even briefly?

Always Sometimes Never Not Answered

0 1 2 3 4 5 6 7 8 9 10

23. Are there activities that make you uncomfortable or nervous because of the way your vision is?

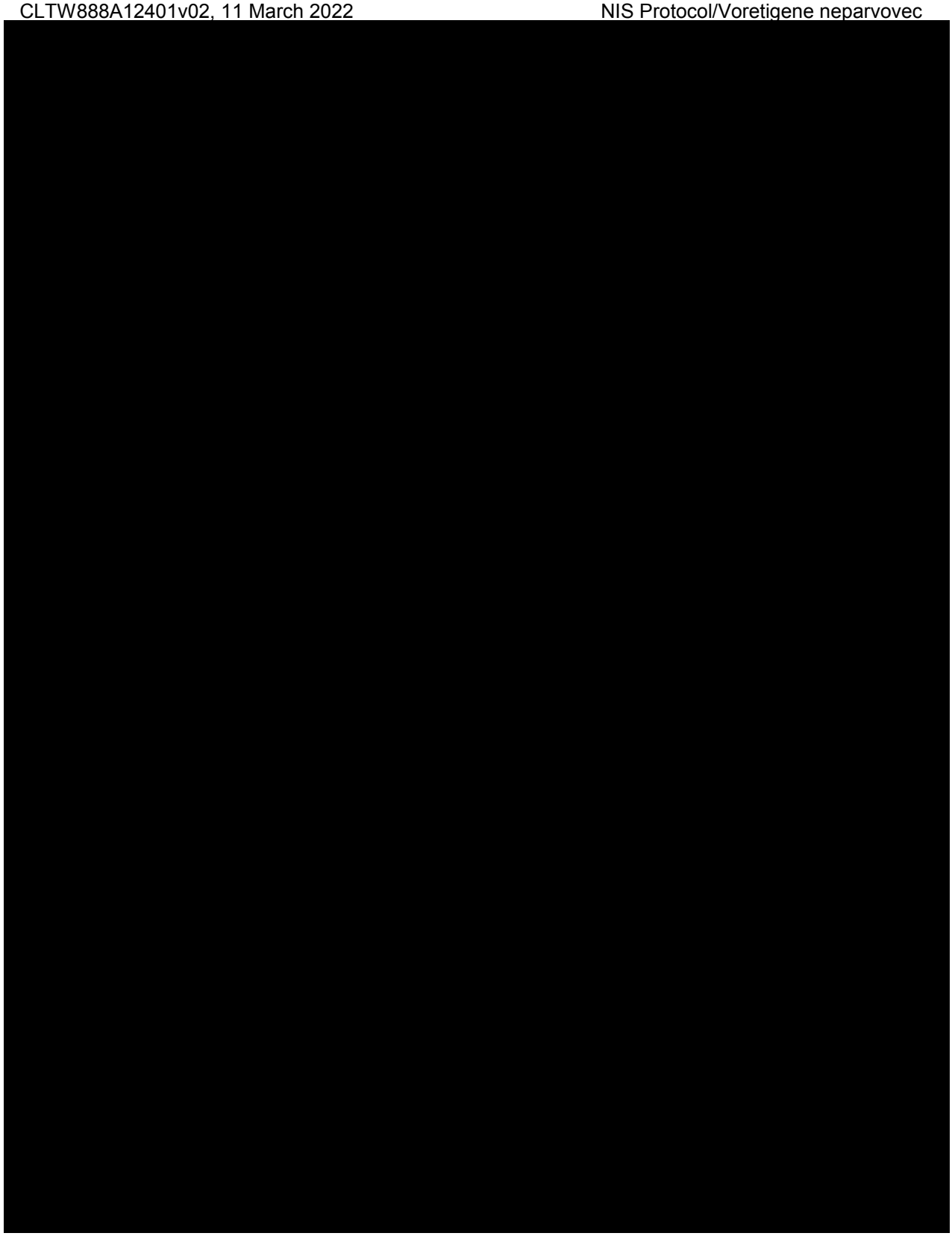
Always				Sometimes						Never	Not Answered
0	1	2	3	4	5	6	7	8	9	10	

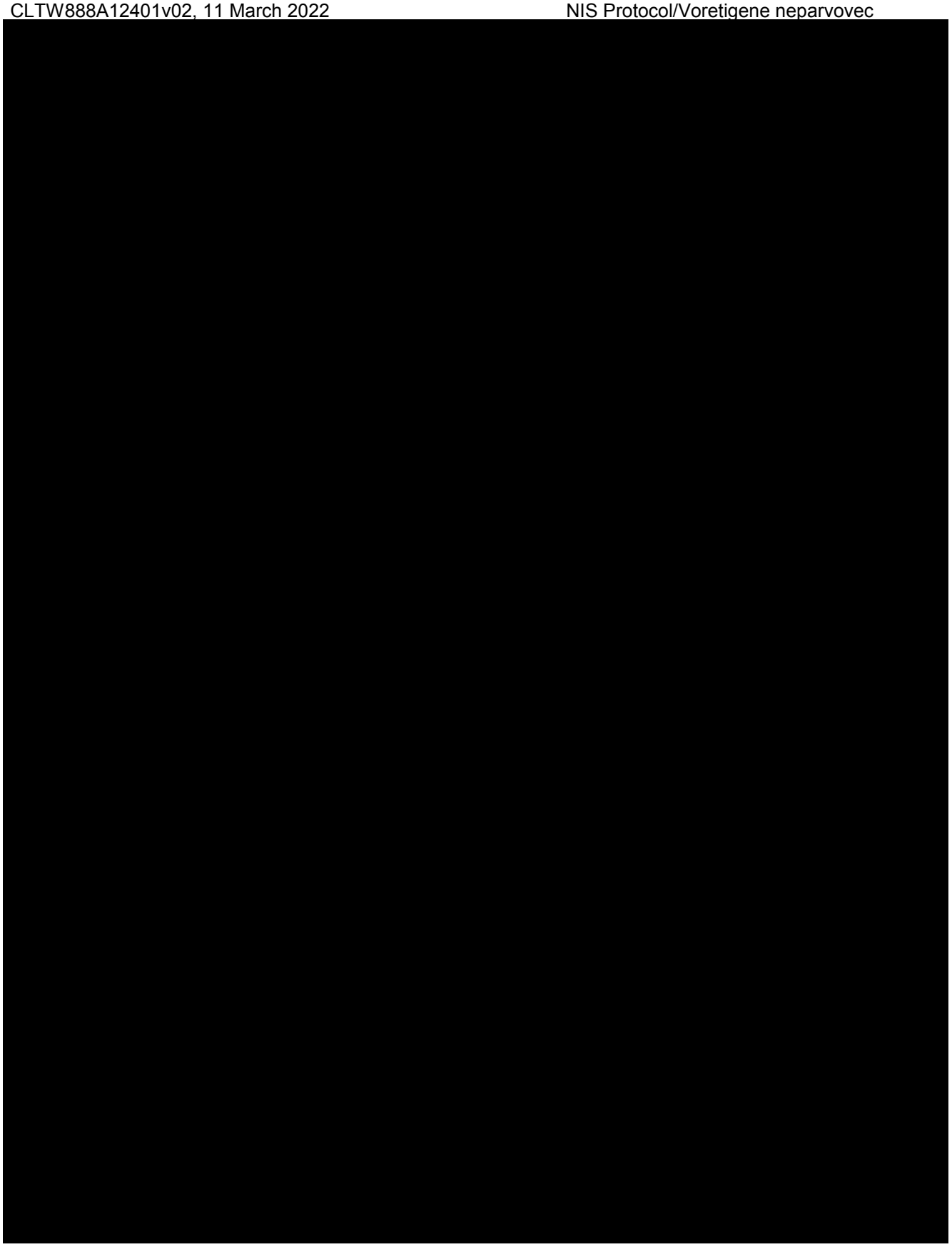
24. Do you hesitate before using stairs or getting onto an escalator or going through a revolving door by yourself because of difficulty seeing?

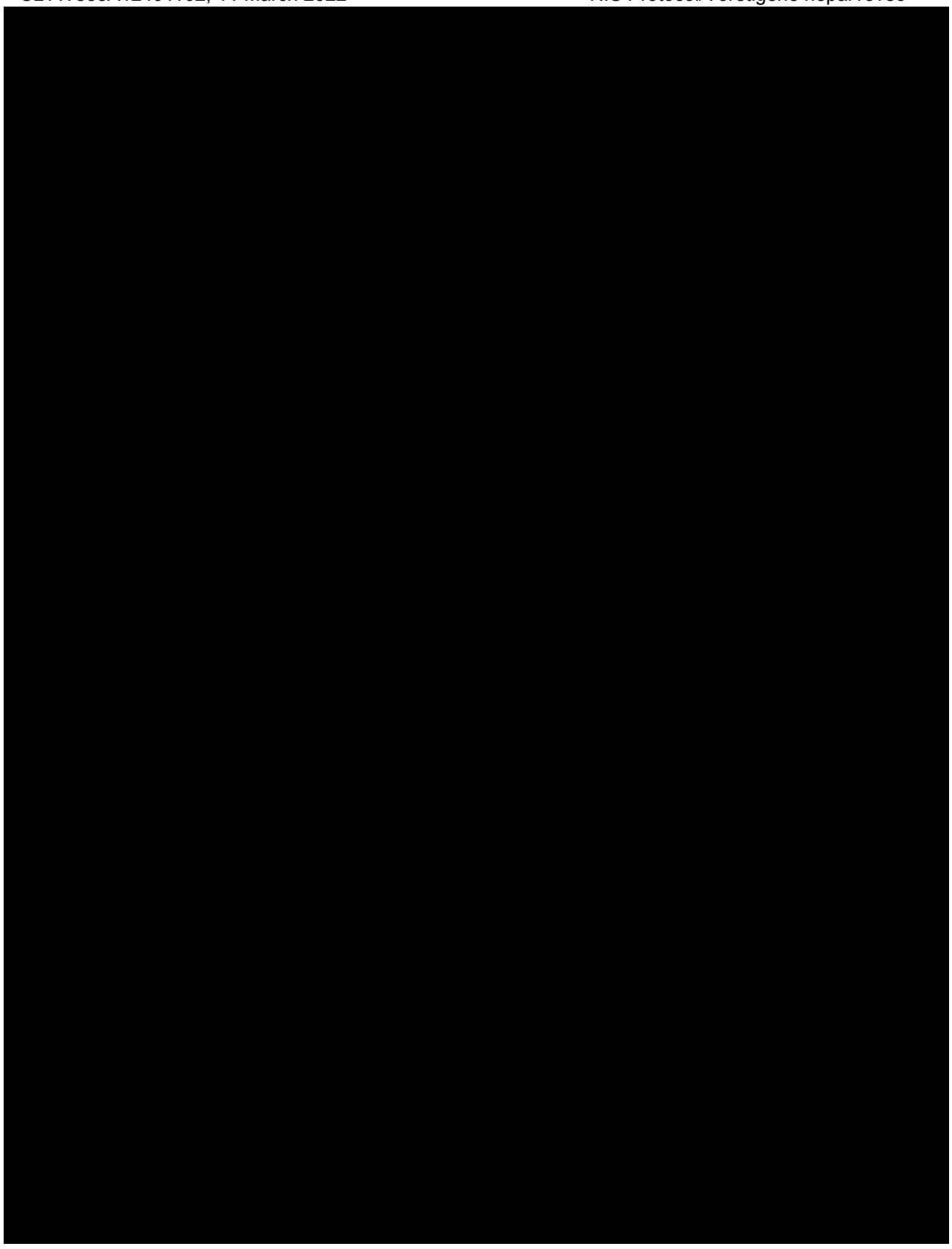
Always				Sometimes						Never	Not Answered
0	1	2	3	4	5	6	7	8	9	10	

25. If you are walking around a familiar place, such as your home, do you overshoot objects or run into things if they have been moved from their usual spot?

Always				Sometimes						Never	Not Answered
0	1	2	3	4	5	6	7	8	9	10	







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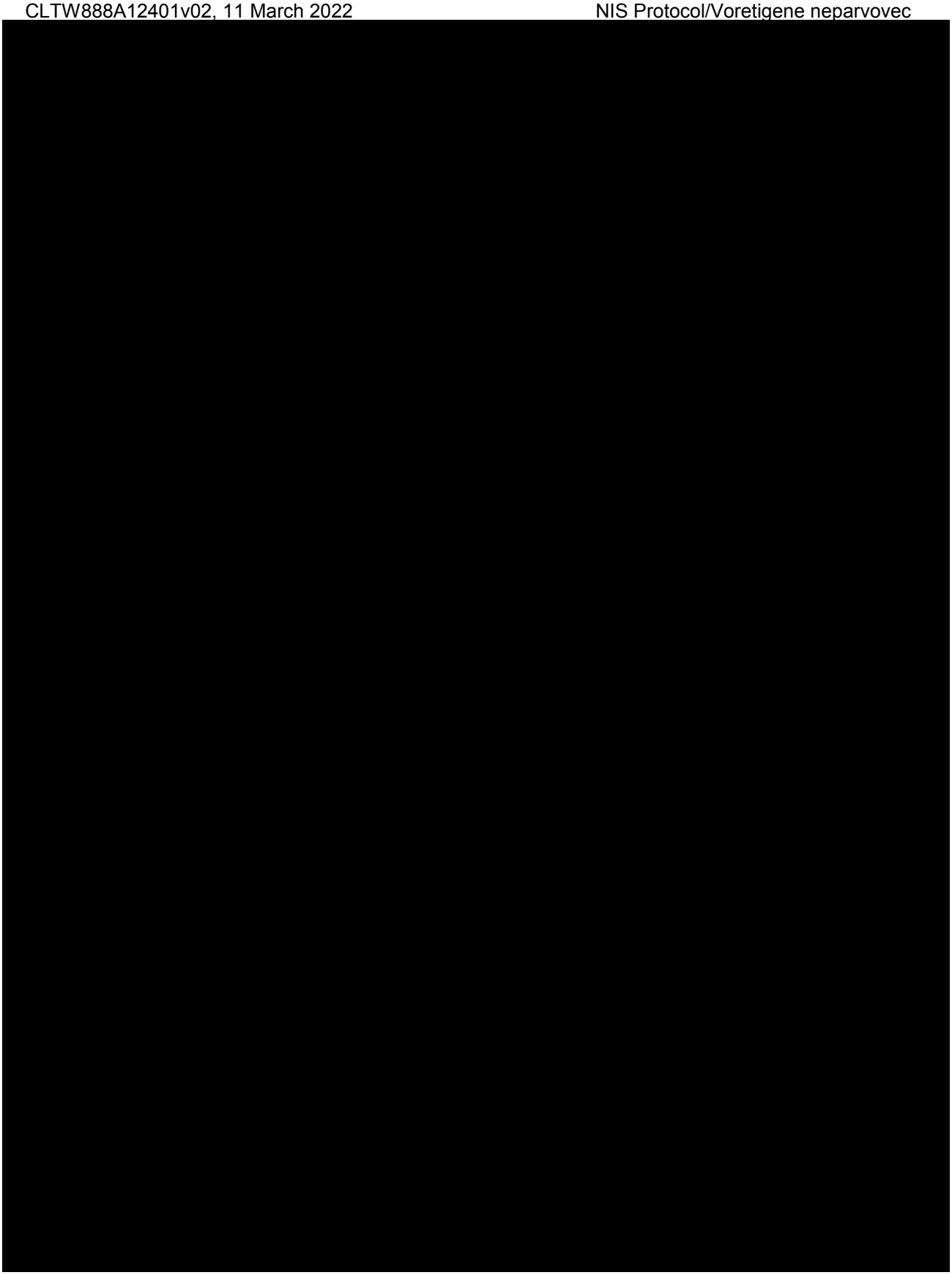

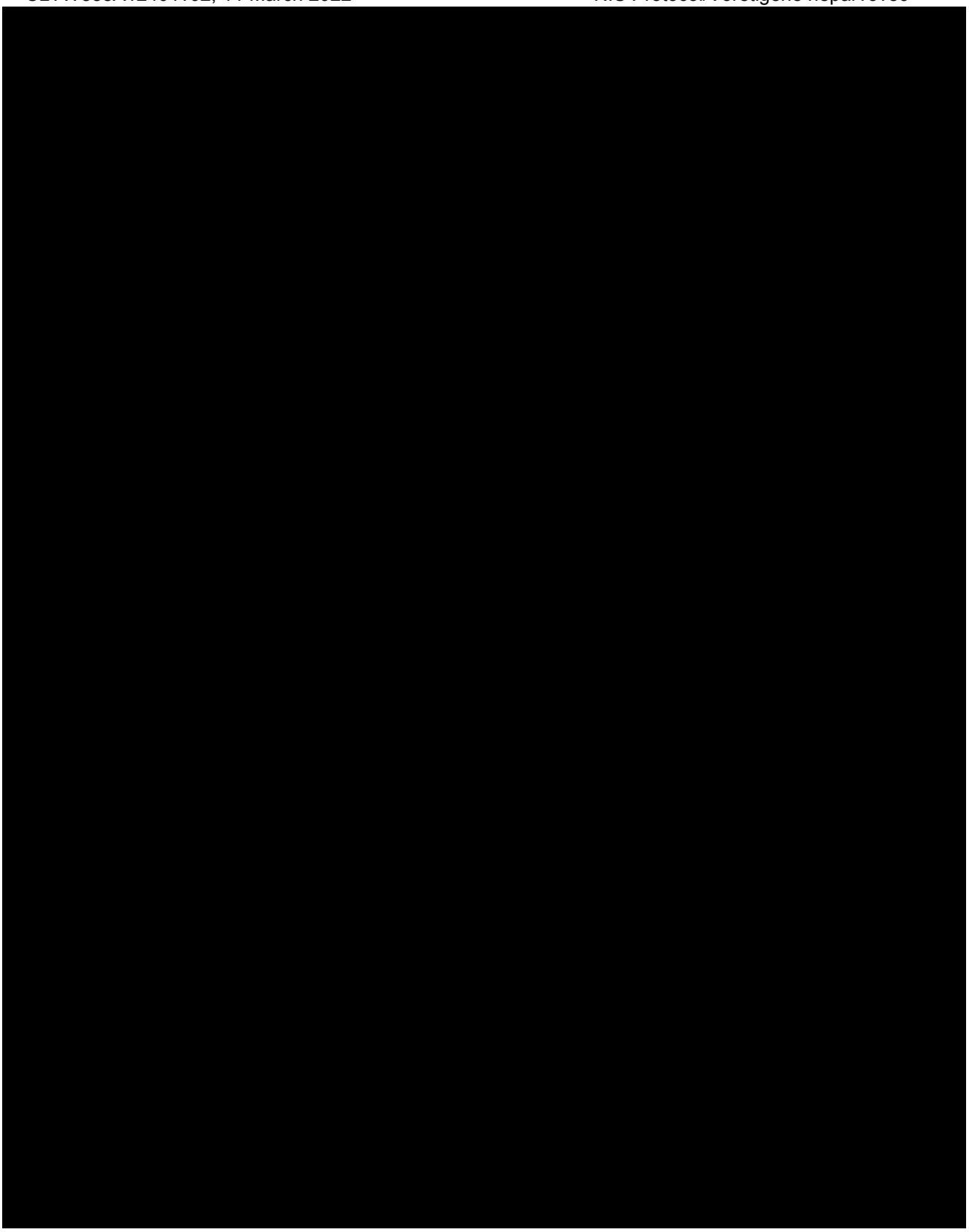

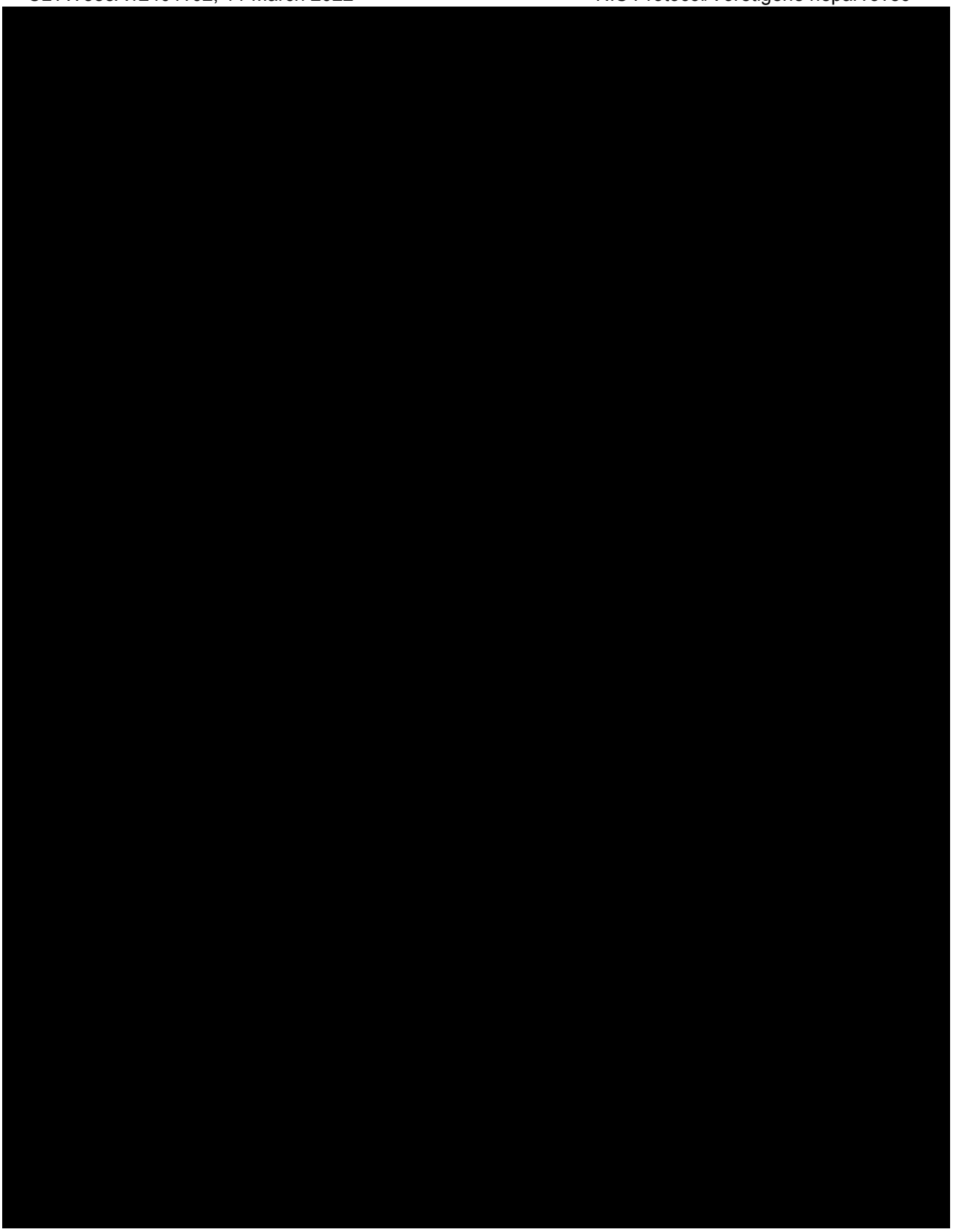

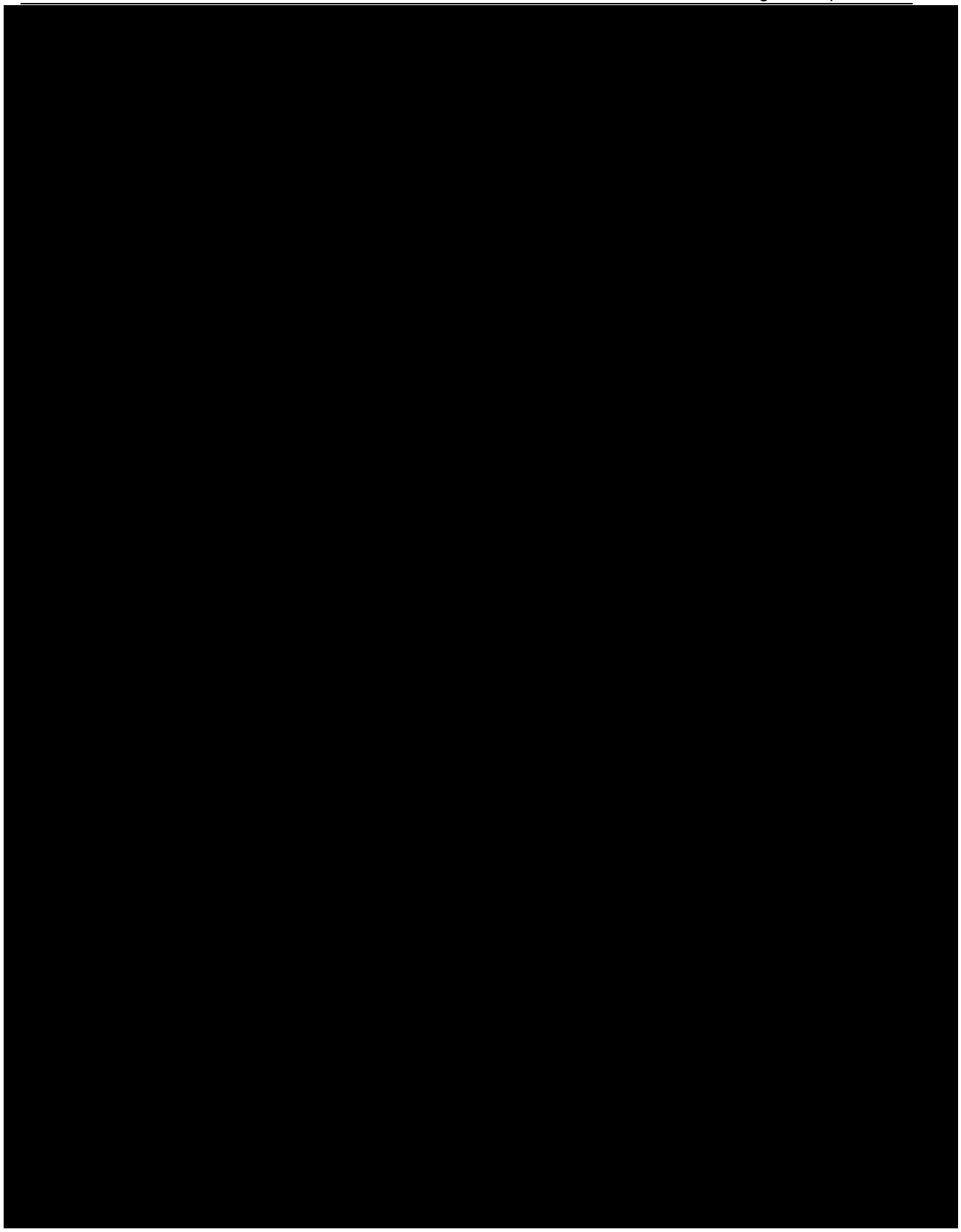

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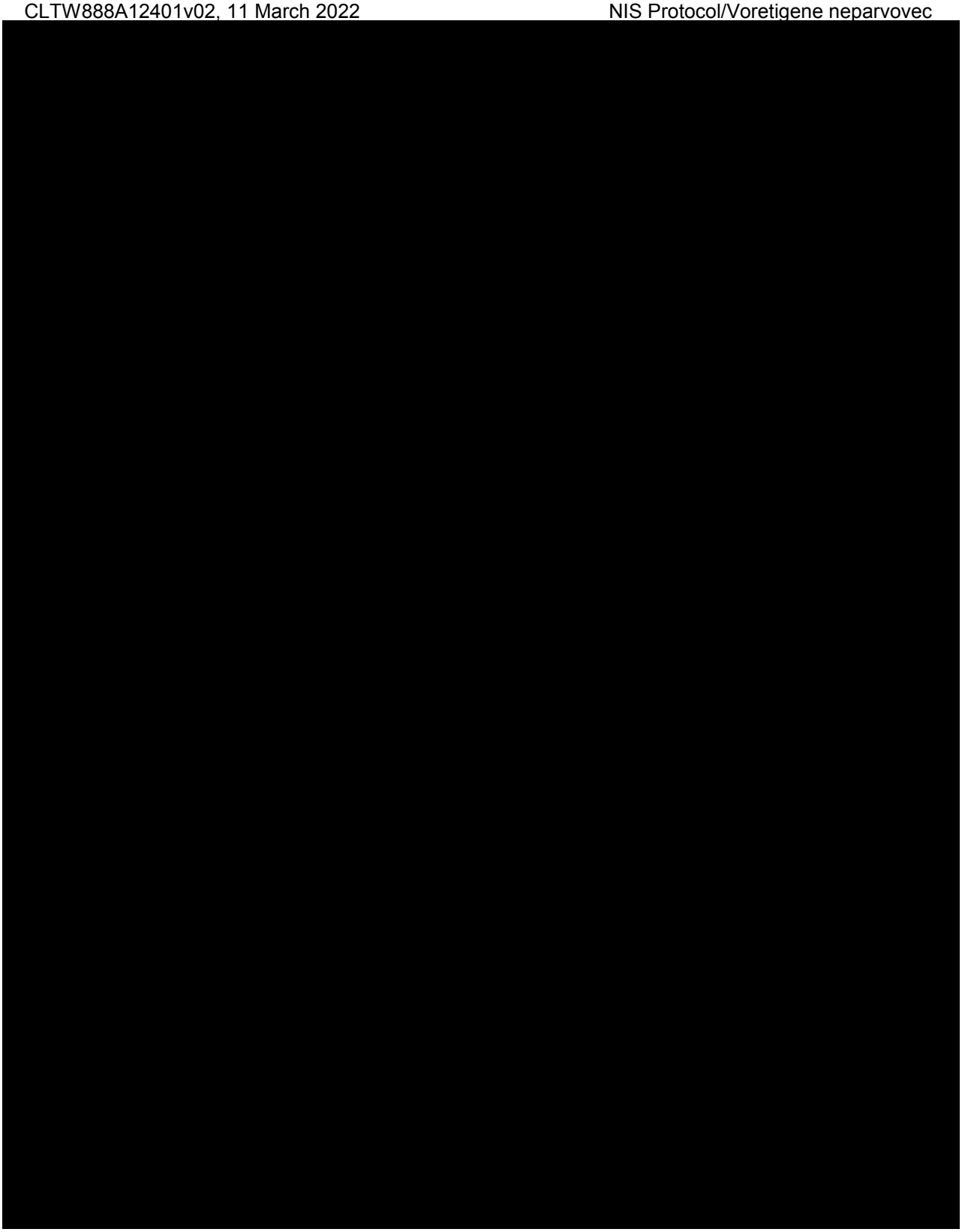

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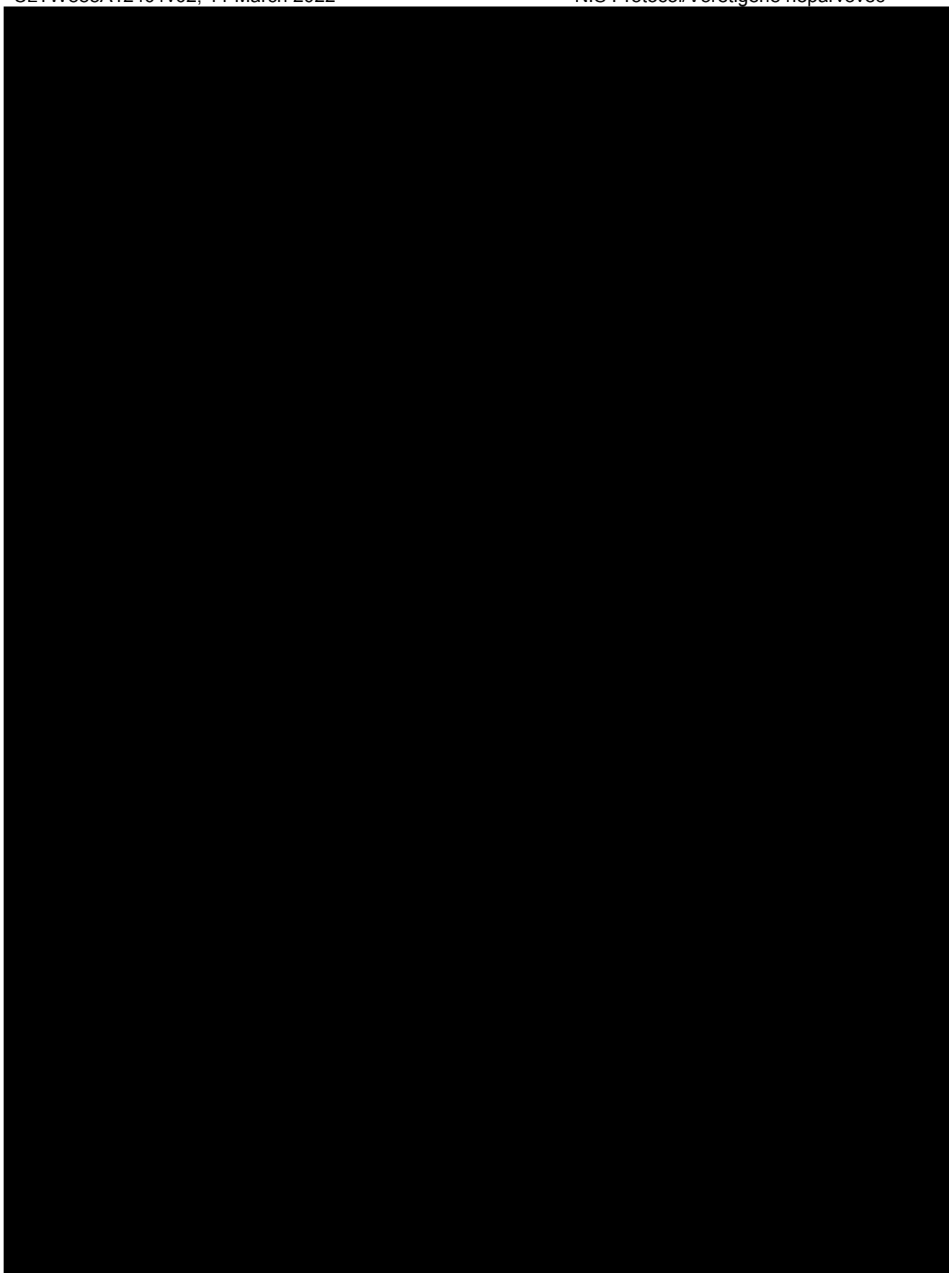

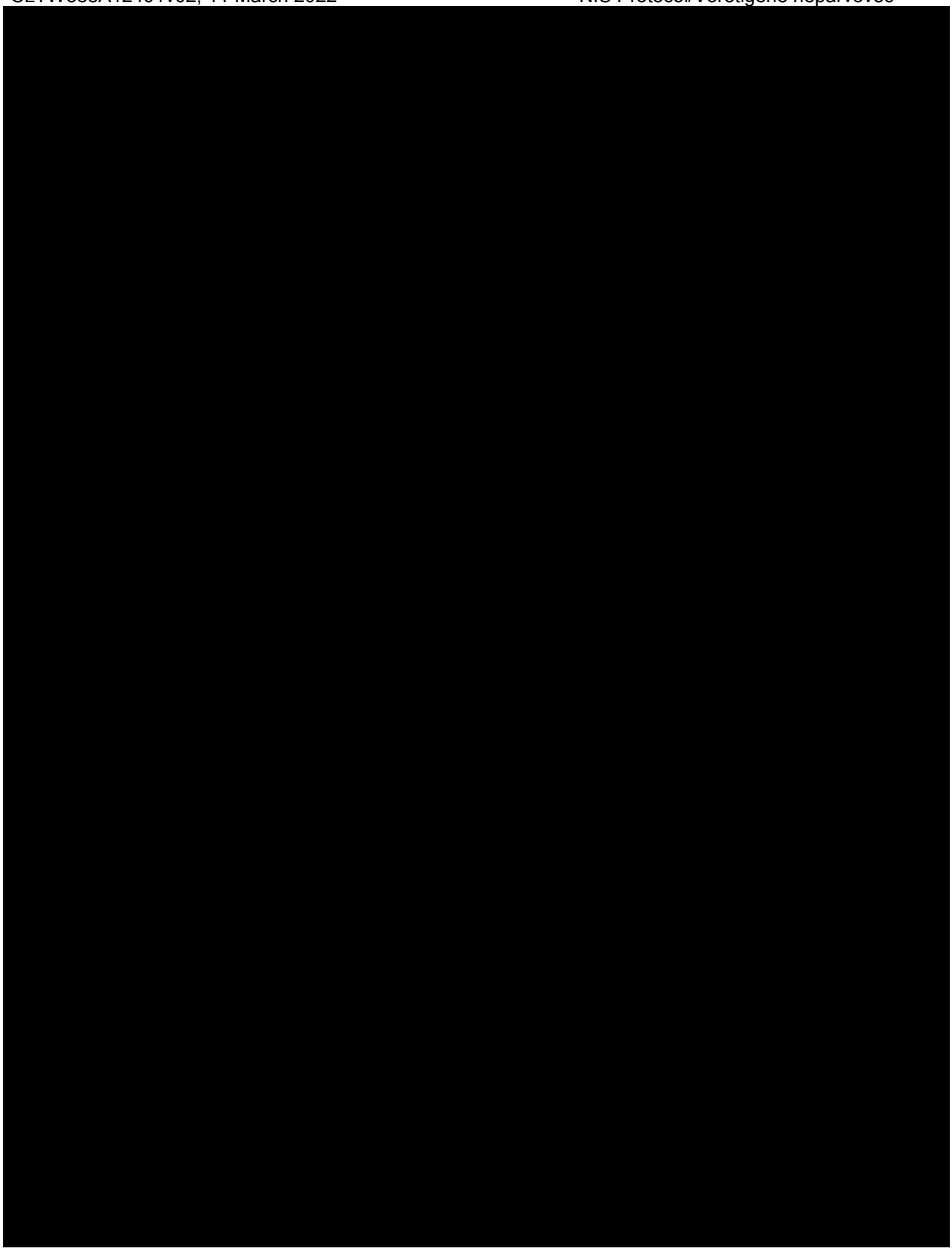

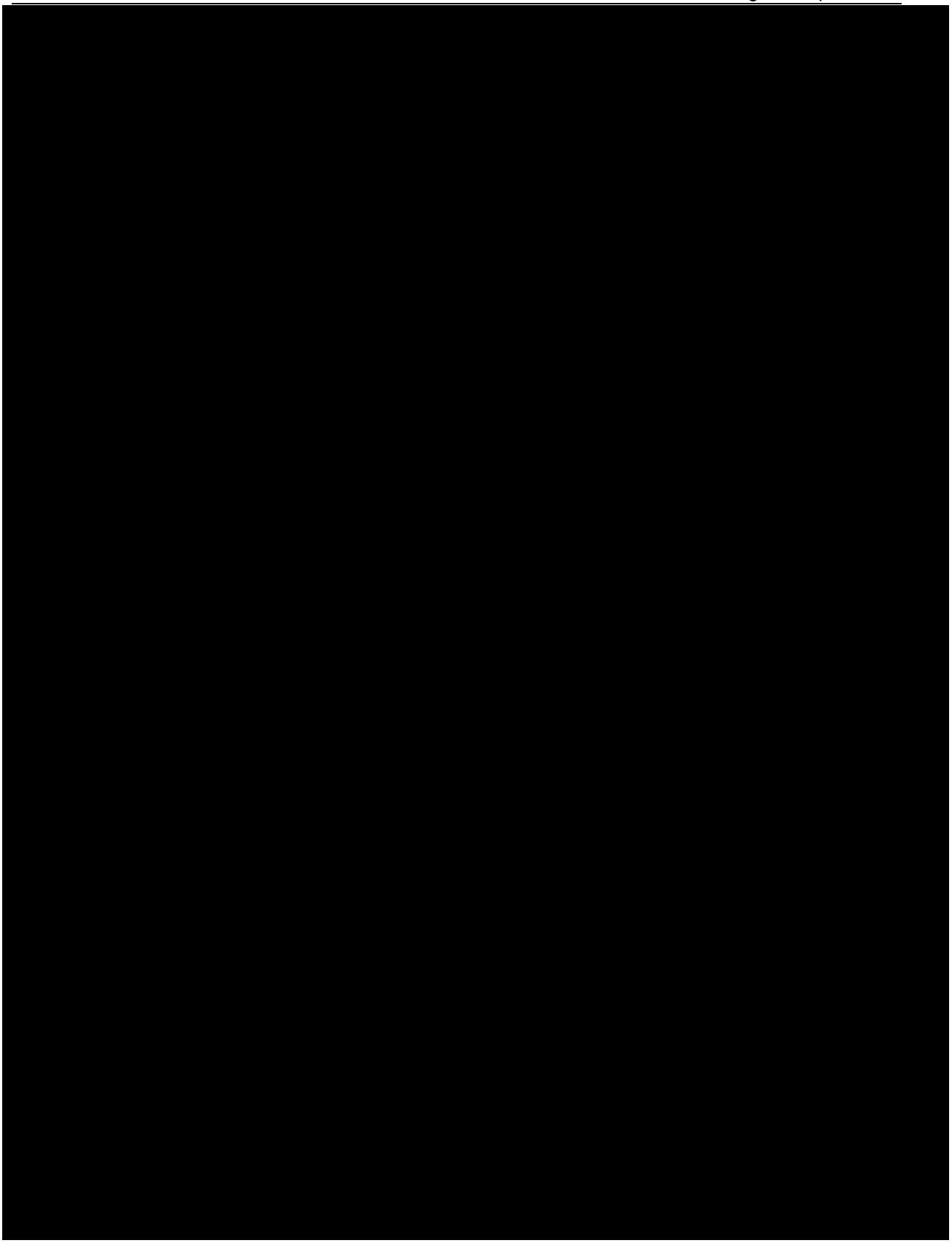

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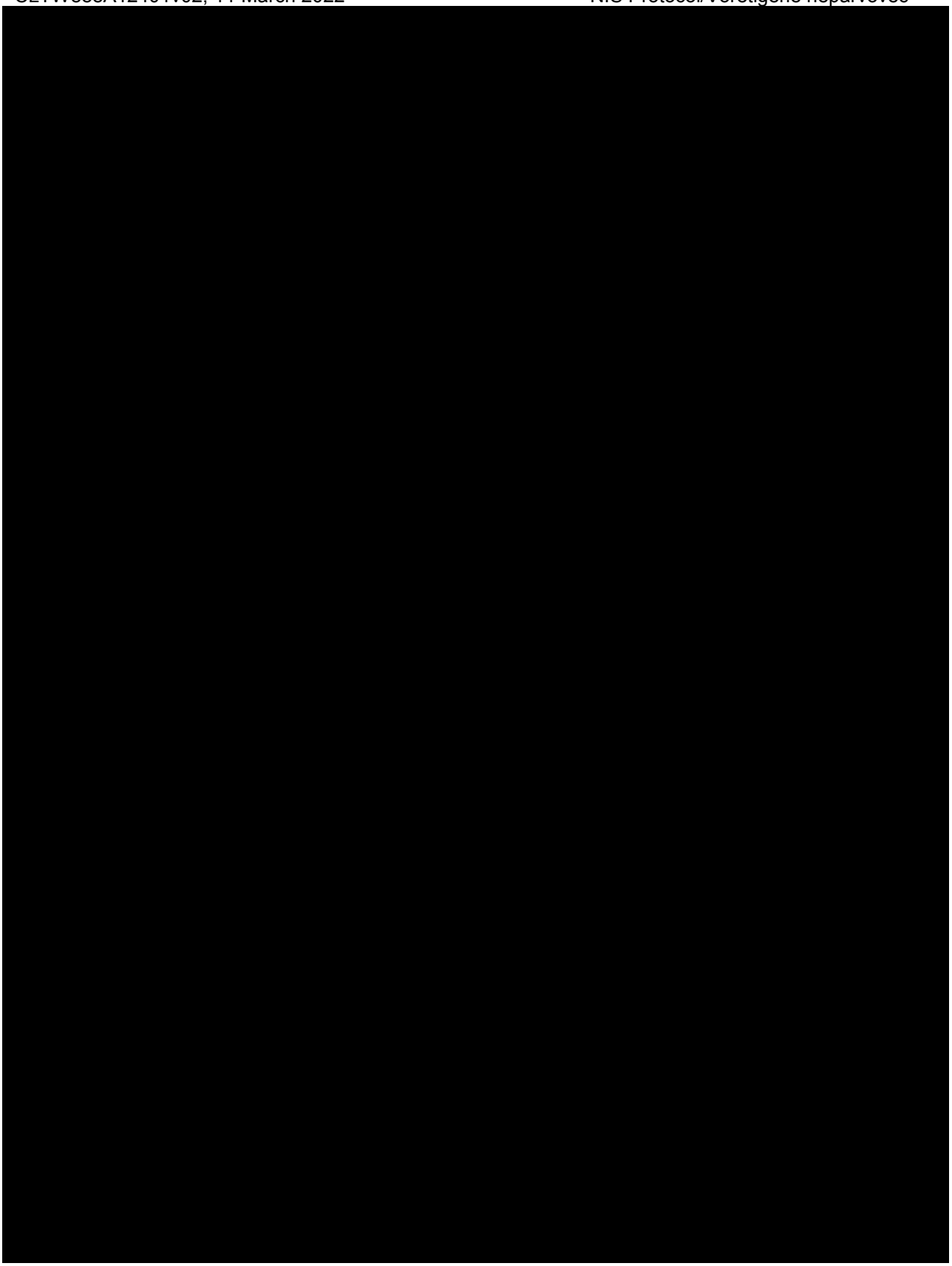

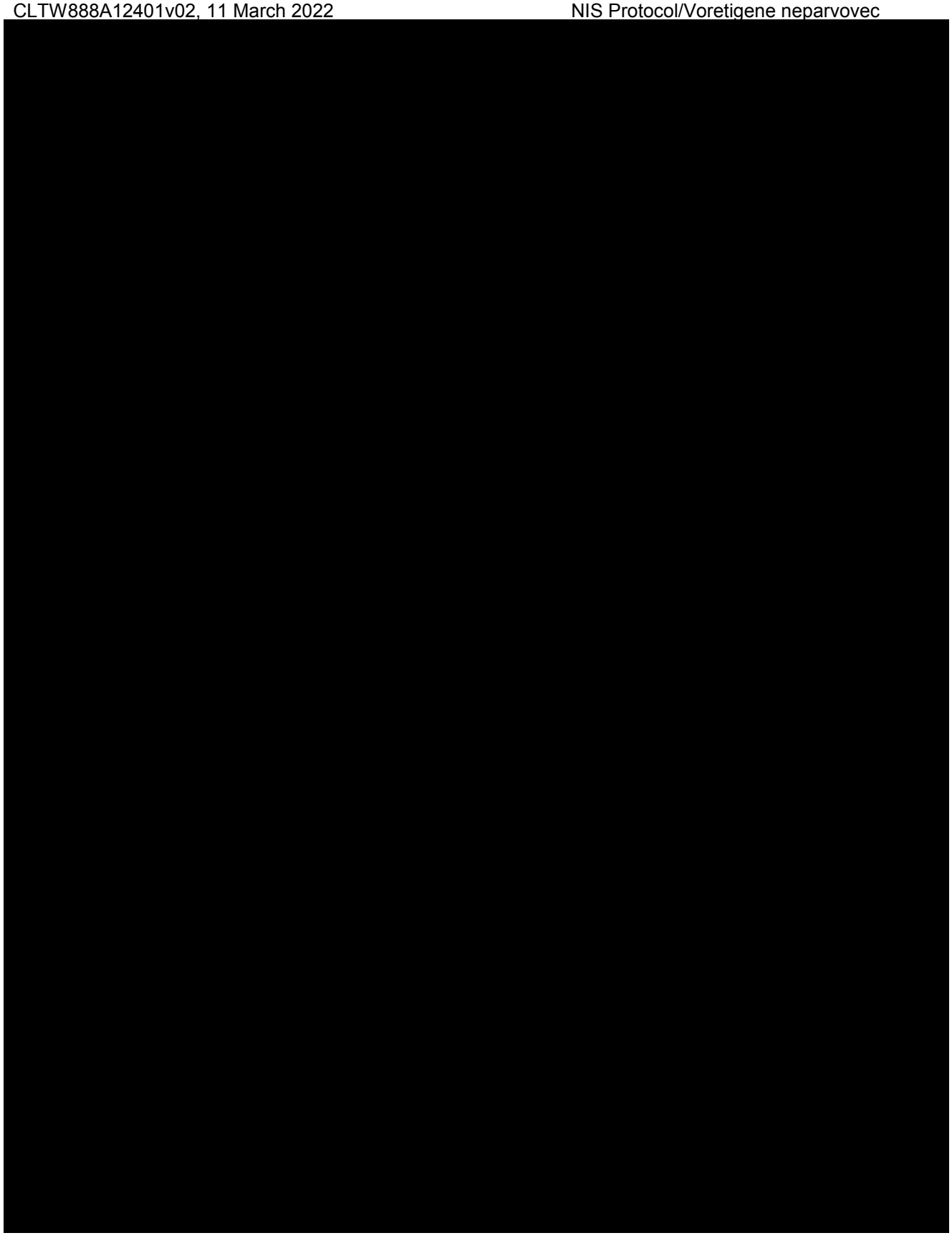

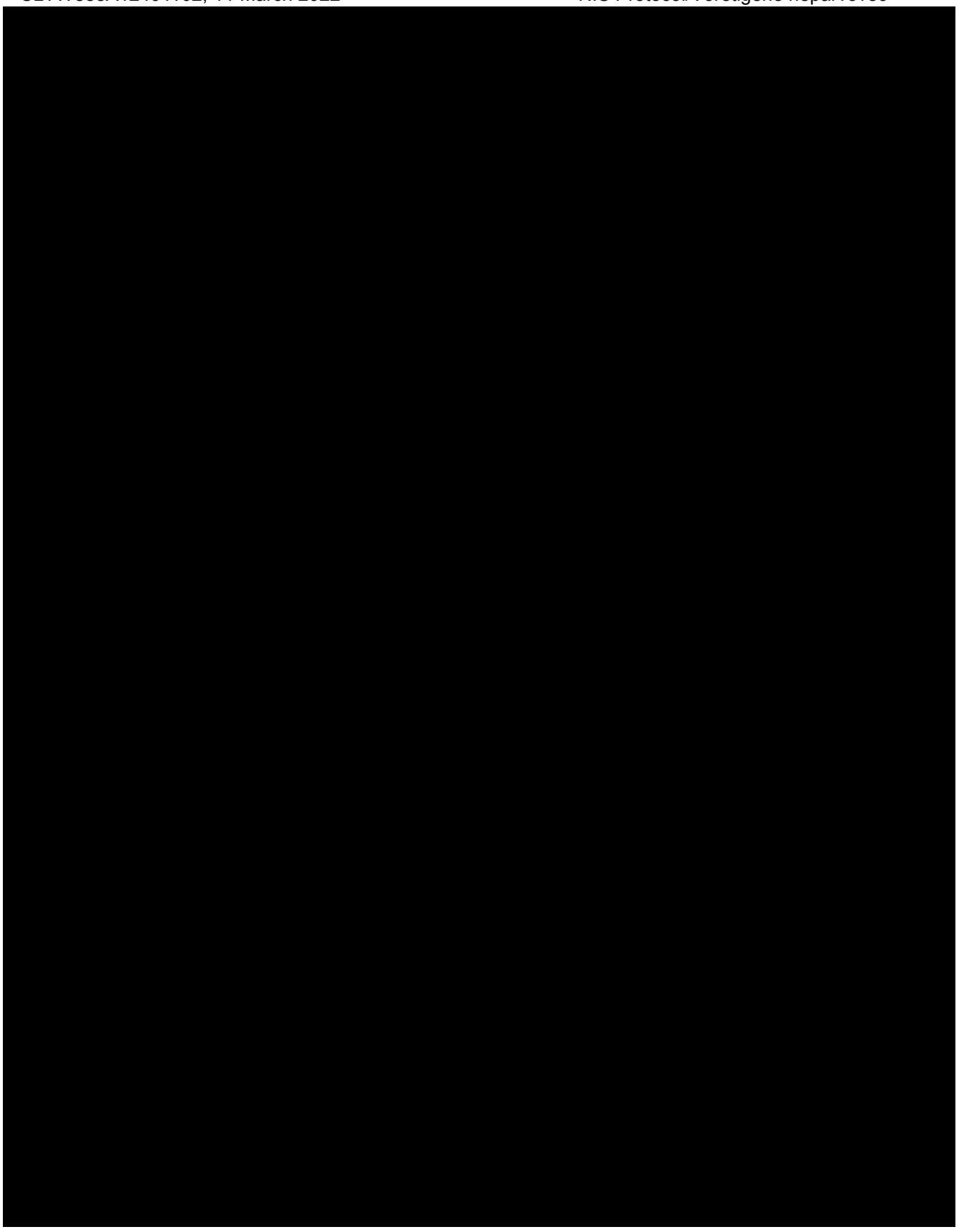

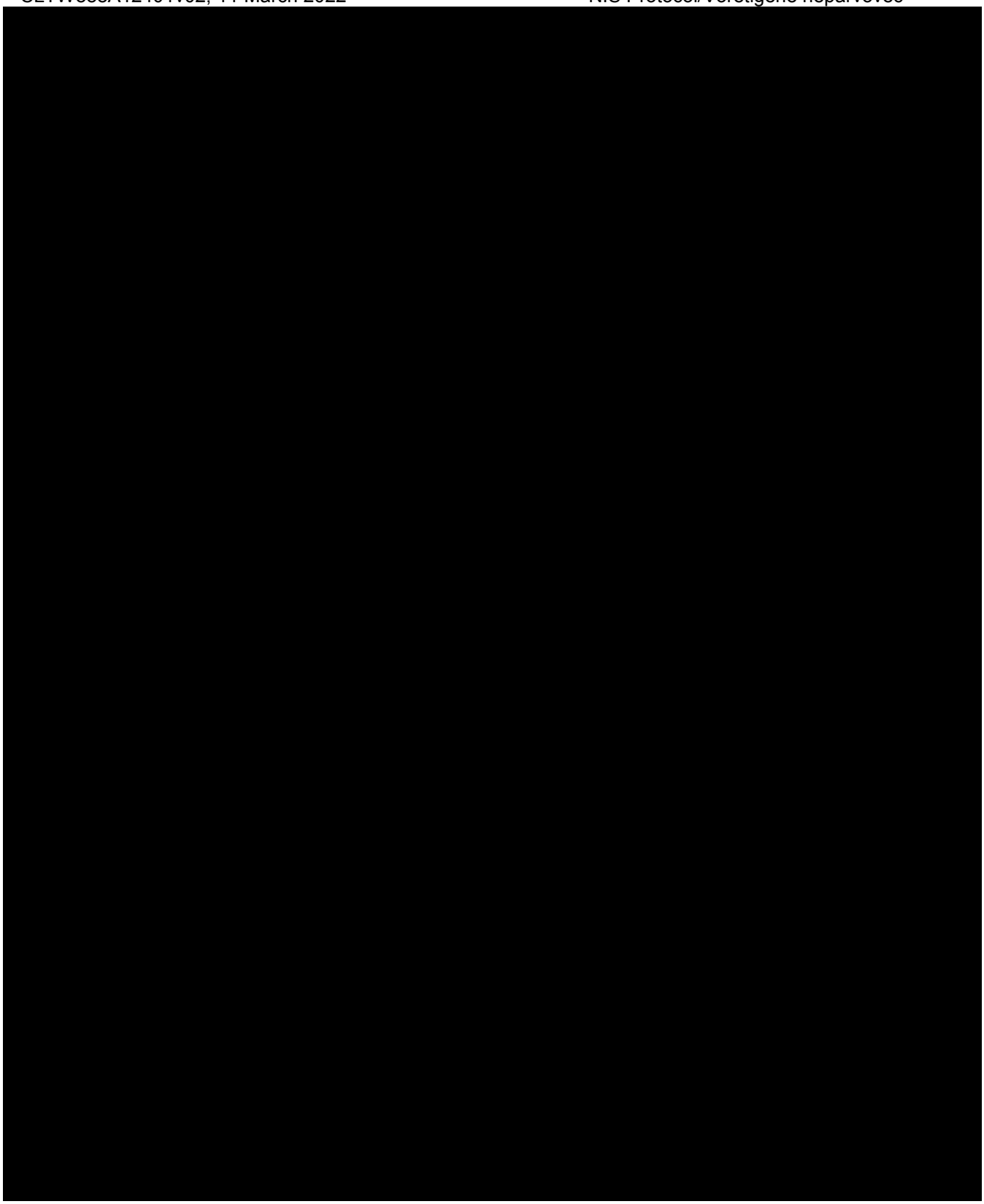

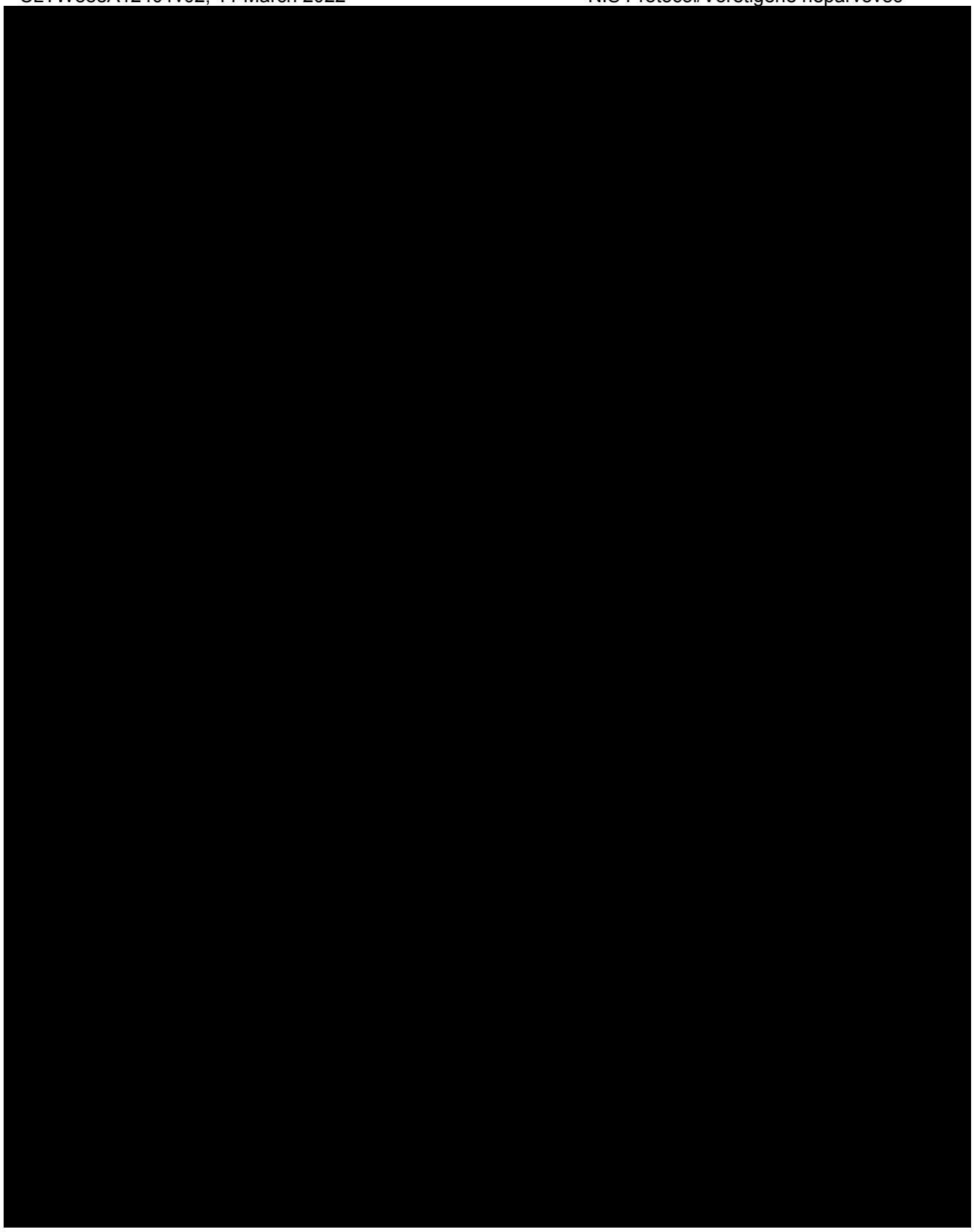

12.5 Burden Index of Caregivers

This questionnaire should be completed by the parent/guardian/caregiver.

- Whenever possible, the same person should complete the questionnaire throughout the duration of the study.

Patient ID:_____

Date of visit: _____

Using the following legend, select how you felt during the last week;

0 – Never / 1 – Almost never / 2 – Sometimes / 3 – Often / 4 – Always

1. I cannot freely leave the house because of care-giving	
2. I do not have enough time for myself because of care-giving	
3. I want to delegate the care to someone else	
4. I am completely distressed by care-giving	
5. I am experiencing hardship because care-giving does not give me a sense of satisfaction	
6. Care-giving is hard because I cannot find the meaning of providing care	
7. My body aches when providing care to my family member	
8. I have ruined my health in the course of providing care	
9. It is a burden that public aid service personnel enter our house	
10. I have a hard time because patients resent receiving public aid care services	
11. How burdensome do you think providing care is to you?	

12.6 ENCePP checklist for study protocol

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
A Post-Authorization, Multicenter, Multinational, Longitudinal, Observational Safety Registry Study for Patients Treated with Voretigene Neparvovec

EU PAS Register® number: EUPAS31153

Study reference number: CLTW888A12401

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4
1.1.2 End of data collection[2]	☒	☐	☐	4
1.1.3 Progress report(s)	☒	☐	☐	4
1.1.4 Interim report(s)	☐	☒	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	4
1.1.6 Final report of study results.	☒	☐	☐	4

1. Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
2. Date from which the analytical dataset is completely available.

Comments:

Progress reports will be provided annually – no other interim reports are planned.

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	5 and 6
2.1.2 The objective(s) of the study?	☒	☐	☐	6
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Safety variables will be summarized by descriptive statistics. No inferential analysis will be done and no hypothesis will be tested. There is no *a priori* hypothesis to be tested.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	7.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7.3
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	7.6
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	9

Comments:

This study is intended to descriptively document the frequency and severity of events of interest. No measures of association will be presented.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	7.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	7.2
4.2.2 Age and sex	☒	☐	☐	7.2
4.2.3 Country of origin	☐	☒	☐	
4.2.4 Disease/indication	☐	☐	☒	
4.2.5 Duration of follow-up	☒	☐	☐	7.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	7.2

Comments:

This is a product registry – patients who receive voretigene neparvovec treatment are eligible. Information on the clinical and genetic diagnoses of the condition that led to voretigene neparvovec treatment will be collected.

This registry will be conducted in multiple countries, and patients can be included regardless of country of origin where Luxturna® is marketed.

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	7.2
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	7.7.1
5.3 Is exposure categorised according to time windows?	☐	☐	☒	
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	7.2
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☒	☐	

Comments:

Voretigene neparvovec is administered by specialist ophthalmologists (retinal surgeons) as a single dose to each eye in a hospital setting. Exposure data will be collected in the medical records. There are no appropriate comparators for this treatment.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	6.1, 6.2 & 7.6
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7.3 and 7.6

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	7.2 and 7.3

Comments:

This study is intended to descriptively document the frequency and severity of reported events of interest. There are no additional measures to address the validity of the outcome measurements. The mVFQ-25, [redacted] response scores will be summarized by descriptive statistics to provide HRQoL data. The Burden Index of Caregivers (BIC) Questionnaire will be administered to obtain data describing the burden of care-giving imposed by the disease.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☒	☐	
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☒	☐	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☒	☐	

Comments:

As described in Section 7.8, the lack of randomization and a control group in this single arm study is not able to account for selection bias. The observational nature of the study, without using standardized assessment procedures, is also not able to account for potential information bias. Nonetheless, this study design will be able to describe what is observed when voretigene neparvovec is used in the real-world setting, when patients are treated as per the current standard of care.

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	7.6

Comments:

Analysis by age categories is planned.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	7.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	7.3
9.1.3 Covariates and other characteristics?	☒	☐	☐	7 .3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	7.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	7.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	7.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	7.6.2
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	7.7.2

Comments:

This is a product registry for patients who receive voretigene neparvovec treatment. No additional coding of the exposure is required.

This study is intended to descriptively document the frequency and severity of reported events of interest. There is no additional coding for covariate. Each patient would have a unique patient ID which could be used to link CRF information with source documents.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	7.6
10.2 Is study size and/or statistical precision estimated?	☐	☒	☐	
10.3 Are descriptive analyses included?	☒	☐	☐	7.6
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☒	☐	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☒	☐	
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

Comments:

There is no formal sample size estimation. Every effort will be made to enroll all patients treated with voretigene neparvovec, and it is expected that a minimum of 40 adult or pediatric, male or female patient can be enrolled over a five year enrollment period.

No formal statistical evaluations are planned. Output will be limited to data listings and descriptive statistics, where applicable.

Detailed methods for handling missing data will be described in a separate Statistical Analysis Plan document.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	7.7
11.2 Are methods of quality assurance described?	☒	☐	☐	7.7
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	7.7.2

Comments:

All source documents must be maintained to enable any independent data review.

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	7.8
12.1.2 Information bias?	☒	☐	☐	7.8
12.1.3 Residual/unmeasured confounding?	☒	☐	☐	
(e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).				7.8
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	7

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	8
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	8

Comments:

There have been no ethical review procedures for this protocol to date.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	3

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	10
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	10

Comments:

Name of the main author of the protocol: [redacted]

Date: dd/Month/year_____

Signature: _____