PART 1 (COUNCIL DECISION 2002/813/EC)

SUMMARY NOTIFICATION INFORMATION FORMAT FOR THE RELEASE OF GENETICALLY MODIFIED ORGANISMS OTHER THAN HIGHER PLANTS IN ACCORDANCE WITH ARTICLE 11 OF DIRECTIVE 2001/18/EC

In order to tick one or several possibilities, please use crosses (meaning x or X) into the space provided as (.)

A. General information

1. Details of notification

(a)	Member State of notification	Germany
(b)	Notification number	B/DE/17/PEI3212
(c)	Date of acknowledgement of notification	06.10.2017
(d)	Title of the project	"A Phase III Multicenter Randomized, Sham Controlled, Study to Determine the Safety and Efficacy of Renexus in Macular Telangiectasia type 2"
(e)	Proposed period of release through	March 2018 through December 2018

2. Notifier Dr. Zubair Hussain, LE4D Ltd (Legal representative)

Name of institution or company: Neurotech Pharmaceuticals, Inc.

3. GMO characterisation

(a) Indicate whether the GMO is a:

viroid		(.)
RNA virus		(.)
DNA virus		(.)
bacterium		(.)
fungus		(.)
animal		
-	mammals	(X)
-	insect	(.)
-	fish	(.)
-	other animal	(.)

specify phylum, class Chordate, Mammal

(b) Identity of the GMO (genus and species)

Genetically engineered cell line derived from *homo sapiens* donor

(c) Genetic stability – according to Annex IIIa, II, A(10) and II, C(2)(c)

Summary (full description in Annex III as above): Briefly, genotypic characterization of stability for NTC-201 cells was conducted in order to [a] establish that the correct coding sequence of the CNTF product was maintained during culture to the end of production, [b] assess the stability of CNTF gene copy number and [c] verify the integration status of the gene. Stability of the genetic insert would be affected by where in the genome it inserted and instability would be detected by comparing early and late passage cells by southern blot analysis. The MCB (early passage) and EOP (late passage) cells generated for each cell line represent appropriate samples for analysis since the MCB represents a starting point for cell line generation and the EOP cells were expanded under conditions that simulate full-scale conditions and are beyond the in vitro cell age intended for manufacturing. The results from the CNTF gene sequence analysis, quantitative PCR determination of the gene copy number and southern blot analysis are provided for NTC-201-6A MCB and EOP. Finally, the production of CNTF protein remains stable across passage. The following data support the above statements.

CNTF gene sequencing analysis was performed on the 758 bp RT-PCR product derived from the expression plasmid pNUT-IsSP-hCNTF in the cell samples from the MCB (early passage) and EOP (late passage) of NTC-201-6A cell line. This work was performed under contract by Lark Technologies, Inc. (Houston, TX) as described in Reports NTC4A and NTC6A, respectively. No differences were noted between the sequences generated from this study and the expected CNTF sequence. These data indicate that the vector insert is functioning as intended and is an indication of stability.

The CNTF gene copy number was determined for NTC-201-6A MCB and EOP cells by quantitative PCR. This work was performed under contract by Lark Technologies, Inc. (Houston, TX). The results showed that the copy number of the insert was stable, MCB 1.3 +/- .2 and EOP .9 +/- .1.

Southern blot analysis of the NTC-201-6A MCB and EOP cells indicated that there were no major sequence insertions, deletions or rearrangements of the CNTF expression cassette in the genome of these cells. This work was also performed under contract by Lark Technologies, Inc.

4. Is the same GMO release planned elsewhere in the Community (in conformity with Article 6(1)), by the same notifier?

Yes (X) No (.)

If yes, insert the country code(s) GB, FR

5. Has the same GMO been notified for release elsewhere in the Community by the same notifier?

Yes (.) No (X)

If yes:

- Member State of notification …
- Notification number B/../../…

Please use the following country codes:

Austria AT; Belgium BE; Germany DE; Denmark DK; Spain ES; Finland FI; France FR; United Kingdom GB; Greece GR; Ireland IE; Iceland IS; Italy IT; Luxembourg LU; Netherlands NL; Norway NO; Portugal PT; Sweden SE

6. Has the same GMO been notified for release or placing on the market outside the Community by the same or other notifier?

Yes (.) No (X)

If yes:

- Member State of notification …
- Notification number B/../../…

7. Summary of the potential environmental impact of the release of the GMOs.

Risk 1. Theoretical possibility, however remote, that the human allogeneic cell line (NTC201) causes an immunogenic response as 'non-self' human cells are being transplanted into the vitreous of the patient. If relevant, tumorigeni**c** characteristics of a cell line could lead to unforeseen consequences in the eye, to the host or to the environment.

Risk 2. Theoretical possibility, however remote, of CNTF toxicity due to uncontrolled expression or distribution beyond the intended target site, the retina/ or and unforeseen effect of CNTF.

Risk 3. Theoretical possibility, however remote, of gene transfer from GMO to host or environment.

Risk 4. Theoretical possibility, however remote, of effects of the thymidine kinase (TK) open reading frame in the vector.

Risk 5. Theoretical possibility, however remote, of effects of the Dihydrofolate reductase (DHFR) open reading frame in the vector.

B. Information relating to the recipient or parental organism from which the GMO is derived

1. Recipient or parental organism characterisation:

(a) Indicate whether the recipient or parental organism is a:

(select one only)

viroid (.)
RNA virus (.)
DNA virus (.)
bacterium (.)
fungus (.)
animal
- mammals (X)
- insect (.)

- fish (.)
- other animal (.)
  (specify phylum, class) Chordate, Mammal

other, specify the ARPE-19 cell line (NTC-200) was a spontaneously immortalized cell line derived from the retinal pigmented epithelium of a donor. This cell line is attachment dependent and contact inhibited. The parent cell line is available from ATCC and commonly used in research laboratories around the world.

2. Name

(i)	order and/or higher taxon (for animals)	…
(ii)	genus	homo
(iii)	species	sapiens
(iv)	subspecies	…
(v)	strain	…
(vi)	pathovar (biotype, ecotype, race, etc.)	…
(vii)	common name	…

3. Geographical distribution of the organism

(a) Indigenous to, or otherwise established in, the country where the notification is made:
Yes (.) No (X) Not known (.)

(b) Indigenous to, or otherwise established in, other EC countries:
(i) Yes ()

If yes, indicate the type of ecosystem in which it is found:

Atlantic	..
Mediteranean	..
Boreal	..
Alpine	..
Continental	..
Macaronesian	..

(ii) No (X)
(iii) Not known (.)

(c) Is it frequently used in the country where the notification is made?
Yes (.) No (X)

(d) Is it frequently kept in the country where the notification is made?
Yes (.) No (X)

4. Natural habitat of the organism

(a) If the organism is a microorganism

water (.)

soil, free-living (.)
soil in association with plant-root systems (.)
in association with plant leaf/stem systems (.)
other, specify the GMO cell line can only live in cell culture or in the device once implanted in the vitreous of a recipient human eye

(b) If the organism is an animal: natural habitat or usual agroecosystem:
N/A

5. (a) Detection techniques
The cell line can be distinguished from the parent ARPE-19 by the production of human CNTF

(b) Identification techniques
ELISA of conditioned cell culture media

6. Is the recipient organism classified under existing Community rules relating to the protection of human health and/or the environment?
Yes (X) No (.)
If yes, specify

The GMO classifies as a Class 1 hazard for which level 1 containment is appropriate to protect human health and the environment. This assessment is based on 2009/41/EC that states 1) the recipient unlikely to cause disease to humans, animals or plants, 2) the nature of the vector and insert is such that they do not endow the GMO with a phenotype likely to cause disease in humans, animals or plants, or have deleterious effects on the environment and 3) the GMO is unlikely to cause disease in humans, animals or plants.

The recipient of the GMO is a human study participant and is thus protected under the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki.

7. Is the recipient organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (.) No (X) Not known (.)

If yes:

(a) to which of the following organisms:

humans (.)
animals (.)
plants (.)
other (.)

(b) give the relevant information specified under Annex III A, point II. (A)(11)(d) of Directive 2001/18/EC

N/A. Neither the parent cell line nor the genetically modified cell line are pathogenic or infective or have the ability to colonize other organisms, and the GMO has been

screened for adventious viruses. It is highly unlikely to activate latent viruses in patients. The NTC-201-6A MCB was subjected to validation per International Conference of Harmonization Tripartite Guideline, 'Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin'. Test results indicated that the NTC-201 cell banks used in the manufacturing process met established criteria for safety, purity and identity.

8. Information concerning reproduction

(a) Generation time in natural ecosystems:
N/A

(b) Generation time in the ecosystem where the release will take place:
N/A

(c) Way of reproduction: N/A Sexual .. Asexual ..

(c) Factors affecting reproduction:
N/A

9. Survivability

(a) ability to form structures enhancing survival or dormancy:

(i)	endospores	(.)
(ii)	cysts	(.)
(iii)	sclerotia	(.)
(iv)	asexual spores (fungi)	(.)
(v)	sexual spores (funghi)	(.)
(vi)	eggs	(.)
(vii)	pupae	(.)
(viii)	larvae	(.)
(ix)	other, specify	No survivability outside the closure device.

The GMO cell line can only live in cell culture or in the device once implanted in the vitreous of a recipient human eye due to requirements for relevant factors affecting survivability:

10. (a) Ways of dissemination
Device is delivered by surgical implantation into the patient's eye and does not spread from there.

(b) Factors affecting dissemination
None anticipated

11. Previous genetic modifications of the recipient or parental organism already notified for release in the country where the notification is made (give notification numbers)

The parent cell line was not previously modified

C. **Information relating to the genetic modification**

1. Type of the genetic modification

(i)	insertion of genetic material	(X)
(ii)	deletion of genetic material	(.)
(iii)	base substitution	(.)
(iv)	cell fusion	(.)
(v)	others, specify …	

2. Intended outcome of the genetic modification
Expression of therapeutic protein, human CNTF

3. (a) Has a vector been used in the process of modification?
Yes (X) No (.)

If no, go straight to question 5.

(b) If yes, is the vector wholly or partially present in the modified organism?
Yes (X) No (.)

If no, go straight to question 5.

4. If the answer to 3(b) is yes, supply the following information

(a) Type of vector

plasmid	(X)
bacteriophage	(.)
virus	(.)
cosmid	(.)
transposable element	(.)
other, specify …	

(b) Identity of the vector
pNUT-IgSp-hCNTF

(c) Host range of the vector
Mammalian cells

(d) Presence in the vector of sequences giving a selectable or identifiable phenotype
Yes (X) No (.)

antibiotic resistance	(X)
other, specify …	

Indication of which antibiotic resistance gene is inserted
Neomycin and G418

(e) Constituent fragments of the vector

IgSP-hCNTF

- Mouse metallothionein promoter: bases 973-1567 (X15128.1)
- Mouse immunoglobulin mu-chain VDJ4C1 signal peptide: bases 1597-1731 (M18950.1)
- Human genomic ciliary neurotrophic factor: bases 1732-3499 (AP001350.4)
- Human growth hormone polyadenylation signal: bases 3519-3824 (J03071.1)

HSV-TK

- Herpes simplex virus type I thymidine kinase promoter: bases 3896-4201 (J02224)
- Herpes simplex virus type I thymidine kinase: bases 4202-5329 (J02224)
- Herpes simplex virus type I thymidine kinase polyadenylation signal: bases 5330-5938 (J02224)

pUC18

- pUC18 vector backbone: bases 5958-8615 (L08752)
  - pUC18 origin of replication: bases 6312-6985 (L08752)
  - Amp resistance-beta lactamase: bases 7133-7993 (complementary) (GI: 1197676)
  - E.coli Lac Z alpha fragment: bases 5958-5976 and 8342-8615 (complementary) (L08752)

pBR322 ΔTcR: bases 8609-8890 (complementary) (J01749)

DHFR

- SV40 promoter: bases 10140-10507 (complementary) (NC_001669)
- Mouse dihydrofolate reductase: bases 9555-10118 (complementary) (V00734.1)
- Hepatitis B virus 3' untranslated region: bases 8890-9474 (AF090839)

NeoR

- SV40 promoter: bases 596-966 (complementary) (NC_001669)
- E. coli truncated transposon Tn5 (ΔTn5): bases 10973-552 (complementary) (GI: 405822)
  - Neomycin phosphotransferase: bases 11463-517 (complementary) (NC_002086)
  - Bleomycin resistance protein: bases 11062-11442 (complementary) (NC_002086)
  - Streptomycin resistance protein fragment: bases 10973-11023 (complementary) (NC_002086)
- SV40 polyadenylation signal: bases 10523-10817 (complementary) (NC_001669)

(f) Method for introducing the vector into the recipient organism

(i)	transformation	(.)
(ii)	electroporation	(.)
(iii)	macroinjection	(.)
(iv)	microinjection	(.)
(v)	infection	(.)
(vi)	other, specify	… transfect of mammalian cell line

5. If the answer to question B.3(a) and (b) is no, what was the method used in the process of modification?

(i)	transformation	(.)
(ii)	microinjection	(.)
(iii)	microencapsulation	(.)
(iv)	macroinjection	(.)
(v)	other, specify …	

We assume this is a typo in the question and B3a is intended to be C3a. Since we have responded yes o C3a and C3b previously this question is therefore not applicable

6. Composition of the insert

(a) Composition of the insert

Mouse metallothionein promoter, murine immonoglobulin signal peptide, genomic Human CNTF(2 exons), human growth hormone polyadenylation signal

(b) Source of each constituent part of the insert

The CNTF gene was obtained by PCR amplification of human (spleen) genomic DNA. Dideoxynucleotide sequencing of the cloned PCR product confirmed the nucleotide sequence to be identical to the published sequence of the human CNTF cDNA (Genbank accession number X60542). The human cDNA is fused in frame to the mouse immunoglobulin mu-factor VDJ4C1 signal peptide (Genbank accession number M18950.)

(c) Intended function of each constituent part of the insert in the GMO

Secretory human CNTF expression is driven by the mouse metallothionein promoter and contains the human growth hormone polyadenylation signal. To target CNTF for secretion the genomic murine immunoglobulin signal peptide gene is fused in frame to the 5' genomic human CNTF gene, which lacks the codon for the initial methionine.

(d) Location of the insert in the host organism

- on a free plasmid (X)
- integrated in the chromosome ()
- other, specify …

(e) Does the insert contain parts whose product or function are not known?
Yes (.) No (X)
If yes, specify …

D. Information on the organism(s) from which the insert is derived

1. Indicate whether it is a:

viroid (.)
RNA virus (.)
DNA virus (.)
bacterium (.)
fungus (.)
animal
- mammals (X)
- insect (.)
- fish (.)
- other animal (.)
(specify phylum, class) Chordate, Mammal

other, specify Homo sapiens

2. Complete name

(i) order and/or higher taxon (for animals) …
(ii) family name for plants …

(iii)	genus	homo
(iv)	species	sapiens
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	…

3. Is the organism significantly pathogenic or harmful in any other way (including its extracellular products), either living or dead?
Yes (.) No (X) Not known (.)
If yes, specify the following:

(b) to which of the following organisms:

humans (.)
animals (.)
plants (.)
other ..

(b) are the donated sequences involved in any way to the pathogenic or harmful properties of the organism
Yes (.) No (X) Not known (.)

If yes, give the relevant information under Annex III A, point II(A)(11)(d):
…

4. Is the donor organism classified under existing Community rules relating to the protection of human health and the environment, such as Directive 90/679/EEC on the protection of workers from risks to exposure to biological agents at work?
Yes (.) No (X)
If yes, specify …

5. Do the donor and recipient organism exchange genetic material naturally?
Yes (.) No (X) Not known (.)

E. Information relating to the genetically modified organism

1. Genetic traits and phenotypic characteristics of the recipient or parental organism which have been changed as a result of the genetic modification

(a) Is the GMO different from the recipient as far as survivability is concerned?
Yes (X) No (.) Not known (.)
Specify GMO will not survive outside of recipient or cell culture media

(b) is the GMO in any way different from the recipient as far as mode and/or rate of reproduction is concerned?
Yes (X) No (.) Unknown (.)
Specify GMO cell line does not sexually reproduce

(c) is the GMO in any way different from the recipient as far as dissemination is concerned?

Yes (X) No (.) Not known (.)

Specify GMO will not spread or sexually reproduce

(d) is the GMO in any way different from the recipient as far as pathogenicity is concerned?

Yes (.) No (X) Not known (.)

Specify …

2. Genetic stability of the genetically modified organism

Same as A.3.C. above. GMO has been evaluated for stability of the inserted DNA by several methods.

3. Is the GMO significantly pathogenic or harmful in any way (including its extracellular products), either living or dead?

Yes (.) No (X) Unknown (.)

(a) to which of the following organisms?

humans (.)
animals (.)
plants (.)
other N/A

(b) give the relevant information specified under Annex III A, point II(A)(11)(d) and II(C)(2)(i)

N/A. Neither the parent cell line nor genetically modified cell line are pathogenic or infective and the GMO has been screened for adventious viruses. It is highly unlikely to activate latent viruses in patients. The NTC-201-6A MCB was subjected to validation per International Conference of Harmonization Tripartite Guideline, 'Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin'. Test results indicated that the NTC-201 cell banks used in the manufacturing process met established criteria for safety, purity and identity.

Non-viable GMOs are not used. ECT devices are specifically tested for viability of the cell line prior to implantation. No toxic or allergenic effects have been observed in implanted patients. In the theoretical event of device failure it is possible that cells may get out of the device. This could conceivably cause an inflammatory response from the patient. This has been studied in toxicology report P0008 Part B summarized in the non-clinical section of the CTA. The overall comparison of ocular effects after implantation of NT-501 devices (Part A and C) vs. injection of NTC-201-6A cells (Part B), indicates that injection caused fewer and milder effects than implantation. The results of Study P-0008 B indicate that intraocular

release of NTC-201-6A cells from NT-501 implants does not represent a significant safety hazard.

The modified cell line is of human origin and derived from the retinal pigmented epithelium. The GMO cell line is encapsulated in a semipermeable membrane and inserted into the vitreous of the eye. The cells retain characteristics of RPE cells that are already in the recipient. There is no known pathogenicity of the GMO, donor or recipient. The cell line is encapsulated and inserted into the vitreous of the eye. Naked GMO cells were injected into the vitreous of the porcine (P008 Part B) and found to pose less risk than implant of the IMP.

4. Description of identification and detection methods

(a) Techniques used to detect the GMO in the environment

We do not evaluate patient vitreous samples for the GMO, however, all patients are clinically monitored for safety.

(b) Techniques used to identify the GMO

The GMO can be distinguished from the parent cell line by the production of hCNTF as evaluated by ELISA

F. Information relating to the release

1. Purpose of the release (including any significant potential environmental benefits that may be expected)

The IMP is to be evaluated in a clinical trial to test the efficacy of hCTNF in preventing neurodegeneration related to retinal disease. The GMO is inserted and remains contained within a permselective barrier of the IMP, allowing bi-directional protein diffusion while preventing cell release or host contact. CNTF is in a class of molecules called “neurotrophic factors” demonstrated to slow the loss of photoreceptor cells during retinal degeneration. The combined evidence from animal and human studies (Phase 1 and 2) suggests that use of Neurotech’s IMP may provide therapeutic benefit for patients with MacTel. Overall the IMP has been studied in a total of five human Phase 2 safety studies in the treatment of RP (3 studies), MacTel (1 study) and dry AMD (1 study) with resulting safe risk/benefit profiles.

The prevalence of MacTel is estimated at 5 to 23 cases per 100,000 in an Australian and at 0.1% in a Wisconsin, US city population. MacTel has orphan designation status.

2. Is the site of the release different from the natural habitat or from the ecosystem in which the recipient or parental organism is regularly used, kept or found?

Yes (.) No (X)

If yes, specify …

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference): The capsule device containing the GMO is inserted into the a single eye of an individual study participant

(b) Size of the site (m^2): 6^{-6} m^3
(i) actual release site (m^2): 6^{-6} m^3
(ii) wider release site (m^2): 0 m^3

(b) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:
None

(c) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO
None

4. Method and amount of release

(a) Quantities of GMOs to be released:
300,000 NTC-201 cells are contained within the implanted capsule device (IMP)

(b) Duration of the operation:
Device is intended to be in place for at least two years

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release

Patients are scheduled for surgery and assigned a unique device shipment. All shipped products are controlled through QA controlled, chain-of-custody system beginning at Neurotech manufacture and ending with product use or disposal. Documentation (F4000D.08) verifying use and/or disposal are prepared by each site, confirmed by the CRO and the information maintained by Neurotech Quality Assurance. The product traceability system ensures both product qualities as well as mitigates control vulnerabilities.

5. Short description of average environmental conditions (weather, temperature, etc.)

The vitreous of the eye is a gelatinous clear liquid. Temperature of vitreouss environment is approximately 37^{o}C.

6. Relevant data regarding previous releases carried out with the same GMO, if any, specially related to the potential environmental and human health impacts from the release.

The NTC501 device containing the GMO has been implanted in over 247 patients over the past decade with no observed environmental or human health impacts. All clinical investigations of the IMP are monitored for safety.

G. Interactions of the GMO with the environment and potential impact on the environment, if significantly different from the recipient or parent organism

1. Name of target organism (if applicable)
(i) order and/or higher taxon (for animals) …
(ii) family name for plants …

(iii)	genus	homo
(iv)	species	sapiens
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	…

2. Anticipated mechanism and result of interaction between the released GMOs and the target organism (if applicable)

   The GMO remains in the device and secrete CNTF into the vitreous. CNTF provides neuroprotective signals to the neurons of the retina

3. Any other potentially significant interactions with other organisms in the environment
   None

4. Is post-release selection such as increased competitiveness, increased invasiveness for the GMO likely to occur?
   Yes (.) No (X) Not known (.)
   Give details
   …

5. Types of ecosystems to which the GMO could be disseminated from the site of release and in which it could become established

   None

6. Complete name of non-target organisms which (taking into account the nature of the receiving environment) may be unintentionally significantly harmed by the release of the GMO

   None

(i)	order and/or higher taxon (for animals)	…
(ii)	family name for plants	…
(iii)	genus	…
(iv)	species	…
(v)	subspecies	…
(vi)	strain	…
(vii)	cultivar/breeding line	…
(viii)	pathovar	…
(ix)	common name	…

7. Likelihood of genetic exchange in vivo

   (a) From the GMO to other organisms in the release ecosystem:
   None

   (b) From other organisms to the GMO:

None

(c) likely consequences of gene transfer:

Host neurons expressing a neuroprotective gene that is normally expressed in the retina during development and during high activity conditions is unlikely to be problematic. In a murine model of retinal disease, ciliary neurotrophic factor (CNTF)delivered by gene therapy has been shown to confer life-long protection against photoreceptor degeneration(Lipinski, Barnard et al. 2015). Repetitive retinal imaging allowed the survival of intrinsically fluorescent cone photoreceptors to be quantified in vivo. Imaging of the visual cortex and assessment of visually-evoked behavioural responses demonstrated that surviving cones retain function and signal correctly to the brain. The mechanisms underlying CNTF-mediated neuroprotection were explored through transcriptome analysis, revealing widespread upregulation of proteolysis inhibitors, which may prevent cellular/extracellular matrix degradation and complement activation in neurodegenerative diseases.

8. Give references to relevant results (if available) from studies of the behaviour and characteristics of the GMO and its ecological impact carried out in stimulated natural environments (e.g. microcosms, etc.):

No such studies have been conducted

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)

None

H. Information relating to monitoring

1. Methods for monitoring the GMOs

The GMO is implanted to a restricted number of participants in a clinical trial. The clinical trial is monitored for safety. It would be unlikely for GMO DNA to escape the device and be taken up by the host cell. Transfer of the GMO DNA is mitigated by several factors:
1) the NTC-201 cells are encapsulated in a device which restricts the cells,
2) scientific evidence shows that the vitreous of the eye is barrier to gene transfer because of nucleases present in the fluid (Peeters et al., 2005),
3) there is no impetus for the gene transfer to occur between the NTC-201 cells and the host retina, gene transfer in the absence of a driving force provided experimentally (e.g. viral vector or nanoparticle) is exceedingly improbable (van den Berg and Haanen 2010).

2. Methods for monitoring ecosystem effects

No ecosystem effects are anticipated as the implant is contained within the participant's eye.

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms

Due to Neurotech's determination that DNA from the NT-501 product will not replicate in the host, no specific techniques to monitor this event have been developed. The clinical trial is monitored for safety.

4. Size of the monitoring area (m^2)

The participant is monitored as a complete organism although the volume of exposure (patient eye) is 6^{-6} m^3

5. Duration of the monitoring

The participant will be monitored for the duration of the study (24 months). Further monitoring will occur in an extension study.

6. Frequency of the monitoring
Continuous during the course of the study

I. Information on post-release and waste treatment

1. Post-release treatment of the site
Immediately after surgical implantation the eye is treated with prophylactic steroids and topical antibiotics.

2. Post-release treatment of the GMOs
None

3. (a) Type and amount of waste generated:
Cell culture media (approximately 35 mL) and container system; single unused medicinal product

(b) Surgical and Biological waste:
Cell culture media (approximately 35 mL) and container system; single unused medicinal product; surgical sponges and disposable surgical blades; suture material.

(c) Treatment of waste

Neurotech's NTMT03 IP Handling Instructions (v 2.0) instruct sites on handling and disposition of the medicinal product stating "Label damaged or unused Renexus® with "Quarantine for destruction" or "DO NOT USE" and securely store any unused devices from opened smaller cardboard box(es) in accordance with site procedures until accountability is confirmed by the CRA". Disposal of waste and components or unused medicinal product follow adherence to standard operating procedures for biologic precautions and disposal methods. Such standards are employed by all surgical institutions that Neurotech will conduct clinical trials and all follow standard precautions similar to those outlined in ICRC Medical Waste Management document.

J. Information on emergency response plans

1. Methods and procedures for controlling the dissemination of the GMO(s) in case of unexpected spread

The cells are contained within a device barrier all of which is contained within a secured packaging system. Each medical institution adheres to standard operating procedures for environmental control and containment. Due to the limited supply of product per patient per site, used in treatment of the disease macular telangiectasia, no addition response plans have been developed.

2. Methods for removal of the GMO(s) of the areas potentially affected

Institutional clinical center standard operating procedures for performing biologic waste decontamination apply.

3. Methods for disposal or sanitation of plants, animals, soils, etc. that could be exposed during or after the spread

Neurotech's NTMT03 IP Handling Instructions (v 2.0) instructs sites on handling and disposition of the medicinal product stating "Label damaged or unused Renexus® with "Quarantine for destruction" or "DO NOT USE" and securely store any unused devices from opened smaller cardboard box(es) in accordance with site procedures until accountability is confirmed by the CRA". Disposal of waste and components or unused medicinal product follow adherence to standard operating procedures for biologic precautions and disposal methods. Such standards are employed by all surgical institutions that Neurotech will conduct clinical trials and all follow standard precautions similar to those outlined in ICRC Medical Waste Management document.

4. Plans for protecting human health and the environment in the event of an undesirable effect

Due to the above reasons, the chances for an undesirable effect on human health and environment are close to zero and therefore no plans above and beyond patient and user safety precautions have been developed. However in the event of an undesirable effect the device may be removed from the patient eye.