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: Sweden
(b) Notification number: B/SE/08/EU 2007-006721-27
(c) Date of acknowledgement of notification 18/09/2008
(d) Title of the project: A Phase II, Multicenter, Randomized and Controlled Open-Label Trial Comparing the Safety and Efficacy of Bilateral Intraputaminal (IPu) Administration of CERE-120 (Adeno-Associated Virus Serotype 2 [AAV2]-Neurturin [NTN]) Combined with Best Medical Therapy (BMT) versus BMT-alone in Subjects With Idiopathic Parkinson's Disease.
(e) Proposed period of release Anticipated from Dec 2008 until June 2010

2. Notifier

Name of institution or company: Ceregene Inc

3. GMO characterisation

(a) Indicate whether the GMO is a:

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

specify phylum, class …

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

GMO: CERE-120

Genus: Dependovirus
Species: Adeno-associated Virus

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

Several tests have been conducted throughout the CERE-120 development program (from early nonclinical stages to the latest clinical batch manufactured) to ascertain CERE-120 genetic stability: 1) molecular identity test, 2) in vitro transduction/neurturin ELISA to assess transgene expression, 3) in vitro potency assay on target cells to assess biological activity of neurturin and 4) helper-enabled replication competent AAV2 detection test to detect the presence of wild type AAV2 in clinical lots. To date, all test results have confirmed the genetic stability of CERE-120.

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) DE, FR, GB, IT, AT, ES

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.

CERE-120 is derived from a naturally replication defective AAV2 virus. AAV2 virus is not pathogenic and requires the presence of a helper virus (adenovirus or herpes) to replicate. The presence of the wild-type AAV2 in CERE-120, which could potentially be generated by non-homologous recombination events between plasmids during manufacturing, is assessed by a test that can detect replication competent AAV2 upon co-infection with adenovirus. To date replication competent entities have not been detected in CERE-120 clinical lots.

Given that AAV2 is naturally replication defective and requires a helper virus to replicate, the mobilization of the CERE-120 genome which does not encode any viral proteins would require co-infection of transduced cells with both wild type AAV and a helper virus (adenovirus or herpes). Because AAV and adenovirus infections do not occur typically in the central nervous system (CNS) where CERE-120 is delivered, and herpes brain infections are rare, there exists only a remote possibility that the vector could be mobilized beyond initial administration.

CERE-120 has been studied in a series of pre-clinical animal toxicology and biodistribution studies and 2 clinical studies involving administration to humans. To date, there is no evidence that following the administration of CERE-120 to patients, any of the viral products is subsequently shed into the environment.

CERE-120 will be given to the patient as a one-time administration utilizing a stereotactic neurosurgical procedure using a drug delivery system provided by the Sponsor consisting of a guide tube, cannula, stylet, injection needle and syringe. The delivery system is provided to the clinical site as a sterile, single use system. All healthcare professionals involved in the preparation and administration of CERE-120 to the individual patients will be suitably gowned, gloved and will wear the appropriate mask and eye protection when participating in any procedures involving the product. These healthcare professionals will also receive training in relation to the handling of the product. In addition, should any accidental spillages or breakages occur with CERE-120, healthcare professionals involved in the clean-up procedure will also be gowned, gloved and will wear the appropriate eye protection per the institution's hazardous biological material handling guidelines. Each clinical site will also receive a Material Safety Data Sheet for CERE-120 describing the material and the appropriate precautions and handling instructions. If the guidance is followed, the risk of the occurrence of an adverse effect will be negligible. However, even if they are not followed it is unlikely that CERE-120 would cause any problems given that AAV2 has not been associated with any pathology or linked to any human illnesses. Following surgery, used CERE-120 vials, as well as the used delivery system components (guide tube, cannula, stylet, injection needle and syringe) will be disposed of in a manner consistent with the standard practice of the institution for biohazardous materials including sharps. In addition, any disposable surgical instruments or other disposable materials used during the procedure will be disposed of in a manner which is also consistent with the standard practice of the institution for biohazardous materials. All non-disposable surgical equipment and other materials used during the procedure will be cleaned using a chemical disinfectant capable of virocidal activity, e.g. Virkon®, and then sterilized by autoclaving consistent with the standard practice of the institution.

Collectively, based on the characteristics of this vector system, the administration routes and negative shedding results, and the environmental protection measurements, it is our judgment that upon unwanted exposure to the environment CERE-120 would not cause harm to humans, animals or plants.

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	(X)
bacterium	(.)
fungus	(.)

animal

- mammals (.)
- insect (.)
- fish (.)
- other animal (.)
  (specify phylum, class) …

other, specify …

2. Name

(i)	order and/or higher taxon (for animals)	Parvoviridae
(ii)	genus	Dependovirus
(iii)	species	Adeno-associated Virus
(iv)	subspecies	…
(v)	strain	serotype 2
(vi)	pathovar (biotype, ecotype, race, etc.)	…
(vii)	common name	AAV2

3. Geographical distribution of the organism

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

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

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

Atlantic	X
Mediteranean	X
Boreal	X
Alpine	X
Continental	X
Macaronesian	X

(ii) No (.)
(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	human

(b) If the organism is an animal: natural habitat or usual agroecosystem:
…

5. (a) Detection techniques
- The quantitative PCR detecting DNase-resistant CERE-120 vector genomes by the amplification of a 110-bp region of the vector genome spanning the 3'-end of the CAG promoter and the 5'-end of the NGF pre-pro coding regions.
- AAV2 capsid ELISA technique quantifying conformationally intact AAV2 capsids

(b) Identification techniques
- multiple primer quantitative PCR method to identify CAG promoter and NGF pre-pro domain of CERE-120
- polyacrylamide gel electrophoresis and a silver nitrate staining to identify AAV2 viral capsid proteins (VP1, VP2, and VP3)

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
AAV2 viruses are classified Group/ Class 1.

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
No pathological, ecological and physiological traits are present. In natural conditions, wild type AAV2 in the presence of a helper virus (adenovirus) is found to transmit to humans only and is not known to colonize other species.

8. Information concerning reproduction

(a) Generation time in natural ecosystems:
Not relevant given that CERE-120 lacks all of the viral protein-coding sequences.

(b) Generation time in the ecosystem where the release will take place: Not relevant

(c) Way of reproduction: Sexual .. Asexual ..
Not relevant

(c) Factors affecting reproduction:
Not relevant

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	co-infection of transduced cells with both wild type AAV2 and a helper virus (adenovirus or herpes)

(b) relevant factors affecting survivability:
CERE-120 is susceptible to 1% sodium hypochlorite, 5% phenol, or common virocidals e.g. Virkon®. CERE-120 is sensitive to heat (>80°C for 60 minutes), UV radiation and extreme pHs (<2 and >12).

10. (a) Ways of dissemination
Once injected into the patients there is no evidence that the CERE-120 gene vector is shed into either the serum or urine of these individuals. Therefore, it is unlikely that CERE-120 will be disseminated into any ecosystems.

(b) Factors affecting dissemination
Not applicable

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)
…, B/../../… Not applicable

C. Information relating to the genetic modification

1. Type of the genetic modification

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

2. Intended outcome of the genetic modification

CERE-120 is a genetically engineered adeno-associated virus serotype-2 (AAV2) vector that lacks all of the wild-type viral protein-coding sequences and instead encodes a human neurturin (NTN) complementary deoxyribonucleic acid (cDNA). The deletion of native AAV2 coding sequence makes CERE-120 replication incompetent. In the CERE-120 vector, NTN expression is controlled by the constitutive CAG promoter (a fusion of the minimal cytomegalovirus (CMV) enhancer with the chicken β-actin gene promoter and splice donor and a rabbit β-globin gene splice acceptor intron) and the human growth hormone gene polyadenylation signal. This NTN expression cassette is flanked by the AAV2 inverted terminal repeats (ITRs). To promote efficient secretion of mature NTN from transduced cells, the natural pre/pro domain of the human NTN cDNA was replaced with that of the human β-nerve growth factor (NGF). The resulting hybrid precursor protein (pre-pro-hNGFnNTN cDNA hybrid) generates the mature secreted NTN protein upon proteolytic processing along the cellular secretary pathway.

NTN, a functional and structural analog of glial cell line-derived neurotrophic factor (GDNF), has demonstrated neuroprotective and neuroregenerative properties in rodent and nonhuman primate models of Parkinson's disease (PD). CERE-120 will be administered by bilateral intraputaminal (IPu) injection to allow the delivery of NTN to the intended target sites, thus providing continuous NTN to the neurons degenerating in PD, while minimizing NTN in regions outside the nigrostriatal system.

3. (a) Has a vector been used in the process of modification?

Yes (X): No (.)

Cere-p521 (CERE-120 genome)
Cere-p509 (AAV helper)
Cere-p511 (Ad helper)

If no, go straight to question 5.

(b) If yes, is the vector wholly or partially present in the modified organism?

Cere-p521:	Yes	(X)	No	(.)
Cere-p509:	Yes	(.)	No	(X)
Cere-p511:	Yes	(.)	No	(X)

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

Cere-p521 a.k.a. pK-AAV-CAG-NGF/NTN

(c) Host range of the vector
Escherichia coli

(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: Kanamycin
Note that the Kanamycin-resistant gene is not present in the final CERE-120 vector.

(e) Constituent fragments of the vector
- CAG promoter
- human NGF pre-pro domain
- human mature NTN cDNA
- human growth hormone gene polyadenylation signal
- 5' and 3' AAV2 ITRs
- pUC plasmid backbone modified to replace ampicillin resistance gene by that of kanamycin

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

(i)	transformation	(.)
(ii)	electroporation	(.)
(iii)	macroinjection	(.)
(iv)	microinjection	(.)
(v)	infection	(.)
(vi)	other, specify	CERE-120 is manufactured under cGMP by a helper virus-free, triple plasmid transfection techniquein HEK 293 cells. The vector is purified from clarified cell lysates through multiple step chromatography and filtration processes.

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	molecular cloning

6. Composition of the insert

(a) Composition of the insert
A cDNA hybrid contains human neurturin (NTN) cDNA, of which the natural pre-pro domain has been replaced by that of human-nerve growth factor (NGF) to promote the efficient secretion of mature NTN from transduced cells.

(b) Source of each constituent part of the insert

The full-length human NTN was obtained by PCR amplification from a universal cDNA library (Clontech 7108-1).

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

The pre-pro-hNGFnNTN cDNA hybrid will be translated into a precursor protein that generates the mature secreted NTN protein upon proteolytic processing along the cellular secretary pathway. NTN could protect existing nigrostriatal neurons from degeneration and death as well as restore dopaminergic function to existing dysfunctional neurons.

(d) Location of the insert in the host organism

- on a free plasmid (.)
- integrated in the chromosome (.)
- other, specify The insert is cloned into the viral vector genome.

(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 (.)
- insect (.)
- fish (.)
- other animal (.)
  (specify phylum, class) …

other, specify human

2. Complete name

(i) order and/or higher taxon (for animals) …
(ii) family name for plants …
(iii) genus Homo
(iv) species Homosapiens
(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 (.) No (X) Not known (.)
Specify …

(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 The GMO is replication incompetent.

(c) is the GMO in any way different from the recipient as far as dissemination is concerned?
Yes (.) No (X) Not known (.)
Specify …

(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

Several tests have been conducted throughout the CERE-120 development program (from early nonclinical stages to the latest clinical batch manufactured) to ascertain CERE-120 genetic stability: 1) molecular identity test, 2) in vitro transduction/neurturin ELISA to assess transgene expression, 3) in vitro potency assay on target cells to assess biological activity of neurturin and 4) helper-enabled replication competent AAV2 detection test to detect the presence of wild type AAV2 in clinical lots. To date, all test results have confirmed the genetic stability of CERE-120.

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 …

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

No pathological, ecological and physiological traits are present. In natural conditions, wild type AAV2 in the presence of a helper virus (adenovirus) is found to transmit to humans only and is not known to colonize other species.

4. Description of identification and detection methods

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

The detection and concentration determination of CERE-120 is performed by using a QPCR method as well as an AAV2 capsid ELISA technique. The dose-defining detection technique for CERE-120 is the QPCR method. The QPCR method detects DNase-resistant CERE-120 vector genomes by the amplification of an 110bp region of the vector genome spanning the 3' end of the CAG promoter and the 5' end of the nerve growth factor pre-pro coding regions. The vector genome concentration of each test lot is determined by extrapolation of the number of vector genome copies per reaction from a purified, qualified vector genome DNA standard using a semi-logarithmic curve fit [$\log_{10}$ input copies/reaction versus threshold cycle (CT)] and appropriate correction for sample dilution factors. The AAV2 capsid ELISA is a commercially available kit that allows for the quantitation of conformationally intact capsids via capture by a specific antibody and detection by standard sandwich ELISA methods.

(b) Techniques used to identify the GMO

Two identity tests are performed on CERE-120 that allow for its specific identification. One test is a molecular identity test based on a multiple primer QPCR method which identifies two independent sequences present in the CERE-120 vector genome. Combined, the two primer/probe sets confirm the presence of the CAG promoter contiguous to the NGF pre-pro domain, the NGF pre-pro contiguous to the mature NTN cDNA domain, and uniquely identify CERE-120. The test article conforms if determined to be positive for amplification by both primer probe sets and if the quantitative result obtained by both primer probe sets does not differ by more than 5-fold.

The other identity test is based on separation of polypeptides by polyacrylamide gel electrophoresis and a silver nitrate staining method which is used to confirm the protein identity of CERE-120. The AAV2 viral capsid proteins, VP1, VP2, and VP3 are identified based on size by comparison to molecular weight markers of known size. The test sample conforms when the critical bands (VP1, VP2, and VP3) are comparable in MW to the reference standard.

F. Information relating to the release

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

Parkinson's disease (PD) is a slowly progressive, neurodegenerative disorder. Its pathogenesis involves the progressive loss of function, and eventual death, of dopaminergic nigrostriatal neurons. NTN is a neurotrophic factor that can promote neuronal growth, restore function, and prevent neuronal death. The aim of this study is to study the safety and efficacy of gene therapy with CERE-120 in comparison with an optimized and stable regimen of antiparkinsonian medication, "Best Medical Therapy" (BMT), in subjects with idiopathic PD. In this study, patients will receive a single bilateral intraputaminal injection of CERE-120, a replication-defective AVV2 vector expressing human NTN. It is assumed that functional NTN would be synthesized and secreted in the targeted brain tissue eliciting a neurotrophic response.

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 (.)

If yes, specify The GMO will be administered by bilateral intraputaminal injection.

3. Information concerning the release and the surrounding area

(a) Geographical location (administrative region and where appropriate grid reference):

CERE-120 will be only loaded to the delivery system in the operating theatre of Lund University Hospital, department of Neurology.

(b) Size of the site (m^2): … m^2

(i) actual release site (m^2): … m^2

(ii) wider release site (m^2): … m^2

The patients will be kept in the operating theatre (hospital room) until the surgery is finished.

(c) Proximity to internationally recognised biotopes or protected areas (including drinking water reservoirs), which could be affected:

Not applicable

(d) Flora and fauna including crops, livestock and migratory species which may potentially interact with the GMO
Not applicable

4. Method and amount of release

(a) Quantities of GMOs to be released:
The total dose of CERE-120 that will be given to each patient will be $5.4x10^{11}$ viral genome (vg) as a one-time administration. It is anticipated that each of the 11 sites will enroll 4-5 subjects. Two-thirds of these (approx 3-4 pts/site) will receive CERE-120 (versus best supportive care); therefore maximum CERE-120 release per site would be 2.16×10^{12} vg ($4 \text{ pts} \times 5.4 \times 10^{11}$ vg).

(b) Duration of the operation:
CERE-120 is administered bilaterally into the putamen during a single surgical procedure. The expression of CERE-120 is expected to be sustained.

(c) Methods and procedures to avoid and/or minimise the spread of the GMOs beyond the site of the release
All healthcare professionals involved in the preparation and administration of CERE-120 to the individual patients will be suitably gowned, gloved and will wear the appropriate mask and eye protection when participating in any procedures involving the product. These healthcare professionals will also receive training in relation to the handling of the product.
In addition, should any accidental spillages or breakages occur with CERE-120, healthcare professionals involved in the clean-up procedure will also be gowned, gloved and will wear the appropriate eye protection per the institution's hazardous biological material handling guidelines. Each clinical site will also receive a Material Safety Data Sheet for CERE-120 describing the material and the appropriate precautions and handling instructions.

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

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.
Not applicable

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)	Hominidae
(ii)	family name for plants	…
(iii)	genus	Homo
(iv)	species	Homo 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 goal of therapy with CERE-120 is to enhance the function of nigrostriatal dopaminergic neurons, thereby providing symptomatic improvement of motor function and reduction of "off" time in patients with Parkinson's disease (PD). Other important goals of CERE-120 are to protect nigrostriatal neurons from further degeneration and thus slow or prevent disease progression. CERE-120 encodes the gene for neurturin, a growth factor known to restore and protect nigrostriatal dopamine neurons, within an AAV2 vector that selectively transduces neurons with minimal proinflammatory or other undesirable side effects. CERE-120 is being developed as a medical therapy that has the potential to improve the symptoms of PD while at the same time potentially reducing disease progression.

CERE-120 is a genetically engineered adeno-associated virus serotype-2 (AAV2) vector that lacks all of the wild-type viral protein-coding sequences and instead encodes the human neurturin (NTN) complimentary deoxyribonucleic acid (cDNA). NTN, a functional and structural analog of glial cell line-derived neurotrophic factor (GDNF), has demonstrated neuroprotective and neuroregenerative properties in rodent and nonhuman primate models of Parkinson's disease (PD). By incorporating the gene for NTN into an AAV2 vector, it is possible to deliver NTN to the nigrostriatal system in the brain in a controlled, sustained, and targeted fashion, thus providing continuous NTN to the neurons degenerating in PD, while minimizing NTN in regions outside the nigrostriatal system.

3. Any other potentially significant interactions with other organisms in the environment

Not known.

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

CERE-120 is replication-defective. CERE-120 is only able to replicate if it infects a cell that is co-infected by wild-type AAV2 and a helper virus (adeno or herpesvirus). A theoretical risk is that the GMO infects a human cell that is already infected by wild type AAV and helper virus, which will result in replication of the vector. This risk is extremely small.

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

Not applicable

(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:
Not expected

(b) from other organisms to the GMO:
Not expected

(c) likely consequences of gene transfer:
Local expression of human NTN

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.):
The CERE-120 genome consists of the following genetic elements flanked by the AAV2 inverted terminal repeats (ITRs):

- 1.7-kb CAG promoter comprised of the human CMV enhancer, the chicken β-actin promoter and splice donor, and the rabbit β-globin gene splice acceptor
- 0.36-kb human nerve growth factor (NGF) pre-pro domain cDNA
- 0.3-kb human NTN mature protein cDNA
- 0.48-kb human growth hormone gene polyadenylation signal

Since CERE-120 genome does not encode any viral proteins, its replication would require co-infection of transduced cells with both wild-type AAV2 and a helper virus (adenovirus or herpes). Because AAV2 and adenovirus infections do not occur typically in the central nervous system (CNS) where CERE-120 is delivered, and herpes brain infections are rare, there exists only a remote possibility that the vector could be mobilized beyond initial administration.

In the non-clinical pharmakodynamic studies, NTN expression following CERE-120 administration into striatum is stable for at least for one year observed thus far. The volume of distribution of NTN can be controlled by manipulating the dose of CERE-120. These data allow the selection of non-clinical and clinical dose that provide reasonable coverage of the striatum with NTN without significant distribution to neuroanatomically unrelated structures. Further experiments establish that the NTN protein expressed following CERE-120 administration is robust and bioactive, capable of protection/restoration of nigral neurons function and improving clinical motor behavior function in PD animal models. Nonclinical safety/toxicology studies and Phase 1 and US Phase 2 studies of CERE-120 in human subjects with PD showed no clinically important adverse events related to CERE-120.

CERE-120 and its product NTN are not able to penetrate across blood-brain barrier. In the two studies involving human subjects with PD, no evidence of viral shedding has been detected by quantitative PCR in the urine of the 12 subjects enrolled in the Phase I study in the US. Blood samples have also all been negative for presence of CERE-120 in all subjects participating in Phase I and Phase II studies.

No impact on the environment has been observed in any of the studies referred to above.

9. Possible environmentally significant interactions with biogeochemical processes (if different from the recipient or parental organism)
Not applicable

H. Information relating to monitoring

1. Methods for monitoring the GMOs
   - Detection of CERE-120 concentrations in serum, urine, feces and buccal swab by quantitative polymerase chain reaction (QPCR)
   - Changes from baseline in serum antibodies to NTN and AAV2

2. Methods for monitoring ecosystem effects
Not applicable

3. Methods for detecting transfer of the donated genetic material from the GMO to other organisms
Not applicable since there is no risk of transfer of donated genetic material form the patient to other organisms. The batch to be used in the trial is tested to confirm that no replication competent viruses are present.

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

5. Duration of the monitoring
According to the protocol, i.e. 12 months post-surgery

6. Frequency of the monitoring
Serum, Feces, Urine and Buccal Swab CERE-120 Vector Testing (QPCR) will be performed at Baseline, Day Post-Surgery, Month 1 and Month 12. In addition, if there are positive titers at Month 1, repeat testing will performed at the Month 3 Visit. Serum AAV2 Antibody Testing (ELISA) will be performed at Baseline, Month 1, Month 3 and Month 12. Serum NTN Antibody Testing (ELISA) will be performed at Baseline, Month 3 and Month 12.

I. Information on post-release and waste treatment

1. Post-release treatment of the site
Virocidal agent such as Virkon® will be used to disinfect working area.

2. Post-release treatment of the GMOs
All equipment used during the procedure will either be disposed of in line with current biological hazard procedures or decontaminated with virocidal agents as dictated by the institution's biological hazard waste management plan. This will prevent any possible spread to other patients who are subsequently operated on in the surgical facility.

3. (a) Type and amount of waste generated

- Used CERE-120 vials containing less than 0.05 mL of product and the used delivery system components (guide tube, cannula, stylet, injection needle and syringe).
- All non-disposable surgical equipment and other materials used during the procedure.

The amounts of waste as described above will be very small.

3. (b) Treatment of waste

Following surgery, used CERE-120 vials, as well as the used delivery system components (guide tube, cannula, stylet, injection needle and syringe) will be disposed of in a manner consistent with the standard practice of the institution for biohazardous sharps. In addition any disposable surgical instruments or other materials used during the procedure will be disposed of in a manner which is also consistent with the standard practice of the institution for biohazardous materials.

All non-disposable surgical equipment and other materials used during the procedure will be cleaned using a chemical disinfectant capable of virocidal activity e.g. Virkon® and then sterilized by autoclaving consistent with the standard practice of the institution.

J. Information on emergency response plans

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

When CERE-120 is administered it will be given via neurosurgical stereotactic injections directly into the brain of patients with Parkinson's disease in an operating theatre. Once injected into the patients there is no evidence that the CERE-120 gene vector is shed into either the serum or urine of these individuals. The spread outside of the area, other than at the site of the injection into the brain of the patient, will therefore be negligible.

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

Allow aerosols to settle. Wear protective clothing and gently cover spill with paper towels. Apply chemical disinfectant capable of virocidal activity such as Virkon®). Start at the perimeter of the spill and work towards the centre. Allow disinfectant a minimum of 30 minutes contact time before clean up.

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

Not applicable

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

If an undesirable effect occurs than the use of CERE-120 would stop until the effects are fully assessed and measures are put in place to mitigate further risk. All areas and facilities that had been used to administer the product would be cleaned and decontaminated using virocidal agents.