Environmental Protection Authority
Te Mana Rauhī Taiao

DECISION

Date of decision	09 February 2018
Application code	APP202854
Application type	To import for release or release from containment a qualifying organism under section 38I of the Hazardous Substances and New Organisms Act 1996
Applicant	Oncolys Biopharma Inc
Date application received	1 February 2018
Considered by	The Chief Executive of the Environmental Protection Authority (EPA)[1]
Purpose of the application	To import for release a genetically modified conditionally replicative oncolytic human adenovirus type 5 (Telomelysin) for use in a Phase 2 clinical trial for patients with stage IIIa and IV inoperable metastasised melanoma.
The new organism approved	Telomelysin (OBP-301); as described in Table 1

1. Summary of decision

1.1 Application APP202854 to import for release a genetically modified conditionally replicative oncolytic adenovirus (Telomelysin) for use in a Phase 2 clinical trial for patients with inoperable stage IIIa and IV metastasised melanoma was lodged under section 34 of the Hazardous Substances and New Organisms (HSNO) Act 1996 (the Act).

1.2 I considered the application in accordance with the relevant provisions of the Act and of the HSNO (Methodology) Order 1998 (the Methodology).

1.3 I **approve** the application in accordance with section 38I(1)(b) of the Act, subject to the following controls:

Control 1 – The applicant must ensure that the organism (Telomelysin, OBP-301 as described in Table 1) is only administered:

[1] The Chief Executive of the EPA has made the decision on this application under delegated authority in accordance with the delegation dated 21 June 2013 from the EPA to the Chief Executive pursuant to section 19(2)(a) of the Act.

a) to individuals enrolled in a Phase 2 clinical trial approved under the Medicines Act 1981 to examine the safety and efficacy of Telomelysin in patients with inoperable stage IIIa and IV metastasised melanoma;
b) intratumourally;
c) by a suitably trained medical practitioner(s); and
d) at a Phase 2 clinical trial site[2].

Control 2 - The New Zealand sponsor of the Phase 2 clinical trial[3] must notify the EPA and Ministry for Primary Industries (MPI), in writing, and at least one calendar month before Telomelysin is administered for the first time at each clinical trial site, of:

a) the location of the Phase 2 clinical trial site; and
b) the qualifications of the suitably trained medical practitioner(s) who will administer the organism.

Control 3 – The New Zealand sponsor must ensure a suitably qualified person(s), before treatment:

a) educates patients who will be treated with the organism about the potential for Telomelysin to be transmitted to untreated individuals, particularly immunocompromised individuals, and the potential adverse effects of Telomelysin transmission;
b) educates patients in infection control; and
c) advises the patients to avoid contact with immunocompromised individuals

Control 4 – The New Zealand sponsor must ensure that a suitably qualified person(s):

a) before treatment, provides the patient with a biohazard container for any bandages, plasters or other dressings applied to the site of injection of the organism
b) before treatment, instructs the patient to return such containers to the Phase 2 clinical trial site for disposal as medical waste; and
c) disposes of such containers in accordance with medical waste disposal procedures in place at that Phase 2 clinical trial site.

Control 5 – The New Zealand sponsor must:

a) before the commencement of the Phase 2 clinical trial, ensure that protocols and suitably qualified people are available to investigate reports of adverse effects suspected to be related to Telomelysin transmission from treated individuals to untreated individuals;
b) ensure that reports of adverse effects reasonably suspected to be related to Telomelysin transmission are investigated to confirm whether or not transmission has occurred, and whether or not adverse effects have resulted from confirmed transmission; and
c) notify the EPA and MPI, in writing, of any occurrence of Telomelysin-induced adverse effects resulting from confirmed events of Telomelysin transmission from Telomelysin-treated individuals to untreated individuals as soon as practicable.

[2] A clinical trial site is a physical clinical setting where trial participants are administered with the organism.

[3] The New Zealand sponsor assumes responsibility (including legal liability) for the clinical trial in New Zealand. The New Zealand sponsor must be a person in New Zealand.

Control 6 – The New Zealand sponsor must submit a report describing compliance with the above controls to the EPA and MPI, initially to be submitted six months after the commencement of the Phase 2 clinical trial, then on or before 30 June every year thereafter until the conclusion of the Phase 2 clinical trial.

2. Application and consideration process

Application receipt

2.1 Application APP202854 was formally received by the EPA for processing on 1 February 2018.

Purpose of the application

2.2 The applicant, Oncolys Biopharma Inc, sought approval to import for release a genetically modified conditionally replicative oncolytic adenovirus (Telomelysin, OBP-301). The applicant intends to use Telomelysin in a Phase 2 clinical trial to examine safety and efficacy of Telomelysin as an oncolytic immunotherapy in patients with inoperable stage IIIa and IV metastasised melanoma.

The organism

2.3 Telomelysin is a conditionally replicative oncolytic Human adenovirus species C, serotype Ad5 that contains two genetic modifications, specifically a substitution of the adenoviral E1A promoter with the promoter of the human telomerase reverse transcriptase (hTERT) gene, and an insertion of an internal ribosome entry sequence (IRES) derived from encephalomyocarditis virus, between the E1A and E1B genes. An important feature of Telomelysin is that there are no protein-coding genes that have been removed or inserted relative to wild-type Ad5. Instead, its genetic modifications solely affect the regulation of the transcription and translation of the E1A and E1B genes, which make the modified virus more specific for replication in tumour cells, as described in more detail below

2.4 The use of the hTERT promoter results in a diminished capability of Telomelysin to replicate within normal cells of the body, making Telomelysin conditionally replicative in cancer cells. The use of the hTERT promoter exploits the fact that cancer cells generally have high levels of telomerase to maintain chromosome ends, and thus they express the hTERT gene. This characteristic has been described in numerous peer-reviewed publications as ‘selective replication’ within cancer cells. Like adenovirus, Telomelysin causes replication-dependent cell disintegration (cell lysis), which is the mechanism for its cancer cell-lysing (oncolytic) property.

Comments from DOC, Medsafe and MPI

2.5 In accordance with section 58(1)(c) of the Act, the Department of Conservation (DOC), Medsafe and MPI were advised of, and provided with the opportunity to comment on, the application.

2.6 DOC stated that they did not consider that Telomelysin would establish an undesirable self-sustaining population, nor did they expect any adverse environmental effects from its release. MPI did not comment on the application.

2.7 Medsafe provided an overarching assessment that the benefits of a Telomelysin trial outweigh its risks, and they noted that they consider this release application to present a minimal public health risk because:

- Human Adenovirus 5 is ubiquitous in the environment and most people will have immunity to the virus.
- Telomelysin shed from treated individuals is unlikely to infect and replicate within healthy people because it exhibits tumour selectivity (if it did manage to infect a healthy person, the resulting infection would be minor to non-existent in most people);
- Telomelysin is genetically stable; and
- Telomelysin recombination with other adenoviruses is unlikely.

2.8 Medsafe noted that there is an increased risk of complications in immunocompromised people, and that a Human Adenovirus 5 infection can persist without symptoms at a low level for some time, with potential for shedding. Additionally, current antiviral therapies have low effectiveness against adenoviruses, and there is no approved treatment for infection with Human Adenovirus 5. Medsafe therefore recommended that Telomelysin recipients should be educated in infection control and avoid contact with immunocompromised people.

2.9 I acknowledge that immunocompromised people are at greater risk of developing clinical complications if infected with Telomelysin, and therefore I require that this risk be managed by instructing Telomelysin-treated individuals to be educated in infection control and to avoid contact with immunocompromised people during treatment (**Control 3**).

Information available for the consideration

2.10 The information available for my consideration comprised:

- the application and references provided therein;
- the EPA Staff Assessment Report; and
- comments received from DOC, and Medsafe.

2.11 I had sufficient information to assess the application. To the extent that the application may not meet any legislative information requirements, I waive those requirements.

Legislative matters considered

2.12 I considered the application in accordance with section 38I of the Act[4], taking into account the relevant matters in Part 2 of the Act, and the Methodology.

3. Assessment of Telomelysin against legislative criteria

3.1 I note that the applicant intends to intratumourally administer Telomelysin to individuals with inoperable stage IIIa and IV metastasised melanoma who are enrolled in a Phase 2 clinical trial. As such, I am

[4] As detailed in section 3 of this document.

satisfied that Telomelysin is a medicine (as defined in section 3 of the Medicines Act 1981), and I limit the import for release of Telomelysin to use in that specific Phase 2 clinical trial (**Control 1**). Further, I require that the EPA and MPI be notified of the location of all Phase 2 clinical trial sites before Telomelysin is administered at those sites in reliance on this approval (**Control 2**).

3.2 I have made a rapid assessment of the application under section 38I of the Act. Specifically, and in accordance with section 38I(3), I considered the capacity of Telomelysin to have significant adverse effects on:

- the health of the public or any valued species through the dose and route of Telomelysin administration; and
- the health and safety of the public, any valued species, natural habitats or the environment through the formation of an undesirable self-sustaining population.

3.3 In considering the potential significant adverse effects of Telomelysin, I took into account the controls (set out in section 6 of this document), in accordance with section 38I(3) of the Act. I did not take into account any effects of the medicine on the individual who is to be treated with the medicine, in accordance with section 38I(4) of the Act.

Potential for significant adverse effects through the dose and route of administration

3.4 I note that Telomelysin-treated individuals will be allowed to return to their homes after receiving the Telomelysin treatment, and that each patient may receive several doses of Telomelysin over the course of the Phase 2 clinical trial.

3.5 While I acknowledge that Telomelysin could be transmitted to the public through viral shedding, I also note that there is no evidence of Telomelysin transmission from Telomelysin-treated individuals to untreated individuals from previous clinical trials, as is the case for other Human Adenovirus-based treatments and vaccines in general. Therefore, I consider that Telomelysin transmission from Telomelysin-treated patients to untreated individuals or animals is currently only of theoretical concern.

3.6 I note that the management of Telomelysin shedding from patients is important in preventing Telomelysin transmission to untreated individuals and animals. Therefore, I require Telomelysin-treated individuals to be educated about the potential for Telomelysin transmission, and instructed in infection control, by a suitably qualified person prior to being treated with Telomelysin (**Control 3**).

3.7 I note that injection site dressings have the potential to be contaminated with Telomelysin. Therefore, I require that all Telomelysin-treated patients must be provided with a biohazard container for the collection of dressings, and that participants return used biohazard containers to a clinical trial site for appropriate disposal (**Control 4**).

3.8 In light of educating patients on infection control, and Telomelysin injection site dressing management practices, I consider that Telomelysin transmission from a Telomelysin-treated individual to an untreated individual or an animal is highly unlikely. If transmission did occur, the level of exposure via injection site lesions or shed Telomelysin is predicted to be low compared to the doses received by

Telomelysin-treated individuals. In the highly unlikely event of a Telomelysin infection resulting from the exposure of an untreated individual (other than an immunocompromised individual) or an animal to a Telomelysin-treated individual, I note that the immune system of the exposed individual or animal would most likely eliminate Telomelysin rather than the exposed individual or animal experience a significant adverse reaction. This is because Telomelysin replication is significantly impaired or non-existent in healthy tissue, and most people from a young age already have immunity to Human Adenovirus 5, to which Telomelysin is antigenically identical.

3.9 Therefore, taking into account the controls that I have imposed, I am satisfied that it is highly improbable that Telomelysin will have significant adverse effects on the health of the public or any valued species through the intended dose and intratumoural route of Telomelysin administration.

3.10 Nonetheless, I require that any occurrence of Telomelysin-induced adverse effects resulting from Telomelysin transmission from Telomelysin-treated patients to untreated individuals or animals be reported to the EPA and MPI as soon as practicable (**Control 5**).

Potential for significant adverse effects through the formation of an undesirable self-sustaining population

3.11 I note that Telomelysin replication is significantly impaired or non-existent (attenuated) in normal cells due to the use of the human telomerase reverse transcriptase (hTERT) promoter in place of the E1A promoter and the use of the Encephalomyocarditis Virus (EMCV) internal ribosome entry site (IRES) in place of the E1B gene promoter.

3.12 I acknowledge that the genome of Telomelysin could theoretically revert to that of an unmodified Human Adenovirus 5, via recombination with an unmodified Human Adenovirus 5. However, I note that the Telomelysin modifications have been shown to be genetically stable, and that the net effect of such a recombination event would be nil, since Human Adenovirus 5 is already ubiquitous in the environment, and most people will already have immunity to Human Adenovirus 5.

3.13 I considered the likelihood of administered Telomelysin (or shed Telomelysin) recombining with other adenoviruses and forming an undesirable self-sustaining population. However, formation of such a recombinant virus is highly unlikely given the known genetic stability of adenovirus species, and considering that genetic recombination could only occur within treated patients (or within infected individuals or animals) when the adenoviruses were viraemic, or if the other adenoviruses co-infected a cancerous cell. Moreover, I note that in the long history of mass vaccination against adenovirus infections using live, *unattenuated* adenovirus, there were no reports of a transmissible adenovirus strain spreading beyond a vaccinated population and causing infection (either in people or in animals).

3.14 Therefore, I am satisfied that it is highly improbable that Telomelysin will form an undesirable self-sustaining population that would have significant adverse effects on the health and safety of the public, any valued species, natural habitats or the environment.

Qualifying medicine

3.15 In conclusion, I am satisfied that Telomelysin is a qualifying medicine (as defined in section 2(1) of the Act) for the following reasons:

- Telomelysin meets the definition of a medicine as defined in section 3 of the Medicines Act 1981;
- Telomelysin is a new organism in accordance with section 2A(1)(d) of the Act; and
- Telomelysin meets the criteria set out in section 38I(3) of the Act.

4. Associated approvals

4.1 I note that this approval cannot be used until Telomelysin has been approved for use under the Medicines Act 1981, and any requirements under the Biosecurity Act 1993 have been satisfied.

4.2 Further, I note that this approval limits the use of the qualifying medicine Telomelysin to a Phase 2 clinical trial for patients with inoperable stage IIIa and IV metastasised melanoma (**Control 1**), and any other therapeutic use of Telomelysin would require additional HSNO Act approval.

5. Achieving the purpose of the Act

5.1 The purpose of the Act is to protect the environment, and the health and safety of people and communities, by preventing or managing the adverse effects of hazardous substances and new organisms (section 4 of the Act).

5.2 In order to achieve the purpose of the Act, when considering the application I recognised and provided (to the extent necessary) for the following principles (section 5) of the Act:

- the safeguarding of the life-supporting capacity of air, water, soil and ecosystems; and
- the maintenance and enhancement of the capacity of people and communities to provide for their own economic, social and cultural well-being and for the reasonably foreseeable needs of future generations.

5.3 I took into account the following matters when considering the application in order to achieve the purpose of the Act (sections 6, 7 and 8 of the Act):

- the sustainability of all native and valued introduced flora and fauna;
- the intrinsic value of ecosystems;
- public health;
- the relationship of Māori and their culture and traditions with their ancestral lands, water, sites, waahi tapu, valued flora and fauna, and other taonga;
- the economic and related benefits and costs of using a particular hazardous substance or new organism;
- New Zealand's international obligations;
- the need for caution in managing adverse effects where there is scientific and technical uncertainty about those effects; and
- the principles of the Treaty of Waitangi (Te Tiriti o Waitangi).

5.4 I am satisfied that this decision is consistent with the purpose of the Act and the above principles and matters.

6. Decision

6.1 After reviewing all of the information contained in the application, I am satisfied that the application meets the requirements of section 38I of the Act.

6.2 I exercise my discretion and approve the import for release of Telomelysin under section 38I of the Act. In accordance with section 38J of the Act, the approval is granted **subject to the following controls**:

Control 1 – The applicant must ensure that the organism (Telomelysin, OBP-301 as described in Table 1) is only administered:

a) to individuals enrolled in a Phase 2 clinical trial approved under the Medicines Act 1981 to examine the safety and efficacy of Telomelysin in patients with inoperable stage IIIa and IV metastasised melanoma;
b) intratumourally;
c) by a suitably trained medical practitioner(s); and
d) at a Phase 2 clinical trial site[5].

Control 2 - The New Zealand sponsor of the Phase 2 clinical trial[6] must notify the EPA and Ministry for Primary Industries (MPI), in writing, and at least one calendar month before Telomelysin is administered for the first time at each clinical trial site, of:

a) the location of the Phase 2 clinical trial site; and
b) the qualifications of the suitably trained medical practitioner(s) who will administer the organism.

Control 3 – The New Zealand sponsor must ensure a suitably qualified person(s), before treatment:

a) educates patients who will be treated with the organism about the potential for Telomelysin to be transmitted to untreated individuals, particularly immunocompromised individuals, and the potential adverse effects of Telomelysin transmission; and
b) educates patients in infection control; and
c) advises the patients to avoid contact with immunocompromised individuals

Control 4 – The New Zealand sponsor must ensure that a suitably qualified person(s):

a) before treatment, provides the patient with a biohazard container for any bandages, plasters or other dressings applied to the site of injection of the organism
b) before treatment, instructs the patient to return such containers to the Phase 2 clinical trial site for disposal as medical waste; and
c) disposes of such containers in accordance with medical waste disposal procedures in place at that Phase 2 clinical trial site.

[5] A clinical trial site is a physical clinical setting where trial participants are administered with the organism.

[6] The New Zealand sponsor assumes responsibility (including legal liability) for the clinical trial in New Zealand. The New Zealand sponsor must be a person in New Zealand.

Control 5 – The New Zealand sponsor must:

a) before the commencement of the Phase 2 clinical trial, ensure that protocols and suitably qualified people are available to investigate reports of adverse effects suspected to be related to Telomelysin transmission from treated individuals to untreated individuals;

b) ensure that reports of adverse effects reasonably suspected to be related to Telomelysin transmission are investigated to confirm whether or not transmission has occurred, and whether or not adverse effects have resulted from confirmed transmission; and

c) notify the EPA and MPI, in writing, of any occurrence of Telomelysin-induced adverse effects resulting from confirmed events of Telomelysin transmission from Telomelysin-treated individuals to untreated individuals as soon as practicable.

Control 6 – The New Zealand sponsor must submit a report describing compliance with the above controls to the EPA and MPI, initially to be submitted six months after the commencement of the Phase 2 clinical trial, then on or before 30 June every year thereafter until the conclusion of the Phase 2 clinical trial.

09 February 2018

Dr Allan Freeth
Chief Executive
Environmental Protection Authority

Date

Table 1: Approval number for the organism approved through application APP202854.

Organism	Approval code
Telomelysin (OBP-301). Telomelysin is a Human adenovirus C (type 5) containing a human telomerase reverse transcriptase transcriptional promoter in place of the E1A gene promoter and an internal ribosome entry sequence (IRES) derived from encephalomyocarditis virus in place of the E1B gene promoter.	GMR00004