



Australian Government

Department of Health

Office of the Gene Technology Regulator

7 July 2021

Summary of the Risk Assessment and Risk Management Plan for Licence Application DIR 181

Decision

The Gene Technology Regulator (the Regulator) has received a licence application to conduct a clinical trial using a genetically modified organism (GMO). It qualifies as a DIR licence application under the *Gene Technology Act 2000* (the Act).

The applicant, Novotech (Australia) Pty Limited (Novotech) proposes to conduct a clinical trial of a genetically modified (GM) *Herpes simplex virus-1* (HSV-1) as a gene therapy treatment for adult patients with cystic fibrosis. The clinical trial is proposed to take place at hospitals within Australia over a period of up to three years. Up to 15 people with cystic fibrosis would receive one of three courses of treatment with the GMO, delivered by inhalation, with the aim of evaluating the safety and efficacy of the treatment.

Clinical trials in Australia are conducted in accordance with requirements of the *Therapeutic Goods Act 1989*, which is administered by the Therapeutic Goods Administration (TGA). Therefore, in addition to approval by the Regulator, Novotech would require authorisation from the TGA before the trial commences. Clinical trials conducted in Australia must also be conducted in accordance with the *National Statement on Ethical Conduct in Human Research* and with the *Guidelines for Good Clinical Practice* of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Novotech would also require approval from the Department of Agriculture, Water and the Environment for import of the GM treatment.

The Regulator has prepared a Risk Assessment and Risk Management Plan (RARMP) for this application, which concludes that the proposed clinical trial poses negligible to moderate risks to human health and safety and negligible risks to the environment, but that these risks can be managed by imposing conditions on the conduct of the trial.

The application

Project Title	Clinical trial of a genetically modified Herpes virus for the treatment of cystic fibrosis ¹
Parent organism	<i>Herpes simplex virus-1</i> (HSV-1)
Genetic modifications	The GMO: <ul style="list-style-type: none"> • has been modified such that it cannot replicate; and • expresses two copies of the full length <i>human cystic fibrosis transmembrane conductance regulator</i> (CFTR) gene. These are intended to replace the dysfunctional CFTR gene in people with cystic fibrosis
Principal purpose	The trial is an initial study of genetically modified (GM) HSV-1 expressing human cystic fibrosis transmembrane conductance regulator (CFTR), intended to assess safety and efficacy in a small group of people with cystic fibrosis.
Previous clinical trials	This is a first-in-human study of this GMO
Limits and controls proposed by applicant	
Proposed duration	3 years
Proposed release size	Up to 15 participants will be enrolled into the trial
Proposed location/s	Clinical trials will be conducted at hospitals within Australia. The number of sites and specific locations are yet to be determined.
Proposed controls	<ul style="list-style-type: none"> • The GMO will be administered to trial participants in a hospital setting • The GMO will be administered in a closed room • Staff administering the GMO will wear personal protective equipment • Waste that may contain the GMO will be disposed of via the clinical waste stream • Persons with discernible oral Herpes lesions will be excluded from participating in the trial • Trial participants will be asked to implement hygiene measures intended to minimise exposure of caregivers and other close contacts • Trial participants will be monitored for signs of active HSV-1 infection and treated with oral antiviral medication if this occurs

Risk assessment

The risk assessment concludes that the proposed clinical trial poses negligible to moderate risks to human health and safety and negligible risks to the environment, but that these risks can be managed by imposing conditions on the conduct of the trial.

The risk assessment process considers how the genetic modifications and proposed activities conducted with the GMO might lead to harm to people or the environment. Risks are characterised in relation to both the seriousness and likelihood of harm, taking into account information in the application (including proposed controls), relevant previous approvals and current scientific/technical knowledge. Both short and long term impacts are considered.

¹ The title of the application submitted by Novotech was 'KB407 for the treatment of Cystic Fibrosis'

Credible pathways to potential harm that were considered include exposure of other people or animals to the GMO, expression of CFTR in transduced cells, and the potential for complementation by, and recombination with, wild-type HSV-1. Potential harms that were considered in relation to these pathways included discomfort or ill health due to inappropriate CFTR expression.

Important factors in reaching the conclusions of the risk assessment included that the GM HSV-1 is replication defective, but also that wild type HSV-1 is highly prevalent in the human population, the route of administration brings the GMO into contact with a common site of HSV-1 infection, and HSVs are known to recombine readily. As a consequence, replication competent recombinant virus carrying the CFTR transgene may be generated.

As risks to the health and safety of people have been assessed as negligible to moderate, and risks to the environment as negligible, the Regulator considers that the dealings involved in the proposed trial of the GM *HSV-1* can be managed so they do not pose a significant risk to people and the environment.

Risk management plan

The risk management plan describes measures to protect the health and safety of people and to protect the environment by controlling or mitigating risk. The risk management plan is given effect through licence conditions, including the following. These measures are considered sufficient to manage the identified risks.

Limits and controls in addition to those proposed by the applicant	
Additional controls imposed by the licence	<ul style="list-style-type: none"> • Trial participants must be seronegative for HSV-1 • After treatment, trial participants must be tested weekly for primary HSV 1 infection by diagnostic laboratory testing and offered oral anti-viral medication if they acquire an infection • Clinical trial staff must be protected from aerosol exposure • A plan to limit exposure of people other than trial participants must be developed in consultation with each clinical trial site • Hygiene measures implemented by trial participants to minimise exposure of close contacts must be in place for 48 hours

Since this is a clinical trial, the licence also includes limits on the number of trial participants, types of facility where the trial may be conducted, and on the duration of the trial. There are also several general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements which include an obligation to report any unintended effects.