



Australian Government

Department of Health

Office of the Gene Technology Regulator

January 2021

Summary of the Risk Assessment and Risk Management Plan (Consultation Version)

for

Licence Application No. DIR 179

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 to evaluate the safety and efficacy of genetically modified (GM) *Vaccinia virus* known as TBio-6517, alone and in combination with an existing cancer therapy (Pembrolizumab), for the treatment of Australian patients with advanced solid cancerous tumours.

Vaccinia virus has been used more extensively for human immunisation than any other vaccine and was employed to provide cross-protection against smallpox, until the disease was declared eradicated in 1980. The proposed GM *Vaccinia virus* has been designed to preferentially multiply in, and kill cancer cells. The GM *Vaccinia virus* would be manufactured overseas and imported into Australia. It would be administered by intratumoural injection or by intravenous infusion in up to 150 Australian patients with advanced solid cancerous tumours at clinical facilities and hospitals in Australia.

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 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 trials pose negligible risks to human health and safety and the environment. Licence conditions have been drafted for the proposed clinical trial. The Regulator invites submissions on the RARMP, including draft licence conditions, to inform the decision on whether or not to issue a licence.

The application

Project Title	Clinical trial with a genetically modified Vaccinia virus based treatment for solid cancerous tumours ¹
Parent organism	<i>Vaccinia virus</i> (Copenhagen strain)
Principal purpose	The proposed trial is a Phase 1/2a study designed to evaluate the safety and efficacy of genetically modified (GM) <i>Vaccinia virus</i> , known as (TBio-6517), alone and in combination with Pembrolizumab, an existing cancer therapy, for the treatment of Australian patients with advanced solid cancerous tumours.
Genetic modifications	Modified <i>Vaccinia virus</i> (Copenhagen strain) Deletion and disruption of multiple genes ² including virulence factors - leading to improved destruction of human tumour cells Introduction of genes conferring enhanced immune response: <ul style="list-style-type: none"> • Anti- Cytotoxic T-lymphocyte-Associated protein 4 (anti-CTLA-4) antibody • FMS-like tyrosine kinase 3 ligand (FLT3L) • Membrane-bound interleukin-12 p35 subunit (IL-12p35) Together, these introduced genes stimulate the human immune system allowing improved detection and destruction of cancerous tumour cells.
Previous clinical trials	A Phase 1/2a trial is currently being conducted in the United States
Proposed limits and controls	
Proposed duration	5 years
Proposed release size	Up to 150 clinical trial participants in Australia
Proposed locations	The proposed trial would be conducted at a number of hospitals and clinics across Australia but the exact sites are yet to be identified
Proposed controls	<ul style="list-style-type: none"> • Transport and storage of the GMO that are appropriate for risk group 2 organisms • Require staff handling the GMO to be trained and to use personal protective equipment • Higher-risk staff are excluded from handling the GMO • Destroy waste that may contain GMO according to clinical site procedures appropriate for risk group 2 organisms • Provide patients with detailed instructions regarding the care of any skin-related reactions post-treatment and the use of good hygiene practices

¹ The title of the project as supplied by the applicant is 'Clinical trial with an oncolytic vaccinia virus vaccine (TBio-6517)'.

² Confidential Commercial Information: Some details about the genes deleted in GM *Vaccinia virus* have been declared as Confidential Commercial Information (CCI) under Section 185 of the Act. This information will be made available to the prescribed experts and agencies that will be consulted on this application. CCI is not available to the public.

Risk assessment

The risk assessment concludes that risks to the health and safety of people and the environment from the proposed clinical trial are negligible. No specific risk treatment measures are required to manage these negligible risks.

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 the short and long term impact are considered.

Credible pathways to potential harm that were considered included exposure of people or animals to the GMOs and whether there is the potential for reassortment with other viruses. Potential harms that were considered in relation to these pathways included ill health and increased disease in people or animals.

Important factors in reaching the conclusions of the risk assessment included: that the GM *Vaccinia virus* treatment selectively replicates in cancer cells, and unintended exposure to the GMOs would be minimised by the limits and controls.

As risks to the health and safety of people, or the environment, from the proposed trial of the GM *Vaccinia virus* as a treatment have been assessed as negligible, the Regulator considers that the dealings involved do not pose a significant risk to either people or 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. Draft licence conditions are detailed in Chapter 4 of the RARMP.

As the level of risk is considered negligible, specific risk treatment is not required. However, since this is a clinical trial, the draft licence includes limits on the number of trial participants, location limited to hospitals and clinical trial sites, limits on the duration of the trial, as well as a range of controls to minimise the potential for the GMO to spread in the environment. In addition, there are several general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements which include an obligation to report any unintended effects.