Australian Government
Department of Health
Office of the Gene Technology Regulator

February 2021

Summary of the Risk Assessment and Risk Management Plan

for

Licence Application No. DIR 177

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, proposes to conduct a clinical trial to assess the efficacy of the genetically modified (GM) human adenovirus for bladder cancer treatment in participants whose tumours are unresponsive to standard treatment.

Transitional cell carcinoma (TCC) is the most common type of bladder cancer. Each year almost 2,700 new cases and approximately 1100 deaths of TCC are recorded in Australia. Current treatment includes surgery to remove the bladder tumour, chemotherapy or immunotherapy. The combination of treatments give the best results but cancer reoccurrence rates are still high.

The proposed GM adenovirus treatment is predicted to significantly increase survival rates and limit the reoccurrence in participants that have been unresponsive to other treatments. The GM human adenovirus would be manufactured overseas and imported into Australia. It would be administered into the bladder to a maximum of 60 participants at hospitals located in New South Wales (NSW) and Victoria (VIC).

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 (Australia) Pty Limited 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.

The international sponsor for the trial is a privately held, clinical-stage biopharmaceutical company CG Oncology, which is based in the United States. Novotech, a clinical research organisation, is applying for authorisation to conduct the proposed clinical trial in Australia and is responsible for ensuring that the licence conditions are met.

Novotech (Australia) Pty Limited would also require approval from the Department of Agriculture, Water and the Environment for import of the GMO.

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

The application

Project Title	Clinical trial of a genetically modified human adenovirus for treatment of bladder cancer [1].
Parent organism	Human adenovirus type 5 (Ad5)
Principal purpose	The proposed trial is a phase 3 study designed to evaluate the efficacy of the genetically modified human adenovirus for bladder cancer treatment in participants whose tumours are unresponsive to standard treatment.
Genetic modifications	Modified human adenovirus: Partial deletion of viral *gene E3 and E1a promoter* and insertion of*:* - A promoter providing tumour specificity – *human hE2F-1 promoter* - A gene stimulating anti-tumour response – *human hGM-CSF gene* - pA signal protecting from transcriptional read-through
Previous clinical trials	Three clinical trials have been conducted: Phase 1 clinical trials in the United States and Canada Phase 2 clinical trial in the United States (study 1) Phase 2 clinical trial in the United States (study 2)
Proposed limits and controls	
Proposed duration	5 years
Proposed trial size	Up to 60 clinical trial participants in Australia
Proposed locations	Hospitals in NSW and VIC

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

[1] The title of the project as submitted by the applicant was: 'Clinical Trials with an Oncolytic Treatment Vaccine (CG0070)'

Important factors in reaching the conclusions of the risk assessment include: that the GMO replicates preferentially in cancer cells; the GMO has limited ability to stimulate the immune response in healthy hosts and other animals; and the exposure to the GMO would be minimised by the imposed limits and controls.

As risks to the health and safety of people, or the environment, from the proposed trial of the GMO have been assessed as negligible, as they 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.

As the level of risk is considered negligible, specific risk treatment is not required. However, since this is a clinical trial, the licence includes limits on the size, location and 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.