Australian Government
Department of Health
Office of the Gene Technology Regulator

INFO 18

November 2020

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

for

Licence Application No. DIR 177

Introduction

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 patients in which 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 gives 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 patients 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 patients 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.

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 genetically modified human adenovirus for bladder cancer treatment[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 patients 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 were 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 included 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 included ill health and increased disease in people or animals.

Important factors in reaching the conclusions of the risk assessment included: that the GMO replicates preferentially in cancer cells; the GMO has limited ability to stimulate the immune response in healthy

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

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.

Questions & Answers on licence application DIR 177 – clinical trial of genetically modified human adenovirus

What is this application for?

Novotech (Australia) Pty Limited is seeking approval for a clinical trial of genetically modified human adenovirus for bladder cancer 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 the above gives best results but cancer reoccurrence rates are still high.

The proposed GM human adenovirus treatment is predicted to significantly increase survival rates and limit the reoccurrence in patients 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 patients at hospitals located in New South Wales (NSW) and Victoria (VIC).

What other regulatory processes apply to this trial?

Clinical trials must be conducted in accordance with requirements of the Therapeutic Goods Administration (TGA), which address the safety of trial participants. Before commencing, the trials would require ethics approval, and must be conducted in accordance with the *Guidelines for Good Clinical Practice*. Import of the GM human adenovirus treatment will also require approval from the Department of Agriculture, Water and the Environment.

How has the GM vaccine been created?

The vaccine is based on a modified human adenovirus. The GM treatment has been modified so that it reproduces preferentially in cancer cells. Two genes have been introduced into the GM vaccine that inhibit viral replication in normal cells and stimulate immune response in tumours.

Has the GM vaccine been previously tested or used?

The GM treatment has been tested in the United States and in Canada. These studies have shown that people receiving the GM treatment have mild to moderate urinary-tract effects (sudden and frequent need of urination, bladder discomfort, presence of blood in urine and painful urination) and occasionally mild-flu symptoms. There have been no severe reactions to the GM treatment.

What controls are proposed for this release?

The consultation Risk Assessment and Risk Management Plan (RARMP) prepared for this application concluded that the trial poses negligible risks to people or the environment. However, as this is a trial under limited and controlled conditions, a number of licence conditions have been drafted to restrict when and where the trial can take place, limit the size of the trial, and restrict the spread and persistence of the GM treatment. For example, there are conditions relating to preparation and administration of the treatment, secure transport and storage of the treatment and appropriate waste disposal. Details of the draft licence conditions are available in the consultation RARMP.

How can I comment on this application?

The full consultation RARMP and a summary of the RARMP for application DIR 177 are available on the What's New page of the OGTR website or via the contacts listed below. You are invited to submit your written comments (including email) on the consultation version of the RARMP, related to any risks to the health and safety of people or to the environment from the proposed trial. Comments must be received by the close of the consultation period on **22 December 2020**.

What are the next steps in the evaluation process?

The RARMP will be finalised, taking into account submissions related to the protection of people or the environment. A de-identified summary of all comments received and consideration of those comments is included in the Appendices to the final RARMP. The finalised RARMP will inform the Regulator's decision on whether or not to issue a licence.

The Office of the Gene Technology Regulator

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