



Summary of the Risk Assessment and Risk Management Plan for Licence Application DIR 222

Decision

The Gene Technology Regulator (the Regulator) has decided to issue a licence for this application for the intentional release of a genetically modified organism (GMO) into the environment. A Risk Assessment and Risk Management Plan (RARMP) for this application has been prepared by the Regulator in accordance with the *Gene Technology Act 2000* (the Act) and corresponding state and territory legislation, and finalised following consultation with a wide range of experts, agencies and authorities, and the public. The RARMP concluded that the proposed trial poses negligible risk to human health and safety and the environment and that any risks posed by the dealings can be managed by imposing conditions on the release.

The applicant, Novotech (Australia) Pty Limited (Novotech), proposes to conduct a clinical trial to evaluate the safety and efficacy of a genetically modified (GM) human adenovirus for the treatment of Australian patients with locally advanced rectal cancer.

The proposed GM adenovirus preferentially replicates in and kills cancer cells and delivers transgenes that enhance local anti-tumour response. The GM adenovirus would be manufactured overseas and imported into Australia. It would be administered by intravenous (IV) administration in approximately 40 patients with advanced rectal cancer 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 also 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, Fisheries and Forestry (DAFF) for import of the GMO into Australia.

The application

Project Title	Clinical trial of genetically modified adenovirus for the treatment of locally advanced rectal cancer
Parent organism	Human chimeric adenovirus type 11p (Ad11p)/Ad3, with deletions in E3 and E4 gene regions
Genetic modifications	Insertion of transgenes for agonist anti-CD40 antibody heavy and light chains to enhance local immune response
Principal purpose	The proposed trial is designed to evaluate the safety, tolerability and efficacy of a GM adenoviral vector (NG-350A), in combination with

	chemoradiotherapy, for the treatment of Australian patients with locally advanced rectal cancer.
Previous clinical trials	<p>NG-350A has been approved for clinical trials in the United Kingdom and the United States. The following clinical studies have been or are being conducted with NG-350A:</p> <ul style="list-style-type: none"> • Fortitude (Phase 1a/1b) in adult patients with metastatic or advanced epithelial tumours • Fortify (Phase 1a/1b) in adult patients with metastatic or advanced epithelial tumours • Revolution (Phase 1) in patients with pancreatic adeno-carcinoma with metastatic disease
Proposed limits and controls	
Proposed duration	4 years
Proposed release size	Approximately 40 participants in Australia
Proposed locations	This trial will include multiple clinical trial sites and hospitals across Australia. The exact sites are yet to be identified.
Proposed controls	<ul style="list-style-type: none"> • The transport and storage of the GMO will be according to the <i>Regulator's Guidelines for the Transport, Storage and Disposal of GMOs</i> • The staff preparing or administering the GMO would be required to wear appropriate personal protective equipment (PPE) • Only trained staff would conduct dealings with the GMO • Used or unused study drugs will either be returned to the study Sponsor or destroyed via the clinical waste stream • The waste that may contain GMO will be disposed of via clinical waste stream • Participants will refrain from egg and sperm donation and will use effective barrier contraception during treatment and for at least 6 months following the last dose of study treatment

Risk assessment

The risk assessment process considers how the genetic modification 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 risks are considered.

Credible pathways to potential harm that were considered include the potential exposure of people and animals to the GMO, the potential for the GMO to recombine with other similar viruses and the potential for the GMO to integrate into the host genome.

The risk assessment concludes that the trial poses negligible risks to human health and safety and to the environment. No specific risk treatment measures are required to manage these negligible risks.

Important factors in reaching the conclusions of the risk assessment included that the GMO preferentially replicates in cancer cells, unintended exposure to the GMO would be minimised by the

limits and controls outlined in the risk management plan and that the likelihood of complementation and recombination of the GMO with other adenoviruses is very low.

Risk management

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 number of trial participants, administration locations 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.