Australian Government
Department of Health
Office of the Gene Technology Regulator

22 November 2021

Summary of the Risk Assessment and Risk Management Plan

(consultation version) for

Licence Application DIR 187

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, VRT Pharmaceutics Ptd Ltd (VRT Pharmaceutics) proposes to conduct a clinical trial of a genetically modified *Getah virus* as a treatment for cancer. The clinical trial is proposed to take place at Flinders Private Hospital in Bedford Park, South Australia and at other locations in Australia as required. The trial will run for a period of up to five years. Its objectives are to evaluate the safety and tolerability of the GMO in adult participants with locally advanced or metastatic cancer. Trial participants' immune response to the GMO, as well as its biodistribution and shedding, will also be assessed. A maximum of 18 cancer patients would receive up to seven treatments with intravenously delivered GMO. Four different dose levels would be tested. Patients who respond well to the treatment would have the opportunity to continue to receive the GMO for another two years after the study protocol is complete.

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, VRT Pharmaceutics 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. VRT Pharmaceutics would also require approval from the Department of Agriculture, Water and the Environment for import of the GMO into Australia. In addition, they may require approval from the Chief Inspector of Stock before bringing the GMO into South Australia, and a Prohibited Matter Permit from New South Wales, Queensland and Western Australia if they wish to conduct dealings in those states.

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. 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 of a genetically modified alphavirus for treatment of cancer [1]
Parent organism	*Getah virus* (M1 strain), a member of the *alphavirus* genus
Genetic modifications	Two single nucleotide changes have been introduced into the *Getah virus* (M1) genome, each altering one amino acid in separate viral proteins.
Principal purpose	The trial will evaluate the safety and tolerability of the GMO in adult participants with locally advanced or metastatic cancer. Trial participants' immune response to the GMO, as well as its biodistribution and shedding, will also be assessed.
Previous clinical trials	The proposed study is the first formal clinical trial to be undertaken. However, 14 patients with different solid tumours have been treated with the GMO under compassionate use access in China.
Proposed limits and controls	
Proposed duration	5 years
Proposed release size	Up to 18 participants will be enrolled in the trial
Proposed locations	Flinders Private Hospital, Bedford Park SA; Royal Adelaide Hospital, Adelaide SA; and Austech Medical Laboratories, Bankstown NSW. Additional clinical trial sites in Australia may be engaged if sufficient participants cannot be recruited in Adelaide.
Proposed controls	• The GMO will be administered to trial participants in a hospital setting • Staff preparing and administering the GMO will use personal protective equipment • Waste that may contain the GMO will be disposed of by high temperature incineration • Participants will remain in hospital for at least 24 hours after the first treatment and 2 hours after subsequent treatments • Trial participants will take the following precautions: – Take measures to avoid exposure to mosquitoes for 7 days after each treatment – If sexually active, use barrier contraception for 30 days after each treatment – Avoid contact with newborns, immunocompromised and severely immunodeficient individuals • Pregnant women will be excluded from the trial • Trial participants may not donate blood or organs during the trial • Immunocompromised or pregnant clinical trial staff should avoid direct contact with the GMO and with participant injection sites, excreta and secretions

[1] The title of the application submitted by VRT Pharmaceutics Pty Ltd was 'Clinical trials with alphavirus M1 GMO (M1-c6v1) in patients with solid tumours'.

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 short- and long-term impacts are considered.

Credible pathways to potential harm that were considered include transmission of the GMO from trial participants to other people and animals via mosquitoes or direct contact with blood or body fluids, transmission of the GMO from exposed clinical trial staff to other people and animals, and transplacental transmission from a pregnant clinical trial staff member to their unborn child. Potential harms that were considered in relation to these pathways included more severe forms of *Getah virus* (GETV)-associated disease.

Important factors in reaching the conclusions of the risk assessment that unintended exposure to the GMO would be minimised by proposed limits and controls.

As risks to the health and safety of people, or the environment, from the proposed trial of the GM GETV as a cancer 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 **Error! Reference source not found.** 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, locations limited to facilities similar to the hospitals and associated storage and distribution site described in the application, limits on the duration of the trial, as well as a range of controls to minimise the potential for exposure of people other than trial participants, and exposure of animals, to the GMO. 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.