Australian Government
Department of Health and Aged Care
Office of the Gene Technology Regulator

August 2023

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

for

Licence Application No. DIR 198

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 (GM) Getah virus (GETV) as a treatment for cancer. The clinical trial is proposed to take place at Flinders Private Hospital in Bedford Park, South Australia (SA) and at other locations in SA as required.

The purpose of the clinical trial is 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 12 cancer patients would receive up to 15 doses of the GMO over a three-month period. 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, Fisheries and Forestry (DAFF) 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; an authorisation from the Department of Jobs, Skills, Industry and Regions - Agriculture Victoria in Victoria 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 **moderate** risks to 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 (Getah virus) for cancer treatment [1].
Parent organism	Getah virus (M1 strain, variant M1-c6), a member of the *Alphavirus* genus
Genetic modifications	Two single nucleotide changes have been introduced into the Getah virus 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 will be the first clinical trial to be undertaken in Australia. However, the applicant has applied for clinical trial approval in China, Japan, and United States of America (USA), which are under consideration. Furthermore, 27 participants have been administered with the GMO under an investigator-initiated trial for compassionate use in China, including 13 patients with advanced hepatocellular carcinoma (HCC) and 14 patients with different solid tumours.
Proposed limits and controls	
Proposed duration	5 years
Proposed release size	Up to 12 participants will be enrolled in the trial.
Proposed locations	Flinders Private Hospital, Bedford Park, South Australia (SA). Additional clinical trial sites in SA may be engaged. Other sites may be engaged for the storage of the GMO in New South Wales.
Proposed controls	• The GMO will be administered to trial participants in a hospital setting. • The GMO will be stored in an OGTR-certified physical containment level 2 (PC2) facility on arrival into Australia. Transport of the GMO and samples that may contain the GMO would be in accordance with IATA requirements UN 3373 or Regulator's *Guidelines for the Transport, Storage & Disposal of GMOs.* • Staff preparing and administering the GMO, or handling items contaminated with blood or body fluids from treated participants, will wear personal protective equipment (PPE). • Waste that may contain the GMO will be disposed of via the clinical waste stream, with destruction by autoclaving or high temperature incineration. • Participants will remain at the clinical trial site as an in-patient during the 5 days of administration and until 2 consecutive negative blood tests for viremia due to the GMO, at each treatment cycle. • Trial participants will be required to use barrier contraception during and for 90 days after treatment.

[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'.

	• Pregnant women will be excluded from the trial. • Trial participants may not donate blood or organs during the trial. • Staff will be informed that immunocompromised or pregnant individuals should not handle the GMO.

Risk assessment

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 the; potential exposure of people and animals to the GMO; and the potential for the GMO to transfer or acquire genetic material from other viruses. The potential for the GMO to be released into the environment and its effects were also considered.

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

The risk assessment concludes that the trial poses negligible risks to human health and safety and moderate risks to the environment. Specific risk treatment measures are included in the licence to manage these risks.

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. Draft licence conditions are detailed in Chapter 4 of the RARMP.

As the level of risk is to the environment was assessed as **moderate**, licence conditions are proposed to manage this risk. In addition, since this is a clinical trial, the draft licence includes limits on the number of trial participants, types of facilities used and 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. There are also several general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements which include an obligation to report any unintended effects.