



Summary of the Risk Assessment and Risk Management Plan for Licence Application DIR 140

Decision

The Gene Technology Regulator (the Regulator) has decided to issue a licence for this application to conduct a Phase 3 clinical trial of a genetically modified virus in patients with advanced liver cancer. A Risk Assessment and Risk Management Plan (RARMP) for this application was prepared by the Regulator in accordance with the requirements of the *Gene Technology Act 2000* (the Act) and corresponding state and territory legislation, and finalised following consultation with a range of experts, agencies and authorities, and the public. The RARMP concludes that this clinical trial poses negligible to low 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 conduct of the trial.

As part of Australia's integrated approach to the regulation of gene technology, regulation under the Act is not intended to override or duplicate the regulatory oversight of agencies that have responsibility for genetically modified organisms (GMOs) or GM products based on their intended use.

Clinical trials in Australia must be conducted in accordance with requirements of the *Therapeutic Goods Act 1989*, which is administered by the Therapeutic Goods Administration (TGA). Clinical trials must have approval from the Human Research Ethics Committee at each trial site before the trial commences, and must be conducted in accordance with the National Statement on the Ethical Conduct in Research Involving Humans.

The application

Application number	DIR 140
Applicant	Clinical Network Services (CNS) Pty Ltd
Project title	Clinical trial of a genetically modified virus for treatment of liver cancer ¹
Parent organism	<i>Vaccinia virus</i> , New York City Board of Health (NYCBH) vaccine strain
Introduced genes and modified traits	<ul style="list-style-type: none">• inactivation of viral <i>thymidine kinase (TK)</i> gene (human therapeutic – attenuation)• insertion of human <i>Granulocyte-Macrophage Colony-Stimulating Factor (hGM-CSF)</i> gene (human therapeutic - enhanced immune response)• insertion of bacterial <i>lacZ</i> gene from <i>Escherichia coli (E. coli)</i> (reporter gene expression)

¹ The title of the licence application submitted by Clinical Network Services (CNS) Pty Ltd is 'A Phase 3 Randomized, Open-Label Study Comparing Pexa Vec (Vaccinia GM CSF / Thymidine Kinase-Deactivated Virus) Followed by Sorafenib Versus Sorafenib in Patients with Advanced Hepatocellular Carcinoma (HCC) Without Prior Systemic Therapy (JX594-HEP024)'.

Proposed release dates	The clinical trial is anticipated to occur over a 12 month period, commencing in 2016. A total period of 5 years has been requested to accommodate follow-up studies, if required.
Proposed location	For administration by medical professionals in hospitals throughout Australia (specific locations are not yet finalised, but would be chosen so as to provide access to patients with advanced liver cancer).
Primary purpose	To assess the effectiveness and safety of the GMO as a treatment for advanced liver cancer when provided in conjunction with a standard treatment, compared with the standard treatment alone.

CNS has proposed a clinical trial of a live GM *vaccinia virus* (VACV) intended to preferentially kill cancer cells and trigger an immune response against the tumour. Up to 50 adult volunteers with advanced hepatocellular carcinoma (HCC), a common type of liver cancer, would be treated with the genetically modified organism (GMO). The purpose of the trial is to assess the effectiveness and safety of the GMO as a treatment for advanced HCC when provided in conjunction with a standard treatment, compared with the standard treatment alone.

The parent organism, VACV, is a member of the Poxvirus family, infects a range of mammalian species and is mildly pathogenic in humans. It is not known to be circulating in any human population but was used world-wide as a vaccine to protect against smallpox infection. VACV has attracted recent interest as a potential cancer therapeutic as it is thought to show a natural selectivity for cancer cells without causing significant adverse effects in the patient.

The GMO is based on the Dryvax™ smallpox vaccine (Wyeth Laboratories), which was used extensively in the USA during the smallpox eradication campaign in the 1960s and 70s. Dryvax™ was prepared from the New York City Board of Health (NYCBH) *vaccinia* strain and contains a mixture of closely related viruses of relatively low pathogenicity. The GMO is derived from a single clone isolated from this mixture.

The GMO has been modified so as to enhance its specificity for cancer cells. The *vaccinia thymidine kinase (TK)* gene, encoding a thymidine kinase enzyme required for DNA synthesis and viral replication, has been disrupted by insertion of the *GM-CSF* and *lacZ* genes. As a result, the GMO can only reproduce in host cells which produce their own TK. TK is expressed at low levels during normal cell division and at higher levels in most cancer cells, but not in non-dividing cells. Thus, the GMO is expected to replicate well in tumours while displaying attenuation in normal tissues, leading to preferential destruction of cancer cells.

A single copy of the human *GM-CSF* gene has been inserted within the viral *TK* gene, so as to promote an anti-cancer immune response. hGM-CSF is a naturally occurring cytokine that encourages the proliferation of certain types of immune cell. When tumour cells are killed by the GMO, hGM-CSF is expected to enhance the immune response to tumour antigens by stimulating specific immune cells in the immediate vicinity. This may also lead to a therapeutic effect on tumours located elsewhere in the body.

A single copy of the *E. coli lacZ* reporter gene has also been inserted within the viral *TK* gene. This gene encodes a β -galactosidase enzyme which can be detected using a biochemical assay, allowing quick and easy detection of the GMO in blood and tissue samples collected from trial participants.

The GMO has not previously been trialled in Australia. However, it has been evaluated overseas in 13 completed and ongoing clinical trials, in countries that include the USA, Canada and South Korea. The proposed study would form part of an international multi-centre Phase 3 clinical trial.

Risk assessment

The risk assessment concludes that risks from the proposed dealings to the health and safety of people, or to the environment, are negligible to low. It is proposed that risk treatment measures be applied to manage these risks.

The risk assessment process considers how the genetic modification and proposed activities conducted with the GMOs could lead to harm to people or the environment. Plausible causal or exposure pathways are postulated that may give rise to harm for people or the environment from dealings with a GMO (risk scenarios) in the short and long term. This included consideration of the absence of the parent organism from the Australian environment and the potential for: expression of the introduced genes and genetic modifications to impact on the disease burden caused by the GM virus; infection of at-risk individuals; infection of animals; and gene transfer to other organisms.

A risk is only identified for further assessment when a risk scenario is considered to have some chance of causing harm. Pathways that do not lead to an adverse outcome, or could not reasonably occur, do not advance in the risk assessment process. Identified risks are characterised in relation to both the likelihood and seriousness of harm, taking into account information in the application (including proposed limits and controls), relevant previous approvals and current scientific/technical knowledge.

The TGA, the trial sponsor, the investigators and the Human Research Ethics Committee (HREC) at each trial site all have roles to play in ensuring participants' safety under the *Therapeutic Goods Act 1989*. Therefore, the Regulator focuses primarily on risks posed to people other than those participating in the clinical trial, and to the environment.

Risks to the health and safety of at-risk individuals from exposure to the GMO through contact with trial participants who are shedding the virus were estimated as negligible to low. Risk evaluation proposed that risk treatment should be applied to mitigate the low risk. No other substantive risks were identified.

Important factors in reaching the conclusions of the risk assessment included: that the GM virus is expected to be attenuated relative to unmodified VACV; the introduced genes have not been associated with toxicity; unintended exposure would be minimised by precautions proposed by the applicant; and previous experience with the GMO in earlier clinical trials.

As risks to the health and safety of people, or the environment, from the proposed clinical trial of the GM virus have been assessed as negligible to low, the Regulator considers that the dealings involved do not pose a significant risk to either people or the environment.

Risk management plan

Risk management is used to protect the health and safety of people and to protect the environment by controlling or mitigating risk. The risk management plan evaluates options for treatment of identified risks, evaluates limits and controls proposed by the applicant, and considers general risk management measures. The risk management plan is given effect through licence conditions.

Treatment measures to mitigate the identified negligible to low risks to human health and safety were considered and licence conditions imposed. These conditions require patients participating in the trial to avoid contact with certain at-risk people following their initial treatment with the GMO, until they have been assessed for the presence of GMO-related lesions by their clinician. These measures are considered sufficient to manage the identified negligible to low risks.

As this is a limited and controlled release, the licence also includes conditions that limit the scope and duration of the trial as well as controls in line with those proposed by the applicant, including administration of the GMO via intratumoural inoculation and by trained medical staff, exclusion

of participants and staff at higher risk of adverse reactions and more likely to shed the GMO, educating trial participants about methods to minimise transmission of the GMO, appropriate containment and disposal of waste, destroying excess GMO that is not required for further studies, and transporting and storing the GMO in accordance with the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*.

The licence also contains a number of general conditions relating to ongoing licence holder suitability, auditing and monitoring, and reporting requirements, which include an obligation to report any unintended effects.

These licence conditions will manage risks to so as to protect human health and safety and the environment.