Australian Government
Department of Health, Disability and Ageing
Office of the Gene Technology Regulator

January 2026

Risk Assessment and Risk Management Plan (Consultation version) for

DIR 222

Clinical trial of GM adenovirus for treatment of locally advanced rectal cancer

Applicant: Novotech (Australia) Pty Ltd

This RARMP is open for consultation until 05 March 2026.

Written comments on the risks to human health and safety and the environment posed by this proposed clinical trial of the GM human adenovirus treatment are invited. You may make your submission

Via the consultation hub:	https://consultations.health.gov.au (search for DIR 222)
via email to:	ogtr@health.gov.au
or mail to:	The Office of the Gene Technology Regulator,
	MDP 54 GPO Box 9848, Canberra ACT 2601

Please note that issues regarding patient safety and the quality of the therapeutic **do not** fall within the scope of these evaluations as they are the responsibilities of other agencies and authorities.

Summary of the Risk Assessment and Risk Management Plan

(Consultation Version) for

Licence Application DIR 222

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 Dealing involving the Intentional Release (DIR) of GMOs into the Australian environment under the *Gene Technology Act 2000*.

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 locally advanced rectal cancer.

The proposed genetically modified (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 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 to issue a licence.

The application

Project Title	Clinical trial of GM adenovirus for 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	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: • 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	• The transport and storage of the GMO will be according to the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* • 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 proposed limits and controls outlined in the draft risk management plan and that the likelihood of complementation and recombination of the GMO with other adenoviruses is very low.

As risks to the health and safety of people, or the environment, from the proposed trial of the treatment with the GMO 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

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 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, 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.

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Abbreviations

AdV	Adenovirus
APVMA	Australian Pesticides and Veterinary Medicines Authority
CDC	Centers for Disease Control and Prevention
DIR	Dealings Involving Intentional Release
DNA	Deoxyribonucleic acid
FSANZ	Food Standards Australia New Zealand
GTTAC	Gene Technology Technical Advisory Committee
GM	Genetically modified
GMO	Genetically modified organism
HREC	Human Research Ethics Committee
IATA	International Air Transport Association
IBC	Institutional Biosafety Committee
ICH-GCP	*Guidelines for Good Clinical Practice* of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IV	intra-venous
mL	Millilitre
min	Minute
NHMRC	National Health and Medical Research Council
NPAAC	National Pathology Accreditation Advisory Council
NSQHS	National Safety and Quality Health Service Standards
OGTR	Office of the Gene Technology Regulator
PPE	Personal Protective Equipment
PFU	Plaque Forming Units
PCR	Polymerase chain reaction
RAF	Risk Analysis Framework
RARMP	Risk Assessment and Risk Management Plan
SOP	Standard Operating Procedure
the Act	The *Gene Technology Act 2000*
the Regulations	The Gene Technology Regulations 2001
the Regulator	The Gene Technology Regulator
TGA	Therapeutic Goods Administration
TSDs	The Regulator's *Guidelines for Transport, Storage and Disposal*
USA	United States of America
vp	Viral particles
WHO	World Health Organization

Chapter 1 Risk assessment context

Section 1 Background

1. An application has been made under the Gene Technology Act 2000 (the Act) for Dealings involving the Intentional Release (DIR) of genetically modified organisms (GMOs) into the Australian environment.

2. The Act and the Gene Technology Regulations 2001 (the Regulations), together with corresponding State and Territory legislation, comprise Australia's national regulatory system for gene technology. Its objective is to protect the health and safety of people, and to protect the environment, by identifying risks posed by or as a result of gene technology, and by managing those risks through regulating certain dealings with GMOs.

3. Section 50 of the Act requires that the Gene Technology Regulator (the Regulator) must prepare a Risk Assessment and Risk Management Plan (RARMP) in response to an application for release of GMOs into the Australian environment. Sections 50, 50A and 51 of the Act and sections 9 and 10 of the Regulations outline the matters which the Regulator must take into account and who must be consulted when preparing the RARMP.

4. The *Risk Analysis Framework* (RAF) (OGTR, 2013) explains the Regulator's approach to the preparation of RARMPs in accordance with the Act and the Regulations. The Regulator has also developed operational policies and guidelines that are relevant to DIR licences. These documents are available from the Office of the Gene Technology Regulator (OGTR website).

5. Figure 1 shows the information that is considered, within the regulatory framework above, in establishing the risk assessment context. This information is specific for each application. Risks to the health and safety of people or the environment posed by the proposed supply are assessed within this context. Chapter 1 describes the risk assessment context for this application.

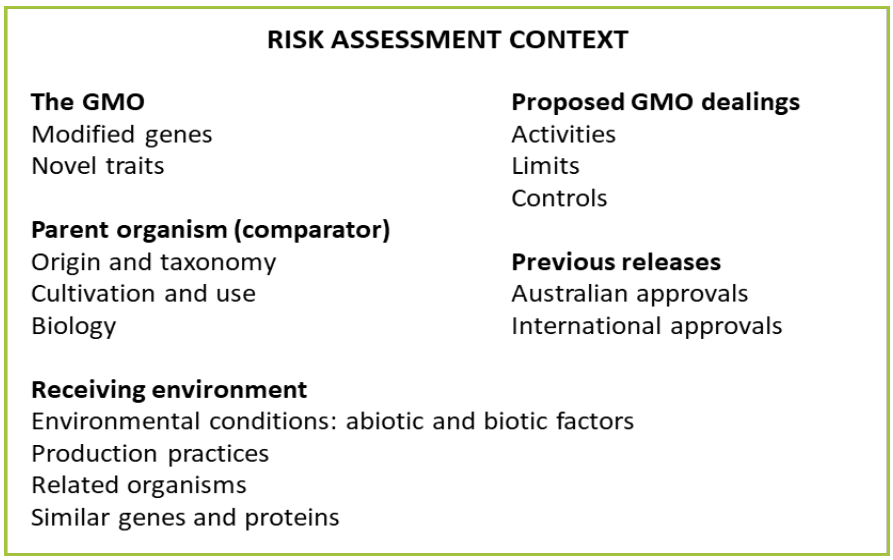

Figure 1. Summary of parameters used to establish the risk assessment context, within the legislative requirements, operational policies and guidelines of the OGTR and the RAF.

6. In accordance with Section 50A of the Act, this application is considered to be a limited and controlled release application, as the Regulator was satisfied that it meets the criteria prescribed by the Act. Therefore, the Regulator was not required to consult with prescribed experts, agencies and authorities before preparation of the RARMP.

1.1 Interface with other regulatory schemes

7. Gene technology legislation operates in conjunction with other regulatory schemes in Australia. The GMOs and any proposed dealings conducted under a licence issued by the Regulator may also be subject to regulation by other Australian government agencies that regulate GMOs or GM products, including Food Standards Australia New Zealand (FSANZ), the Australian Pesticides and Veterinary Medicines Authority (APVMA), the Therapeutic Goods Administration (TGA), the Australian Industrial Chemicals Introduction Scheme (AICIS) and the Department of Agriculture, Fisheries and Forestry (DAFF).

8. Medicines and other therapeutic goods for use in Australia are required to be assessed for quality, safety and efficacy under the *Therapeutic Goods Act 1989* and must be included in the Australian Register of Therapeutic Goods. The TGA is responsible for administering the provisions of this legislation. Clinical trials of therapeutic products that are experimental and under development, prior to a full evaluation and assessment, are also regulated by the TGA through the Clinical Trial Approval (CTA) scheme or the Clinical Trial Notification (CTN) scheme.

9. For clinical trials, the TGA has regulatory responsibility for the supply of unapproved therapeutic products. In terms of risk to individuals participating in a clinical trial, the TGA (as the primary regulatory agency), the trial sponsor, the investigators and the Human Research Ethics Committee (HREC) at each trial site all have roles in ensuring participants' safety under the *Therapeutic Goods Act 1989*. However, where the trial involves a GMO, authorisation is also required under gene technology legislation. To avoid duplication of regulatory oversight, and as risks to trial participants are addressed through the above mechanisms, the Regulator's focus is on assessing risks posed to people other than those participating in the clinical trial, and to the environment. This includes risks to people preparing and administering the GM virus, and risks associated with import, transport and disposal of the GMO.

10. The International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Guidelines for Good Clinical Practice (ICH-GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects (ICH 1996). The guideline was developed with consideration of the current good clinical practices of the European Union (EU), Japan, and the United States of America (USA), as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO). The TGA has adopted the ICH-GCP in principle as Note for Guidance on Good Clinical Practice (designated CPMP/ICH/135/95) (Therapeutic Goods Administration 2000), which provides overarching guidance for conducting clinical trials in Australia which fall under TGA regulation.

11. The National Health and Medical Research Council (NHMRC) has issued the *National Statement on Ethical Conduct in Human Research* (National Health and Medical Research Council, 2023). This document sets the Australian standard against which all research involving humans is reviewed. The *Therapeutic Goods Act 1989* requires that the use of a therapeutic good in a clinical trial must be in accordance with the ethical standards set out in this document.

12. Approval by a Human Research Ethics Committee (HREC) is also a fundamental requirement of a clinical trial. HRECs conduct both ethical and scientific assessment of the proposal and in addition often consider issues of research governance. Other elements of governance of clinical trials that are considered by HRECs include appropriate informed consent, specific inclusion and exclusion criteria, data monitoring and GMO accounting and reconciliation.

13. DAFF administers Australian biosecurity conditions for the importation of biological products under the *Biosecurity Act 2015*. Biological products include animal or microbial derived products such as foods, therapeutics, laboratory materials and vaccines (including GMO).

14. Analysis of biological samples collected from trial participants administered with the GMO would occur at clinical trial sites, or at pathology laboratories. These facilities are regulated by State and Territory governments and adhere to professional standards for safety, disease control (Australian Guidelines for the Prevention and Control of Infection in Healthcare (2019) and handling of pathology samples (National Pathology Accreditation Advisory Council; NPAAC).

15. NPAAC advises Commonwealth, State and Territory health ministers on matters relating to the accreditation of pathology laboratories. NPAAC plays a key role in ensuring the quality of Australian pathology services and is responsible for the development and maintenance of standards and guidelines for pathology practices. The standards include safety precautions to protect the safety of workers from exposure to infectious microorganisms in pathology laboratories. While compliance with NPAAC standards and guidelines is not mandatory, there is a strong motivation for pathology services to comply, as Medicare benefits are only payable for pathology services if conducted in an appropriate Accredited Pathology Laboratory (APL) category, by an Approved Pathology Practitioner (APP) employed by an Approved Pathology Authority (APA). Accreditation of pathology services is overseen by Services Australia (formerly Department of Human Services), and currently, the only endorsed assessing body for pathology accreditation is the National Association of Testing Authorities (NATA).

16. The state and territory governments regulate hospitals and other medical facilities in Australia. All public and private hospitals and day procedure services need to be accredited to the National Safety and Quality Health Service (NSQHS) Standards developed by the Australian Commission on Safety and Quality in Healthcare (the Commission) and endorsed by the state and territory Health Ministers. The Commission coordinates accreditation processes via the Australian Health Service Safety and Quality Accreditation (AHSSQA) scheme. The NSQHS Standards provide a quality assurance mechanism that tests whether relevant systems are in place to ensure that the minimum standards of safety and quality are met. The safety aspects addressed by the NSQHS Standards include the safe use of sharps, disinfection, sterilisation and appropriate handling of potentially infectious substances. Additionally, the Commission has developed the National Model Clinical Guidance Framework, which is based on, and builds on NSQHS Standards to ensure that clinical governance systems are implemented effectively and to support better care for patients and consumers.

17. Hospitals and pathology laboratories, including their workers, managers and executives, all have a role in making the workplace safe and managing the risks associated with handling potentially infectious substances including the proposed GMO. There are minimum infection prevention practices that apply to all health care in any setting where health care is provided. These prevention practices were initially developed by the Centers for Disease Control and Prevention (CDC) and are known as the standard precautions for working with potentially infectious material. The standard precautions are described in the Australian Guidelines for the Prevention and Control of Infection in Healthcare (2019).

Section 2 The proposed dealings

18. Rectal cancer represents the 8th most common cancer in the world (Ferlay et al., 2024) and its incidence is on the rise, especially in younger populations (Lișcu et al., 2025).

19. Oncolytic viruses are a form of immunotherapy which target cancer cells. They preferentially replicate in transformed cells while limiting infection of healthy cells, usually by taking advantage of molecular dysregulation in tumour cells. Their mechanism of action involves both direct killing of infected cells and facilitation of local anti-cancer immune responses (Appleton et al., 2025).

20. Novotech is seeking authorisation to carry out a clinical trial to assess the safety, tolerability and efficacy of a GM human adenovirus (HAdV) that preferentially replicates in cancer cells in combination with chemoradiotherapy in patients with locally advanced rectal cancer.

21. The dealings involved in the proposed clinical trial are:

(a) import the GMO;

(b) conduct the following experiments with the GMO:

i. prepare the GMO for administration to trial participants;

ii. administer the GMO to clinical trial participants by intravenous (IV) injection;

iii. collect samples from trial participants;

iv. analyse the samples;

(c) transport the GMO;

(d) dispose of the GMO;

and the possession (including storage), supply and use of the GMO for the purposes of, or in the course of, any of these dealings.

2.1 The proposed limits of the trial (duration, scale, location, people)

22. The clinical trial is proposed to take place over a 4-year period from the date of issue of the licence. Approximately 40 participants in Australia would receive the GMO.

23. The clinical trial would take place at clinical trial sites and hospitals in Australia. These sites have not yet been identified but will meet the suitability criteria outlined in Section 2.3.3.

24. Only trained and authorised staff would conduct dealings with the GMO. Administration of the GMO to trial participants would be conducted by highly trained staff.

2.2 The proposed controls to restrict the spread and persistence of the GMOs in the environment

25. The applicant has proposed several controls to minimise exposure to the GMO, and to restrict the spread and persistence of the GMOs in the environment. These include:

- The transport and storage of the GMO will be according to the Regulator's *Guidelines for the transport, storage and disposal of GMOs*.
- 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.
- Any waste that may contain the 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.
- Participants will be instructed to avoid close contact (e.g. close physical contact or sharing of cutlery) with individuals who are pregnant or breastfeeding, children under 1 year old, those who have significant immunodeficiencies for 30 days after their last administration of the GMO.
- Staff conducting dealings with the GMO will be informed of the risks associated with the GMO, particularly persons who are immunosuppressed or pregnant.

2.3 Details of the proposed dealings

2.3.1 Manufacturing of the GMO

26. The generation of the GM vector is described in Section 4. The GMO for use in the clinical trial will be manufactured overseas and imported into Australia.

2.3.2 Transport and storage of the GMO

27. The GMO will be supplied as a frozen suspension in glass vials. These vials are packaged in cardboard boxes with tamper seals, the cardboard boxes are sealed in biohazard bags and then packaged in a tertiary container (cryobox) that will be filled with dry ice.

28. The GMO would be imported according to the packaging and labelling requirements of the International Air Transport Association (IATA) code UN 3373. Export of unused GMOs between the premises of the sender and Australian border and export of participant samples would also follow the requirements of IATA UN 3373. The GMO will be transported from a third party storage facility to the clinical trial sites, between clinical trial sites, and from clinical trial sites to analytical facilities.

29. The GMO will be stored in a freezer, within a sealed, unbreakable primary container labelled that it contains GMO, the contact details of the licence holder and instructions to notify the licence holder in case of loss of spill of the GMO. The storage of the GMO would involve storage and distribution depots and pharmacies. The GMO is proposed to be stored and handled as a Risk Group (RG) 1 organism according to the Regulator's *Guidelines for Transport, Storage and Disposal of GMOs*.

30. A consolidated record of all stored GMOs will be maintained, and procedures will be in place to ensure all GMOs can be accounted for and that a loss during storage can be detected. Access to the GMOs will be restricted to authorised persons conducting dealings under the licence, who have been informed by the licence holder of any licence conditions that apply to them.

2.3.3 Clinical trial sites

31. The clinical trial sites have not yet been identified. The trial sites will be selected following a feasibility assessment and site selection visits. Clinical trial sites would be assessed for their ability to comply with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practise (GCP) guidelines (ICH Guideline for Good Clinical Practice). The selection of clinical trial sites and pathology laboratories will consider their ability to adhere to minimum infection prevention practices outlined in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (National Health and Medical Research Council, 2019).

32. The sites must have appropriate facilities to store, prepare, administer and dispose of the GMO. A storage depot must be able to safely store, unpack, re-pack and ship the GMO.

2.3.4 The clinical trial

33. The FORTRESS trial (NG-350A-03) is an open label, single-arm Phase 1b, multicentre trial of the GMO in combination with chemoradiotherapy (CRT) in adults with locally advanced rectal cancer (LARC) and at least one risk factor for local or distant recurrence.

34. The trial will recruit adults aged 18 and over. The study treatment period will be 12 weeks and patients will receive the GMO and CRT for 9 weeks prior to assessment at 12 weeks.

35. The participants will receive an IV infusion of the GMO on Days 1, 3 and 5 of each 4-week cycle (weeks 1, 5 and 9). All patients will receive the same dose level consisting of $1x10^{12}$ viral particles (vp) on Day 1 of the cycle and $3x10^{12}$ vp on Days 3 and 5. The CRT treatment will be administered during Weeks 2-6. The number of cycles and dose may be reduced but no increase in cycles (maximum=3) or dose for corresponding Days of the cycle is allowed.

36. A follow up period will be from Weeks 12-36, with disease assessment being performed at Week 18 and Week 36. Patients will be followed for a minimum of 1 year and maximum of 3 years from the first dose of the GMO.

2.3.5 Selection of trial participants

37. Inclusion criteria proposed by the applicant relevant to this assessment include that trial participants must:

- not be pregnant or breastfeeding
- be willing to refrain from egg or sperm donation during treatment and for at least 6 months following the last dose of study treatment
- patients who are sexually active must agree to use a highly effective method of contraception as well as barrier contraception during treatment and for at least 6 months following the last dose of study treatment.

38. Relevant exclusion criteria include participants who:

- had prior or have planned allogeneic or autologous bone marrow or tissue/organ transplantation
- have a known history of hepatitis B infection or human immunodeficiency infection (HIV) or active hepatitis C infection (no testing is required)
- have active autoimmune disease that required systemic therapy in the past 2 years, have immunocompromised status in the opinion of the Investigator, or current treatment with immunosuppressive therapy (exclusions of conditions such as type 1 diabetes, asthma)
- have active infection requiring antibiotics or physician monitoring, or recurrent fevers associated with a clinical diagnosis of active infection. Infections requiring systemic therapy within one week of the anticipated first dose of study drug
- had treatment with a COVID-19 vaccine in the 30 days before first dose unless confirmed to not be based on an adenoviral vector
- treatment with any other Enadenotucirev-based virus (the parent organism).

2.3.6 Preparation of the GMO for administration

39. The GMO is supplied as a frozen suspension in a glass vial as a single dose with extractable volume of 0.5 mL containing $2x10^{12}$ vp per mL.

40. The person preparing the GMO will wear PPE, including a gown, safety glasses, gloves and a mask. The applicant has proposed that persons dealing with the GMO, including preparation and administration of the GMO, must be informed of the risks associated with the GMO, particularly persons who are immunosuppressed or pregnant.

41. The required number of vials will be taken out of the freezer and allowed to thaw at room temperature for 10 minutes. The GMO will be diluted in the Class I Biosafety Cabinet (BSC 1), if required, by clinical trial staff (e.g. pharmacists) trained in the use and disposal of sharps, as well as OGTR licence conditions. A needle will be used to extract the volume from the vial(s), then the solution will be transferred into the saline bag. The final diluted volume of the GMO will not exceed 50 mL volume. The infusion bag will be labelled according to local practice, noting study number NG-350A-03. The sites will be instructed to store and handle the GMO as per their local procedures for BSL-1 material.

2.3.7 Administration of the GMO

42. Once the GMO is prepared for infusion, the infusion rate will follow the designated volume per minute, administered either via IV pump or IV drip at a predetermined infusion rate.

2.3.8 Decontamination and disposal of the GMO

43. Surfaces and equipment that come into contact with the GMO will be disinfected using an effective disinfectant such as 70% ethanol or 2% sodium hypochlorite. Any waste contaminated with the GMO will be disposed of via the clinical waste stream.

44. The GMO can be destroyed on site either by chemical treatment or by autoclaving, or destroyed by external service providers by incineration, autoclaving or chemical treatment. If the facilities are not able to destroy the GMO on site, a separate waste disposal facility will be identified.

45. Any unused GMO would either be destroyed or returned to the study sponsor.

2.3.9 Sample collection and analysis

46. Samples will be collected during scheduled visits. The details of clinical trial schedule and activities have been declared Confidential Commercial Information (CCI). Under section 185 of the Act, the CCI is made available to the prescribed experts and agencies that are consulted on the RARMP for this application.

47. The samples to be collected include buccal swabs, urine, tumour biopsy, faeces and blood. Site clinical trial nurses, lab staff or pathology staff will collect the various samples. Some samples may be collected at home by the trial participant. The information on the sample collection and analysis protocol has been declared CCI.

2.3.10 Personal protective clothing

48. Clinical trial staff involved in the preparation and administration of the GMO to trial participants and in the clean-up of spills will wear gloves, gown, mask and a face shield/glasses.

2.3.11 Training

49. If the licence is issued, Novotech would have responsibility for ensuring training of personnel and compliance with licence conditions.

50. The handling and administration of the GMO will be performed by qualified clinical trial staff such as nurses and medical doctors who have been trained in Sharps Injury Prevention. Staff are trained in the use and disposal of sharps as well as the relevant OGTR licence conditions to minimise the likelihood of exposure to the GMO.

2.3.12 Accountability and Monitoring

51. The GMO will be stored in secured area with restricted access and there will be procedures in place to ensure that all stored GMOs can be accounted for and that a loss of the GMOs during storage can be detected. Access to the GMOs will be restricted to authorised persons only.

2.3.13 Contingency plans

52. In the event of exposure of people to the GMO the applicant proposes such persons would be instructed to undertake the following steps:

(a) If exposure to the GMO occurs via accidental needle stick injury, no specific intervention other than local wound care is needed. It is recommended that local and institutional needle stick or other exposure guidelines are implemented; that the area is thoroughly washed with soap and water; covered with non-occlusive dressing until complete resolution; and that the event is reported to the Principal Investigator (PI), the Institution's biosafety specialist/physician knowledgeable and experienced in treating infectious disease, and to the licence holder within 24 hours.

(b) If there is any inhalation of the aerosols or airborne droplets containing the GMO, the person should be moved to fresh air and monitored for symptoms; incident would be reported to the PI who would report to licence holder as soon as practical. The licence holder would then notify the Regulator.

(c) If there is exposure of mucous membranes, the area should be irrigated or washed thoroughly with soap and water; the event should be reported to the PI, who would report to licence holder as soon as practical. The licence holder would then notify the Regulator.

(d) In case of ingestion, vomiting should not be induced, and the PI or a doctor should be contacted immediately. The incident would be reported to the PI who would report to the licence holder as soon as practicable. The licence holder would then notify the Regulator.

(e) In case of skin exposure, any contaminated clothing should be removed immediately and absorbent tissue placed over affected area. Skin should be washed thoroughly with soap and water. The clothes that came into contact with the GMO should be disposed of as infectious waste; the skin can also be wiped with 70% alcohol or 4%-10% iodine, left on for 5 minutes and rinsed with water. The event should be reported as indicated above.

(f) In case of eye exposure, rinse the affected eye(s) for 3 minutes, using eye wash station or saline. If a single eye is affected, avoid the contact with the other eye. The person should receive counselling from an ophthalmologist as soon as possible and medical evaluation and follow-up conducted until an active infection is ruled out, or as required by institutional policies. The event is to be reported as indicated above.

53. In the event of unintentional release of the GMO due to spills, personnel would be instructed to follow spill management procedures, including that:

(a) the GMO will be contained to prevent further dispersal

(b) persons cleaning up the GMO will wear PPE including gloves, gown, mask and a face shield or safety glasses

(c) the exposed area will be decontaminated with an appropriate chemical disinfectant effective against the GMO

(d) any material used to clean up the spill or PPE worn during the clean-up will be decontaminated

(e) clinical trial staff will notify the licence holder as soon as reasonably practicable

(f) the licence holder will notify the Regulator as soon as reasonably practicable.

Section 3 Parent organism

54. The GMO is derived from a non-GM chimeric human adenovirus (HAdV) comprised of a type 11p backbone with type 3 genomic components (Ad11p/Ad3) with the majority of the genetic material derived from Ad11p. It has been studied and used under names ColoAd1 and Enadenotucirev (EnAd), hereafter referred to as EnAd for simplicity. EnAd was created through an *in vitro* process involving co-infection of tumour cell lines with a pool of HAdVs (Ad3, Ad4, Ad5, Ad9, Ad16, Ad11p, Ad40) and selecting those with strong proliferative and lytic capacity towards tumour cells and little or no effect on non-tumour cell lines (Kuhn et al., 2008). EnAd has been trialled in the clinical setting as an oncolytic therapy against a variety of epithelial cancers (Clinical trials website, searched for Enadenotucirev/ColoAd1; accessed 10 December 2025).

55. HAdV belongs to genus *Mastadenovirus* in the *Adenoviridae* family. HAdV is classified as a Risk Group (RG) 2 microorganism (Standards Australia/New Zealand, 2022). The characteristics of the parent organism provide a baseline for comparing the potential for harm from dealings with the GMO. As such, the relevant biological properties of HAdVs including EnAd will be discussed here.

56. Up to 116 genotypes of HAdV have been assigned so far (HAdV Working Group, accessed November 2025) and categorised into 7 species (A-G) based on features such as serology, genome organisation characteristics and phylogenetic distances (Harrach et al., 2011; Leikas et al., 2023). HAdV-11 and -3 belong to species B, which is further divided into B:1 (containing HAdV-3, -7, -16 and -21) and B:2 (HAdV-11, -14, -34, -35 and -50) based on genetic similarity and cellular tropism (Hall et al., 2009; Stone et al., 2003). Species B1 viruses mainly cause infections of the upper respiratory tract whereas species B2 are associated with urinary tract infections (Mei et al., 1998).

57. HAdV-11 is divided into 2 types: HAdV-11p which has been identified in Europe, America and Japan and HAdV-11a isolated in China, Spain and Latin America. HAdV-11p is closest to HAdV-35 (Stone et al., 2003).

58. As a result of the *in vitro* selection process, EnAd has a near complete deletion in the E3 gene region and a smaller deletion in the E4 region. It can be considered a derivative of HAdV-11p with majority of the genome derived from HAdV-11p with introduced sequences from Ad3 in the E2B region thought to enhance its tumour potency (Dyer et al., 2017; Kuhn et al., 2008). Since the entire outer capsid of EnAd is identical to wild-type Ad11p, the natural history and features of Ad11p are of most relevance to this risk assessment.

3.1 Pathology

59. HAdVs are common human pathogens and cause a wide range of illnesses such as common cold; sore throat; fever, bronchitis; pneumonia; conjunctivitis, acute gastroenteritis (causing diarrhea and vomiting) and less commonly urinary tract infection and neurologic disease (conditions that affect the brain and spinal cord) (CDC, 2024). Up to half of all adenovirus infections are asymptomatic or with very mild symptoms but could be more serious especially in immunocompromised individuals or in the very young (Allard and Vantarakis, 2017; Leikas et al., 2023).

60. HAdVs account for 5-10% of lower respiratory tract infection in infants and children. Most individuals have serological evidence of prior exposure by the age of 10 (Allard and Vantarakis, 2017; Ghebremedhin, 2014; Kim et al., 2003).

61. Following infection, the incubation period of HAdV can last from 2 days to 2 weeks, depending on the viral type and mechanism of infection. Respiratory symptoms usually appear between 4 to 8 days post-infection and intestinal symptoms can appear from 3 to 10 days post-infection (Allard and Vantarakis, 2017). The symptoms can last from few days to a week; however severe infections can last longer.

62. HAdV-B can impact a variety of organs. HAdV-B3, -B7 and less frequently -B21 are responsible for most epidemics of lower respiratory tract infections in children including severe pneumonia or bronchiolitis (Kim et al., 2003; Liu et al., 2025; Public Health Agency of Canada, 2014). HAdV-B14 caused an epidemic of acute respiratory disease in US military recruits (Mennechet et al., 2019). HAdV-11a infects respiratory system and HAdV-11p is most commonly associated with urinary tract infection (Mei et al., 1998) and is a common cause of acute haemorrhagic cystitis in children (Numazaki et al., 1968).

63. HAdVs can cause serious infections in immunocompromised individuals. Severe cases of disseminated infection have been observed in transplant patients (Kojaoghlanian et al., 2003). The most identified species in haematological stem cell transplant patients were A and C (Al Qurashi et al., 2011) and most of these cases were in paediatric patients. HAdV-11p has been detected in urine from kidney transplant recipients (Shindo et al., 1986).

3.2 Structure and genomic organisation

64. Adenoviruses are non-enveloped, double-stranded DNA viruses with an icosahedral capsid comprising of 3 major (hexon, penton base and fiber) and 4 minor (protein IX, VIII, IIIa and VI)

proteins, core proteins (V, VII, Mu, IVa2, terminal protein and adenovirus protease) with DNA packaged within the core (**Figure 2**) (Pied and Wodrich, 2019; Robinson et al., 2011; Yu et al., 2017).

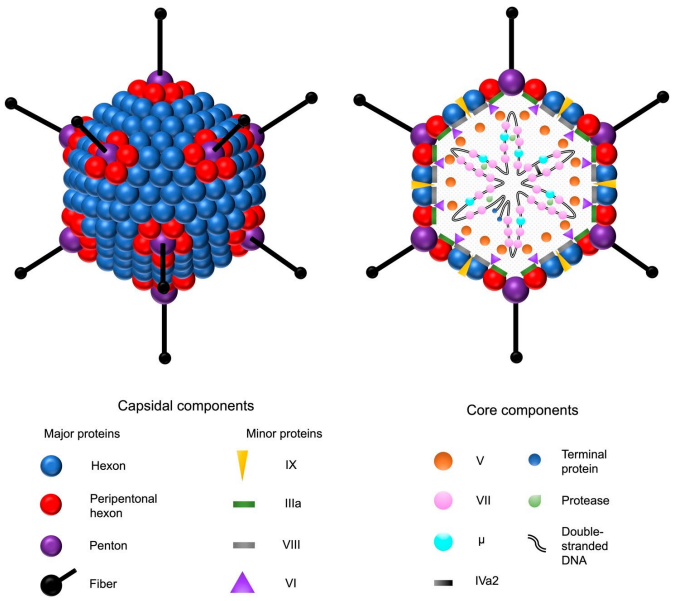

Figure 2: Structural model of human adenovirus (Leikas et al., 2023)

65. The 3 major proteins (hexon, penton base and fiber) form the external capsid structure and "spikes" of the viral particle. The attachment of the virus to the cell is mediated by long protruding fiber protein, with penton base facilitating the internalisation of the virus (Stasiak and Stehle, 2020). The minor proteins (IIIa, VI, VIII and IX) contribute to the structure and stability of the virion by acting as cement proteins, connecting the major structural proteins with each other and with the viral core (Benevento et al., 2014; Pied and Wodrich, 2019). The viral core proteins (V, VII and Mu) mediate the interactions between the core, and the capsid and terminal protein (TP) is covalently bound to each 5' end of DNA. The IVa2 protein is involved in genome packaging. Adenovirus protease (AVP) is required for processing of viral core and minor proteins which are synthesised as precursors during assembly to form a mature infectious particle (Ahi and Mittal, 2016).

66. The genome of AdVs is approximately 30-36 kilobases (kb) which includes 30-40 genes (Charman et al., 2019; Greber and Gomez-Gonzalez, 2021; Harrach et al., 2011). The genome is flanked by inverted terminal repeats (ITRs). The viral replication is initiated at the origin of replication which is located at terminal ends of each ITR where binding sites for pTP and DNA pol is located.

67. HAdV utilises overlapping open reading frames with transcription from both strands of the genome as well as alternate splicing to maximise coding potential (Charman et al., 2019) and is organised into transcription units consisting of early and late genes (**Figure 3**).

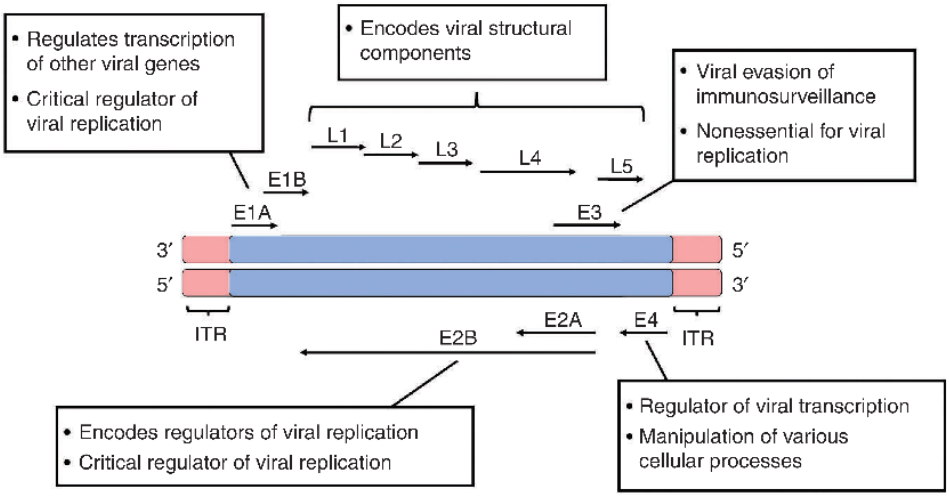

Figure 3: Functions, organisation and structure of adenovirus genome (Afkhami et al., 2016)

68. The early gene expression starts within 1-2 hours post-infection with expression of E1A protein which drives the rest of the early gene expression encoded by E1B, E2, E3 and E4 (Crisostomo et al., 2019; Schwartz et al., 2023). These genes encode for proteins that are involved in activating transcription of other viral regions, supressing the host's antiviral response (including apoptosis, DNA damage response and inflammation) (Pied and Wodrich, 2019) and co-ordinating viral DNA replication (Afkhami et al., 2016). The E1B gene assists in viral replication and is mainly required for the export of viral late mRNA from the host-cell nucleus into the cytoplasm. Together, the E1A and E1B coding regions are essential for viral gene expression and replication (Saha and Parks, 2017). Viruses which are defective in E1 can undergo some replication *in vitro* at a very high multiplicity of infection (MOI), however this is highly inefficient and *in vivo* viruses that lack E1 are replication defective.

69. The E2 gene consists of E2A and E2B, that encode E2 proteins. The E2 proteins are mainly involved in viral DNA replication and transcription of late genes (Saha and Parks, 2017).

70. E2B region encodes the pre-terminal protein (pTP) and viral DNA polymerase (DNA pol) which initiate viral DNA replication by binding to a conserved region located between 9 and 18 base pairs (bp) in the origin of replication (Mysiak et al., 2004). pTP protein also interact with host protein CAD expression of which is higher in cancer cells and correlates with the rate of cellular division (Angeletti and Engler, 1998). The EnAd E2B region is a recombinant product of HAdV-11p and -3 with numerous non-homologous substitutions in this region. The E2B region in EnAd with features of two different HAdVs may have multiple effects on viral replication, lysis and virus spread (Kuhn et al., 2008).

71. E3 genes are not considered necessary for viral replication, and the region is often deleted in oncolytic adenoviruses to make space for transgenes. The E3 region of HAdV is one of the most divergent gene regions between species and the action of some proteins encoded by this region is not yet elucidated (Oliveira and Bouvier, 2019). A major known role of proteins encoded by this gene region is to impede the immune system's clearance of the virus using a variety of approaches and considering this, deletion of E3 genes can be considered a safety feature of oncolytic adenoviruses.

72. Deletion of E3 can result in virus attenuation in experimental animal models (Bortolanza et al., 2009). *In vitro* attenuation was also observed for HAdV-E4 and HAdV-B7 lacking E3 (Guo et al., 2021; Maxfield et al., 2015). An almost complete E3 deletion in EnAd (2,444bp) (Kuhn et al., 2008) is thought to leave the virus vulnerable to immune-mediated attack.

73. The E4 gene segment encodes for 7 open reading frames (orf) producing proteins that contribute to numerous functions required for viral replication, late protein expression, shut-off of host-cell protein synthesis, viral assembly and protection from cellular anti-viral responses (Kleinberger, 2020). Deletion of the whole E4 region impacts viral replication dramatically, however the loss of individual orfs has a modest effect.

74. EnAd has a small region of E4 deleted which maps to a putative E4orf4 genomic region (Kuhn et al., 2008). The E4orf4 protein regulates the expression of some viral and cellular genes, (Brestovitsky et al., 2016; Kleinberger, 2020) and interacts with protein phosphatase 2A (PP2A) to inhibit its actions (Brestovitsky et al., 2016). Since PP2A has a role in the DNA damage response which can be triggered by a viral infection, many viruses, including HAdV, target PP2A. Deletion of E4orf4 contributes to attenuation of the virus in normal cells that have intact DNA damage response machinery (O'Shea et al., 2005).

75. A single late transcription unit generates five populations of late mRNAs, L1 to L5 which encode components of the viral shell and other proteins that are involved in assembly of the capsid and are essential for production of new virus particles. The major late promoter (MLP) mediates transcription of the late virus genes (Schwartz et al., 2023) and is therefore only active during viral replication. Several proteins are produced at an intermediate time during infection, and these include proteins IX and IVa2 (Lichtenstein et al., 2004).

3.3 Cellular tropism, viral infection and replication

76. Adenoviruses can infect a wide range of cells and tissues and replicate efficiently in both dividing and non-dividing cells. AdVs most frequently infect epithelia of the upper or lower respiratory tract, eyes, gastrointestinal and urinary tract tissues. The tropism of AdVs is largely dependent on the species; species A, F and G infect gastrointestinal cells, species C, E and some B species infect the respiratory tract, the rest of species B infect the urinary tract; and species D infect conjunctiva of the eye (Leikas et al., 2023).

77. HAdVs use a variety of receptors for cell entry such as Coxsackie-adenovirus receptor (CAR), CD46, CD80, CD86, desmoglein-2 (DSG-2), glycans, and sialic acid (Stasiak and Stehle, 2020).

78. In contrast to HAdV species A, C, D, E and F for which the fiber capsid protein binds to CAR as a primary attachment receptor, species B HAdVs (includes Ad11) utilise CD46 and/or DSG-2 (Excoffon et al., 2014; Sirena et al., 2004; Stone et al., 2005). Ad11 can use both CD46 and DSG-2 for cell entry (Effantin et al., 2023; Excoffon et al., 2014) and can bind both receptors simultaneously. This is of relevance in oncolytic virus therapy as EnAd can enter the cell via CD46, even in the presence of high serum DSG-2 levels as detected in some cancers (Effantin et al., 2023; Myo Min et al., 2023). CD46 is expressed at various levels on all nucleated cells. A healthy epithelium expresses CD46 only on basolateral surfaces (Maisner et al., 1997), whereas tumour cells express CD46 throughout the surface possibly enhancing virus entry. DSG-2 increases access to CD46 by opening intracellular junctions (Wang et al., 2011). A difference in the tropism between members of HAdV-B may be due to slight variation in binding affinities and accessory molecules that different viruses utilise (Wolfrum and Greber, 2013).

79. HAdV-11p can infect human hematopoietic cells better than some other HAdVs (e.g. HAdV-5), (Segerman et al., 2006), although with very low levels of viral protein and DNA replication detected.

80. *In vitro*, EnAd was shown not to effectively infect healthy human colonic cells (Kuhn et al., 2008) or hepatocytes from any mammalian species tested (including human) (Illingworth et al., 2017) and is inactive in cell lines from a range of non-human species. Even Vero cells (African green monkey kidney epithelial cells) which express primate CD46 were not permissive to EnAd infection. Infection of human hepatocytes, renal epithelial cells, corneal epithelial and bronchial epithelial cells with EnAd is possible *in vitro* but is highly inefficient and abortive (without the release of viral particles).

81. Upon entry into the cell via endocytic pathway, the virus uncoats resulting in the release of viral particles (Flatt and Butcher, 2019; Greber and Gomez-Gonzalez, 2021). The viral genome is transported into the nucleus where the transcription occurs (Charman et al., 2019), before transport into the cytoplasm where viral structural proteins are made and the new virus particles are assembled. The virus particles are released from the cells through cell lysis (Greber and Gomez-Gonzalez, 2021).

82. Progeny viruses released from infected cells usually do not spread further than the regional lymph nodes. Latent HAdV has been found to remain in cells of the immune system within tonsils long-term (Allard and Vantarakis, 2017). In one study, the majority of tonsillar lymphocytes isolated from children undergoing tonsillectomy were found to contain a latent form of HAdVs that could be reactivated upon *in vitro* culture, with the peak of HAdV positive tissue from children aged 4 years old (Garnett et al., 2009).

3.4 Mutation and recombination of adenovirus

83. Adenovirus DNA is maintained as multiple episomal copies in the cytoplasm of infected cells (Harui et al., 1999) and AdVs do not have the machinery for efficient integration into the host genome. Instances of HAdVs integration are rare but have been observed experimentally in *in vitro* and *in vivo* animal models (Desfarges and Ciuffi, 2012; Harui et al., 1999; Robinson et al., 2013; Stephen et al., 2010; Stephen et al., 2008). Some evidence indicates that integration of the HAdV genome is possible through a patchy nucleotide homology of ITR sequences with host cell repetitive elements and that both homologous and heterologous recombination may be involved (Desfarges and Ciuffi, 2012).

84. When a cell is naturally co-infected with different HAdVs, the exchange of genetic material is an important driver of viral evolution. Normally, recombination occurs between the viruses belonging to the same species, although there are instances where HAdV is thought to have arisen from recombination between human and chimpanzee AdVs (e.g. HAdV-E4) (Dehghan et al., 2013; Gruber et al., 1993).

85. Genes for the 3 major capsid proteins (hexon, penton base and fiber) and some E3 region genes readily recombine naturally among viruses within HAdV-D (Ismail et al., 2018; Singh et al., 2013) although this has not been reported for HAdV-C (Dhingra et al., 2019) for which a higher variability in early E1 and E4 genes has been reported instead (Dhingra et al., 2019; Robinson et al., 2013). However, a more recent study demonstrates the fibre gene and E3 may act as recombination hotspots for HAdV-C (Fang et al., 2024).

86. In contrast to HAdV-D and HAdV-C, HAdV-B natural isolates were reported to exhibit a low level of variation due to homologous recombination and diversity within this species was suggested to arise primarily due to mutations (Fang et al., 2024; Robinson et al., 2013). Nevertheless, HAdV-B55 is a recombinant between renal HAdV-B11 and respiratory HAdV-B14 (Fang et al., 2024) retaining respiratory pathogenicity characteristic of HAdV-B14, while incorporating the hexon gene from HAdV-B11 (Cheng et al., 2018). Therefore, although highly unlikely to occur naturally, recombinant HAdV-Bs have been observed.

3.5 Epidemiology

3.5.1 Host range and transmissibility

87. Humans are the natural host for HAdVs and most do not infect animals via natural routes (Liaci et al., 2025). Although there is evidence to suggest that AdVs have crossed the host species barrier especially between human and non-human primates, this is considered a rare event (Borkenhagen et al., 2019; Hoppe et al., 2015). Experimentally, mice, cotton rats, hamsters, guinea pigs, tree shrews and rabbits can be infected with HAdVs (Bertzbach et al., 2021; Ismail et al., 2019). Whereas some animals such as hamsters can be permissive to HAdV replication in experimental conditions

(Tollefson et al., 2017), in most animals, infections with HAdV are abortive even when they induce tissue pathology (Jogler et al., 2006). HAdV-11p was shown to undergo abortive infection in canine (MDCK), hamster (CHO) and mouse (McCoy and C127) cell lines (Gokumakulapalle et al., 2021) but could productively infect Vero cells (kidney epithelial) from African green monkey (Gokumakulapalle and Mei, 2016).

88. Transmission of HAdVs from an infected individual is primarily via direct contact with respiratory aerosols or conjunctival secretions, or via the faecal-oral route (Allard and Vantarakis, 2017; CDC, 2024; Leikas et al., 2023) and urine. The virus can also be spread indirectly via contact with articles e.g. handkerchiefs, linens or utensils contaminated by respiratory discharge from an infected person (Allard and Vantarakis, 2017).

3.5.2 Bio-distribution and shedding

89. Following natural HAdV infection, virus particles are shed via respiratory secretions or in the urine and faeces. Respiratory infections generate the highest viral load early post-infection with residual virus remaining for up to 2 months post-infection (Huh et al., 2019). Disseminated infection in immunocompromised individuals can lead to shedding of the virus for many months (Al Qurashi et al., 2011). The ease of transmission of HAdV is thought to be facilitated by very high levels of viral particles shed from the infected person (Allard and Vantarakis, 2017).

90. Adenovirus genome can be detected in placenta and may be associated with pre-term births (Tsekoura et al., 2010).

91. HAdV shedding was evaluated in faecal and oral swabs after oral administration of a live vaccine containing the HAdV-E4 and HAdV-B7 serotypes. Over 50% of the vaccine recipients tested positive for HAdV faecal shedding between 7-28 days following vaccination. No faecal shedding was detected after 28 days following vaccination or at any time point in throat swabs (Allard and Vantarakis, 2017).

3.5.3 Prevalence

92. An estimation of the seroprevalence for different HAdV has been drawn from published literature. Seroprevalence in different countries ranges from 2%-96%. The highest worldwide seroprevalence is for HAdV4, 5 and 6 belonging to groups C and E (Hong et al., 2025). The distribution varies based on geographical area. For example, seroprevalence of HAdV-5 in Africa is 88%, followed by Asia (72%) and approximately 50% in Europe. An estimation of the seroprevalence of HAdV-E4, -C5, -D26 and -B35 (serotypes commonly tested in the clinics or used in clinical/pre-clinical trials) is shown in **Figure 4**, based on approximately 30 studies published (Mennechet et al., 2019). HAdV-11 has relatively low seroprevalence ranging from 6-23% and this was consistent for other species B2 types such as HAdV-34, -35 and -50 with Seroprevalence of species B2 lowest in Europe and United States and highest in Asia (Vogels et al., 2003). Generally low seroprevalence of B2 HAdV makes vectors derived from HAdV such as Ad11 advantageous in clinical setting (Hong et al., 2025).

93. In Australia, the Laboratory Virology and Serology (LabVISE) reports from the Department of Health and Aged Care (1991-2000) showed an average of about 1400 reported cases of adenovirus infection per year over 10 years, of which only 51 reported cases during this period were identified as HAdV-11 infection and only 11 of the closely related HAdV-35. The most common serotype identified was HAdV-3. In the period between 1981 and 1992, over 4500 faecal samples were collected from children hospitalised with acute gastroenteritis in a Melbourne hospital. In 3.1% of the cases, faecal samples were positive for HAdV, with HAdV-41 being the most prevalent serotype (Grimwood et al., 1995). This may also be an underestimation as HAdV is not a reportable illness. In 2025, Australian Respiratory Surveillance Report, adenovirus was identified in 4.7% of samples tested for respiratory pathogens among people with influenza-like illness attending general practice sites (Australian Respiratory Surveillance Report 2025, accessed November 2025).

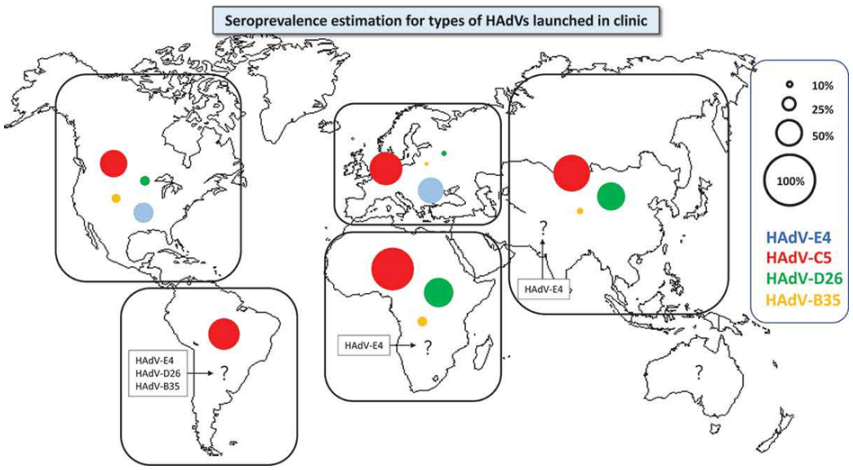

Figure 4: Seroprevalence for adenovirus types used in the clinic (Mennechet et al., 2019)

3.5.4 Control, environmental stability and decontamination methods

94. Infection with HAdV is generally asymptomatic or associated with mild disease in healthy adults and is generally managed through a combination of supportive care and enhanced personal hygiene measures to limit transmission. Antiviral drugs may be used in immunocompromised patients or those with severe disease. Antiviral agents such as cidofovir and ribavarin are commonly used as first line adenoviral therapies (Lion, 2019; Waye and Sing, 2010). There are currently no AdV-specific drugs to treat infection (CDC, 2024; Waye and Sing, 2010).

95. Adenoviruses are resistant to most chemical or physical decontamination processes and agents (including lipid-disrupting disinfectants) as well as high or low pH conditions (Canada, 2011; GC and DD, 2018; Rutala et al., 2006) and UV radiation (Thompson et al., 2003; Thurston-Enriquez et al., 2003). Adenovirus DNA was detected in wastewater and sewage (Fong et al., 2010), rivers (Owliaee et al., 2024), oceans, and swimming pools (Allard and Vantarakis, 2017; Bonadonna and La Rosa, 2019). HAdV are associated with swimming pool-related outbreaks including HAdV-7a, -3 and -4 (Bonadonna and La Rosa, 2019).

96. Adenoviruses are very stable in the environment at pH 6-8 and below 40˚C (Rexroad et al., 2006) and can survive for long periods in liquid or on surfaces in a desiccated state. For example, HAdV can survive up to 10 days on paper under ambient conditions and for 3-8 weeks on environmental surfaces at room temperature (Canada, 2011). Therefore, AdVs survival time depends on the relative humidity, temperature and on the type of surface (Abad et al., 1994).

97. Adenoviruses are reported to be sensitive to 70% ethanol, 0.9% Virkon S (>5 min contact time), 0.2% chlorine, 0.55% ortho-phthalaldehyde and 2.4% glutaraldehyde (McCormick and Maheshwari, 2004; Rutala et al., 2006). In addition, AdVs can be inactivated by heat e.g. heating to 56°C for 30 minutes or 60°C for 2 minutes or autoclaving (Allard and Vantarakis, 2017; Canada, 2011; GC and DD, 2018).

Section 4 The GMO - nature and effect of the genetic modification

98. The GMO (NG-350A) is based on non-GM parent organism EnAd which has oncolytic characteristics and preferentially replicates in and kills tumour cells (as discussed in Section 3.3). The modification is designed to enhance immune stimulation by engineering EnAd to express an agonist antibody to CD40. The GMO is designed to destroy cancer via two modes of action: firstly, it replicates preferentially in cancer cells and kills them through lysis during virus replication; secondly,

it produces an antibody to CD40 which is aimed at stimulating the local immune cells, which will in turn drive an enhanced anti-tumour response.

4.1 The genetic modifications and their effects

99. The GMO genome is comprised of a sequence of the parent organism, EnAd with a transgene cassette inserted in the non-coding region, under the MLP. This allows the transgene cassette to be produced only in cells that undergo productive virus replication as the MLP normally controls transcription of late virus genes (Section 3.2).

100. The transgene is inserted after the L5 gene region which encodes the fibre protein (**Figure 5**). The GMO was generated as described in (Marino et al., 2017).

Figure 5. Schematic representation of EnAd vector construction and transgene integration site (Marino et al., 2017)

101. The linearised vector is transfected into HEK293 cells to make the virus (in supernatant). The virus will undergo a quality control check to ensure that it has the right size transgene (by PCR) that is expressed into a functional protein and that the virus can replicate and is oncolytic (tested in tumour cell lines). The process removes the need for a selectable marker, thereby removing the requirement for an antibiotic resistance gene within the transgene cassette.

102. The transgenes encode for the heavy and the light chains of a humanised CD40 agonist antibody homologous to selicrelumab, which mimics the endogenous CD40 ligand (CD40L) and when bound to CD40 induces signalling via CD40. Selicrelumab is a fully humanised IgG2 antibody and the most extensively studied CD40 agonist in clinical trials. It activates CD40 signalling without a need for cross-linking, unlike some other CD40 agonists (Zhou et al., 2024). The encoded antibody has a sequence modification to the heavy chain C terminus compared to selicrelumab.

103. CD40 is a co-stimulatory molecule found on antigen presenting cells (APC) such as dendritic cells, B cells and macrophages, and its engagement is important for robust initiation and progression of adaptive immune responses. Its ligand, CD40L, is expressed transiently on T cells and other non-immune cells under inflammatory conditions. In addition to the cells of the immune system, CD40 is expressed on a wide range of tumours.

104. Tumour environments can supress activation of immune cells. Systemic administration of a CD40 agonist to reverse this suppression has been a part of cancer immunotherapy (Vonderheide and Glennie, 2013) for many years, with demonstrated clinical benefits. Selicrelumab administered to pancreatic cancer patients resulted in enhanced infiltration of activated T cells into the tumour, maturation of intra-tumoral dendritic cells and enhancement of systemic cytokine response (Byrne et al., 2021). CD40 agonists can also have a direct effect on tumour cells by inducing apoptosis, as demonstrated *in vitro* by culturing colon cancer cells expressing cell surface CD40 with CD40 agonist (Georgopoulos et al., 2007). Alongside benefits, systemic administration of CD40 agonists has been associated with serious side effects such as liver toxicity, lymphopenia and cytokine release syndrome (CRS) (Beatty et al., 2013; Vonderheide and Glennie, 2013). The applicant aims to provide a therapeutic level of the CD40 agonist within the tumour microenvironment that is proposed to avoid systemic toxicity.

105. The antibody is secreted from the infected cells.

4.2 Characterisation of the GMO

4.2.1 Genetic stability and molecular characterisation

106. Oncolytic viruses, like live attenuated viruses, have the potential to regain their pathogenic properties over the course of multiple replication cycles. Theoretically, reversion to virulence of oncolytic HAdVs could occur with homologous recombination between wildtype AdV and recombinant HAdV, however this has not been reported in clinical trials (Buijs et al., 2015).

107. Adenovirus vectors are considered non-integrating vectors and do not tend to integrate or reactivate in a host (EMEA, 2007; FDA, 2020). The viral DNA is maintained as multiple episomal copies in the infected nuclei. However, some studies in cell lines and mice have suggested plausible integration of AdV vectors into host genomes at very low frequencies (Hillgenberg et al., 2001; Stephen et al., 2010; Stephen et al., 2008). A study on cell lines from human, hamster, monkey and mice calculated the integration frequency of approximately one in every 10^3 to 10^5 transduced cells (Harui et al., 1999).

4.2.2 Stability in the environment and decontamination

108. The stability of this GMO in the environment (surfaces, water types and sediments) has not been tested. Methods of decontamination effective against HAdV, are expected to be equally effective against the GMO (see Chapter 1, Section 3.5.4).

4.2.3 Pre-clinical studies using EnAd and the GMO (NG-350A)

109. EnAd demonstrated strong ability to replicate in and lyse cancer cells, when passaged on HT-29 cell line (human colorectal carcinoma cell line) (Kuhn et al., 2008; Naing et al., 2024). This virus could also grow in a variety of other tumour cell lines with a strong preference for epithelial tumour cell lines. *In vitro* studies confirmed that the parent organism is oncolytic (with preferential replication in tumour cells over normal cells) by comparing its killing capacity of primary endothelial and epithelial cells (HUVEC, HMEC) to that of tumour cell line, which was 100-fold lower in normal cells (Illingworth et al., 2017).

110. EnAd causes non-apoptotic cell death which enhances the anti-cancer immune response as it causes release of inflammatory mediators from infected cells (Dyer et al., 2017). It drives enhanced T lymphocyte activation when compared to other oncolytic viruses such as HAdV-5 and mediates higher potency against tumour cell lines with shorter life cycle and faster cytotoxicity compared to wild type (WT) HAdV-11p or HAdV-5.

111. The specificity of EnAd for human cells restricts animal models of pre-clinical testing and there is a lack of permissive animal species for generating replication selectivity data. In CD46 transgenic mice (CD46tg) expressing human CD46, IV injection of $1x10^{11}$ vp of EnAd or replication defective variant was conducted to compare infection rates and biodistribution. Viral DNA was highest at 1-hour post-administration in spleen, liver and lungs. There was no difference in biodistribution between replication-competent and -incompetent EnAd and there was a transient increase in the level of cytokines TNFα, IFNα, MCP-1 and IL-6 (Illingworth et al., 2017). This data indicates that EnAd can enter the cells expressing CD46, but it cannot replicate successfully in non-cancerous cells. In pre-clinical studies, NG-350A was indistinguishable from EnAd regarding virus replication and selectivity (Naing et al., 2024).

112. Replication of NG-350A was compared in colon tumour cell line HT-29 and normal human primary cells to determine if it behaves similarly to the parent organism, EnAd. Cells were inoculated with 1 or 10 particles per cell (ppc) of GMO or EnAd for 72 hours. Viral genomes were detected in both supernatant and cell lysate from HT-29 cells but were absent from the majority of normal cell types infected at 1ppc including endothelial cells, PBMCs, myofibroblasts, astrocytes, renal proximal tubules, muscle cells, bronchial cells and CD34+ hemopoietic cells. Two normal cell types had very low level of detectable GMO DNA which were hepatocytes (0.031% of HT29 control) and renal

cortical cells (0.0002%). No viable virus was isolated from the cell supernatant. At 10ppc infection, all primary cell types tested negative or low for GMO DNA, ranging from 0.2% for hepatocytes, to undetectable in human umbilical vein endothelial cells (HUVEC).

113. The transgene mRNA was expressed at very high levels in the HT-29 cell line and 0.7%-0.19% of this in hepatocytes and at 0.01% renal proximal tubular epithelial cells although the infection in these cells was abortive. The expression of the transgene from normal healthy cells is therefore likely to be minimal. There was no transgene expressed in cardiac microvascular, lung microvascular, dermal microvascular endothelial cells, renal cortical epithelial cells, bronchial epithelial cells, intestinal myofibroblasts, astrocytes, CD34+ cells or aortic smooth muscle cells.

114. When human PBMCs were exposed to the GMO, very low levels of viral DNA could be detected in the PBMC or monocyte derived dendritic cells (MoDCs), with levels ranging from 0.009% to less than 0.001% of the positive control. Similarly, very low transgene mRNA was detected from these cells (less than 0.083% of positive control), and no transgene protein was detected in the supernatant of PBMCs or MoDCs whereas high levels were observed in the permissive HT-29 cell line. Provision of anti-CD40 antibody to the culture of MoDCs inoculated with the GMO did not provide conditions that would enhance replication of the GMO in MoDCs. The GMO induced a comparable increase in cytokines MIP1a and IFNα by PBMC at 24, 48 and 72 hours post-inoculation to that of EnAd, with a possible slight increase in IFNα at 48 and 72 hours in response to the GMO compared to EnAd (Figure 6, application, shown also here for context). The applicant did not comment on this possible difference although it is plausible that very low, undetectable levels of anti-CD40 antibody are produced in these cultures offering a stimulatory signal. Subsequent experiments with MoDCs cultured with supernatants from the GMO infected tumour cell line resulted in higher levels of activation (as seen by increased levels of CD83, CD86 and CD54) than supernatants of EnAd-infected tumour cell line, which was due to anti-CD40 protein expression.

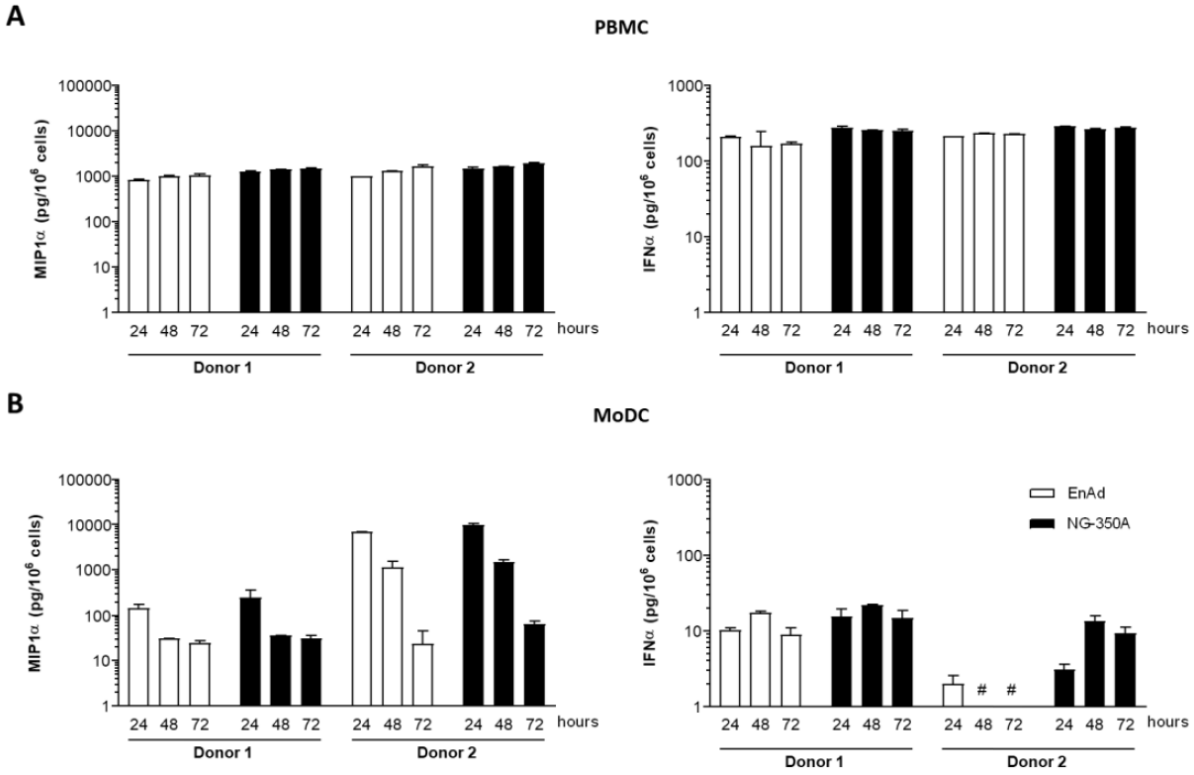

Figure 6. Normalised NG-350A and EnAd mediated cytokine production from innate immune cells. Cells were treated with 1000ppc of two viruses and at different times culture supernatants were harvested and cytokine levels determined.

115. In tumour cell lines, the GMO and EnAd were indistinguishable in terms of viral replication, whereas transgene was detected only in GMO-infected lines. The oncolytic activity of the GMO and EnAd in tumour cell lines were also indistinguishable. In tumour cells infected with the GMO, anti-CD40 antibody was detected at days 3, 8 and 11 in 5/7 cell lines tested, with no transgene detected in the ovarian cancer cell line (Caov-3). Although Caov-3 cells produced transgene mRNA, its level was much lower than in other cells. Furthermore, one cell line, PA-1, which is derived from a teratocarcinoma rather than carcinoma, did not support transgene mRNA expression. The applicant suggests this may be due to selective preference of the virus to replicate in cancers of epithelial origin and transgene expression occurs at the later stages of viral infection cycle.

116. When MoDCs and B cells were stimulated with the GMO infected tumour cell line supernatant or transgene-enriched supernatant, it caused a stimulatory effect on both MoDCs and B cells with enhanced activation and cytokine production.

117. Biodistribution, clearance and live virus recovery of the GMO from murine tissues was evaluated after administration of a single IV injection of $2.2x10^{10}$ vp in immunocompetent CD1 mice. Tissues from liver, lung and spleen were harvested at 6 and 24 hours, 8 days and 28 days after treatment, homogenised and plated onto virus-permissive cell line monolayer to determine live virus recovery (using immunostaining for viral hexon protein). Live virus was detected at 6 and 24 hours in spleen and lung and after 6 hours in the liver. No live virus was recovered at 8 or 28 days. Viral genomic DNA was also quantified from a variety of organs at 6 hours with similarly high recovery from liver, lungs and spleen. At 24 hours, viral DNA could be detected in liver and at lower levels in spleen and there was minimal DNA detected at Day 28.

118. A single-dose toxicity study with the GMO and EnAd was carried out in 54 immunocompetent female CD1 mice that received $2.2x10^{10}$ vp II and several parameters such as inflammatory cytokine profile and plasma alanine aminotransferase (ALT) levels evaluated at 6, 24 and 48 hours, and 7 and 28 days later. The GMO administration resulted in an increase of pro-inflammatory cytokines such as MCP-1, TNFα and IL-6, which were comparable to EnAd. Plasma ALT levels were also comparable between the two viruses and were elevated at 6-48h post-administration but reduced to baseline at Day 7.

119. Repeat dosing experiments with EnAd demonstrated that a higher initial dose results in subsequent doses evoking diminished cytokine response compared to the initial dose, supporting clinical evaluation of a dosing schedule where the higher first dose is followed by a lower second dose.

120. In severe combined immunodeficiency (SCID) mice (n=7-8/group) implanted with either HCT-116 (colon) or A549 (lung) tumours, the GMO and EnAd were administered IV on days 1, 3 and 5 or administered intratumorally (IT) on day 1 in doses of $2.2x10^9$ vp and $4.4x10^9$ vp. The GMO demonstrated replication in tumours after either IT or IV injection at 7- or 21-days post-delivery which was comparable to EnAd. The transgene was produced in tumours and was detected to a lesser extent in the serum of treated mice on Day 7, and on Day 21 the transgene was only detected in the serum of IT treated mice and not IV treated mice.

4.2.4 Clinical trials using EnAd and NG-350A

121. The terminology associated with safety reporting can vary globally. However, common terminology often used include: *adverse event* (AE) which is considered to be any untoward medical occurrence in a clinical trial participant administered a medicinal product and that is not necessarily related to the medical treatment or procedure; *serious AE* (SAE) is any AE that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation or results in persistent or significant disability or incapacity (NHMRC Safety monitoring and reporting in clinical trials 2016, accessed November 2025; CTCAE, 2025, accessed November 2025).

122. Grades of AE refer to the severity of AE. The National Care Institute Common Terminology Criteria for Adverse events provides general guidelines: grades 1 - mild or asymptomatic with clinical or diagnostic observation only, and no intervention needed; grade 2 -moderate local or non-invasive intervention is indicated; grade 3 -severe and medically significant but not immediately life-threatening; grade 4 - severe and medically significant and life-threatening (CTCAE, 2017, accessed November 2025).

123. The clinical trials are summarised in Table 1 below.

Table 1 Summary of clinical trials with GMO or parent organism

Study	Mechanism of Action (MOA) trial (Garcia-Carbonero et al., 2017)	EVOLVE trial (Machiels et al., 2019)	SPICE trial (Fakih et al., 2023)	FORTITUDE (Naing et al., 2024)
Treatment	EnAd	EnAd	EnAd and nivolumab (anti PD-1 antibody)	GMO
Route, dose and frequency	- IV (n=12) to patients with epithelial tumours on days 1,3, 5 at a dose of $1x10^{12}$ vp - intra-tumourally (IT) (n=5) at a dose of ≤$3x10^{11}$ vp on day 1	- IV to patients with epithelial cancers as a single cycle on days 1, 3, 5 (n=20) at doses $1x10^{10}$-$1x10^{13}$ vp - Repeat dosing (n=13-15) in patients with colorectal cancer or urothelial cell carcinoma in either 3-weekly or 1-weekly dosing regiments	-IV (n=51) to patients with colorectal cancer or squamous cell carcinoma of the head and neck at doses of $1x10^{12}$ vp on day 1 and $6x10^{12}$ vp on 3-6 days over 1-2 cycles	IV (n=15) and IT (n=9) to patients with metastatic or advanced epithelial cancers on Days 1, 3 and 5 of a 57-day treatment period (IV) and IT (on Day 1 or Days 1, 8, 15 and 22) at doses of $1x10^{12}$ vp to $6x10^{12}$ vp (in a dose-escalation regimen) in IV group and $1x10^{11}$ vp IT
Sampling	Tumour (viral protein and DNA), blood, urine (IT), saliva (IT), rectal swab (IT)	Tumour, blood, urine, rectal swab, buccal swab	Blood, tumour	Blood, urine, rectal swab, buccal swab, tumour
Biodistribution (Blood)	Viral DNA detected in blood after IV, but below limit of quantification (LOQ) after IT; Viral DNA in the blood reached a mean value of close to 10^7 vp/mL at the end of infusion and dropped quickly	High viral DNA was detected during treatment period. By day 61 viral DNA in blood was below LOQ in 92.9% of samples.	Viral DNA present in most samples and diminishing within 48h to below LOQ in some samples	GMO DNA detected in blood for sustained period and was still observed on Day 57 after IV dosing. Over $1x10^8$ vp/mL of blood detected on day 5 reducing afterwards.

Study	Mechanism of Action (MOA) trial (Garcia-Carbonero et al., 2017)	EVOLVE trial (Machiels et al., 2019)	SPICE trial (Fakih et al., 2023)	FORTITUDE (Naing et al., 2024)
	afterwards between 3-5 days.	Infectivity assay revealed that blood samples contained live infectious virus ranging from 100% on day 1 cycle 1 to 25% on day 1 cycle 3.		
Virus detection in the tumour	EnAd hexon protein detected in most histology sections in epithelial-derived tumour cells (day 8 onwards and as late as day 47) but not in local healthy cells; influx of activated CD8 T cells	EnAd protein detected at day 107 (39 days after the last dose of 4 cycles) in the tumour, indicating active replication	EnAd DNA detected in 19% of tumour samples (29-36 days after first dose).	GMO DNA detected in some patients as late as Day 57 (52 days after last dose)
Shedding (Urine)	Not detected at meaningful levels after IT (one patient at day 8)	Detected in all samples at levels mainly below LOQ with higher detection in patients with urothelial cell carcinoma	NA	Detected at Day 8 in some samples
Shedding (faeces)/rectal swab	Detected in all colorectal cancer patients after IT, could be detected up to day 56 (last day of sampling)	Related to dose, detected mostly between days 6-8 (24-72h post last dose)	NA	Low levels, peaked at Day 8 – 15; some samples positive on Day 57 (52 days after last dose).
Shedding (oral mucosa/saliva)	Not detected at meaningful levels after IT (one patient had viral DNA detected at day 22)	Related to dose, detected in most patients between days 6-8 (24-72h post last dose).	NA	Detected at Day 8 and Day 15 in some samples
Clinical findings	All patients had at least one AE. No grade 3 or 4 treatment associated AE (TEAE); TEAE more frequent after IV	Grade 3 AE was observed in 2 patients (pyrexia and chills) within	All patients experience at least one TEAE and majority (61%) experienced at least one	All patients experienced at least 1 TEAE and over half experienced more than one grade 3 or 4 TEAE.

Study	Mechanism of Action (MOA) trial (Garcia-Carbonero et al., 2017)	EVOLVE trial (Machiels et al., 2019)	SPICE trial (Fakih et al., 2023)	FORTITUDE (Naing et al., 2024)
	administration but mild.	24h. AE highest after first dose. Treatment-related laboratory findings include coagulation events and neutropenia correlated with higher dose. -Acute respiratory symptoms associated with higher dose.	grade 3-4 TEAE. -Serious TEAE was observed in 25% of patients with 14% (7 patients) experiencing serious TEAE related to EnAd. The only TEAE related to EnAd occurring in more than 1 patient was infusion-related reaction (in 2 patients).	-Serious TEAE related to the GMO was kidney injury in 1 patient. -Grade 2 cytokine release syndrome (CRS) in 1 patient and was related to the GMO.
Scientific findings	Serum cytokine levels for IL-6, IL-10 and MCP-1 increased after IV and returned to normal within 48h suggesting no serious cytokine-related events sometimes associated with oncolytic viral therapies.	Half-life in blood is 16.7 min. -Serum cytokines IL-6, IFNγ, MCP-1 and TNFα were increased transiently in most patients.	-Cytokine response between Days 1-5; persistent increase in cytokines (IFNγ, IL-12 and IL-17) from day 15 including CD8 T cell infiltration into tumour observed -Antibodies to EnAd detected after treatment and decreased over time.	Antibodies to the GMO detected in 88% of patients. Transgene mRNA (but not protein) detected in serum at Day 8 or Day 15 in 42% of IV cohort patients and in 11% of IT cohort. Serum cytokines (IL-12, IFNα and IL-17) increased following treatment, from Day 8 and persisting at Day 57.

NA=not available

In conclusion, active EnAd or GMO replication can be detected for a prolonged period in the tumour, and live virus can be isolated from the blood. Viral shedding in the urine, buccal swab or faeces/rectal swabs as assessed by viral DNA indicates low level shedding with prolonged shedding possibly associated with the type of tumour being treated, dose and route of administration.

124. The pooled clinical data was assessed to determine whether any AE could be related to the expression of the transgene. A temporal analysis of AE was performed to assess whether any pattern of increased toxicity is observed during the period when the transgene would be expressed (after the initial and around Day 15). In all studies analysed by the end of 2022, 54% of all treatment emergent AE and 60% of treatment-related AE occurred by study Day 8. There were no apparent increases in the incidence of TEAE at later timepoints and between Study Days 15 and 30, only 3 events (8%) were Grade 3 or above (including fatigue, prolonged aPTT and blood creatine phosphokinase increase), indicating no clear evidence of delayed toxicity due to anti-CD40 expression.

125. The FORTIFY study includes a parallel multicycle dose-escalation to assess the effects of multiple cycles of the GMO. It is conducted in combination with pembrolizumab. Additional information from this clinical trial and other information from pooled clinical data have been declared CCI.

126. There are no data on transmission of the GMO to babies via breastfeeding or to foetuses if pregnant, as pregnant and breastfeeding women were excluded from the trials.

Section 5 The receiving environment

127. The receiving environment forms part of the context for assessing risks associated with dealings with the GMO (OGTR, 2013). It informs the consideration of potential exposure pathways, including the likelihood of the GMO spreading or persisting outside the site of release.

5.1 Site of administration

128. The intended primary receiving environment will be the clinical trial recipient as the GMO will be delivered via IV administration.

129. The secondary receiving environment would be the room and the clinical trial site where the GMO is dispensed, administered and waste disposed of, however none of the procedures are expected to generate aerosols. All clinical sites involved in the study would be equipped to handle infectious agents and procedures would be conducted in accordance with institutional policies based on Standard Precautions for handling potentially infectious substances and the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (National Health and Medical Research Council, 2019).

130. The principal route by which the GMO may enter the wider environment following administration is via shedding, principally via faeces. Based on published literature, the GMO was still shed in faeces 52 days after last administration of the GMO. As the method of testing included detection of the viral DNA, this would include both residual, fragmented viral DNA and live viral particles. Further, the GMO may also enter the environment via accidental spills of unused GMO. Another route by which the GMO may enter the wider environment is via accidental spills of the GMO during or after administration, or during transport or storage, or following disposal of the vials or syringes contaminated with the GMO.

5.2 Presence of related viral species in the receiving environment

131. The presence of related viruses may offer an opportunity for introduced genetic material to transfer between the GMO and other organisms in the receiving environment.

132. AdVs belong to 5 genera: *Aviadenoviruses* (infecting birds), *Mastadenovirus* (infecting mammals), *Atadenovirus* (infecting a broad range of hosts including reptiles, lizards and some mammals), *Siadenovirus* (infecting one species of frog and one species of tortoise and multiple species of domestic, wild and captive birds) and *Ichtadenovirus* (infecting fish) (Lange et al., 2019; Tong et al., 2010; Vaz et al., 2020). As such, they are a common cause of infection in humans and animals and can be found in all environments where humans or animals congregate in groups

(Usman and Suarez, 2025). A more detailed description of AdVs presence in the environment is in Section 3.5.4.

5.3 Presence of similar genetic material in the environment

133. The balance of a system could be perturbed by the introduction of new genetic material through release of GMO into the environment. However, the effect of perturbation would be relatively small if the genetic material was already present in the system and did not confer any selective advantage to an organism that gained this genetic material.

134. All of the viral genes in the GMO are the same or similar to those present in naturally occurring HAdVs.

Section 6 Previous authorisations

135. The GMO 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:

- 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.

136. The GMO has not been previously trialled in Australia.

Chapter 2 Risk assessment

Section 1 Introduction

137. The risk assessment identifies and characterises risks to the health and safety of people or to the environment from dealings with GMOs, posed by or as the result of gene technology (Figure 7). Risks are identified within the established risk assessment context (Chapter 1), taking into account current scientific and technical knowledge. A consideration of uncertainty, in particular knowledge gaps, occurs throughout the risk assessment process.

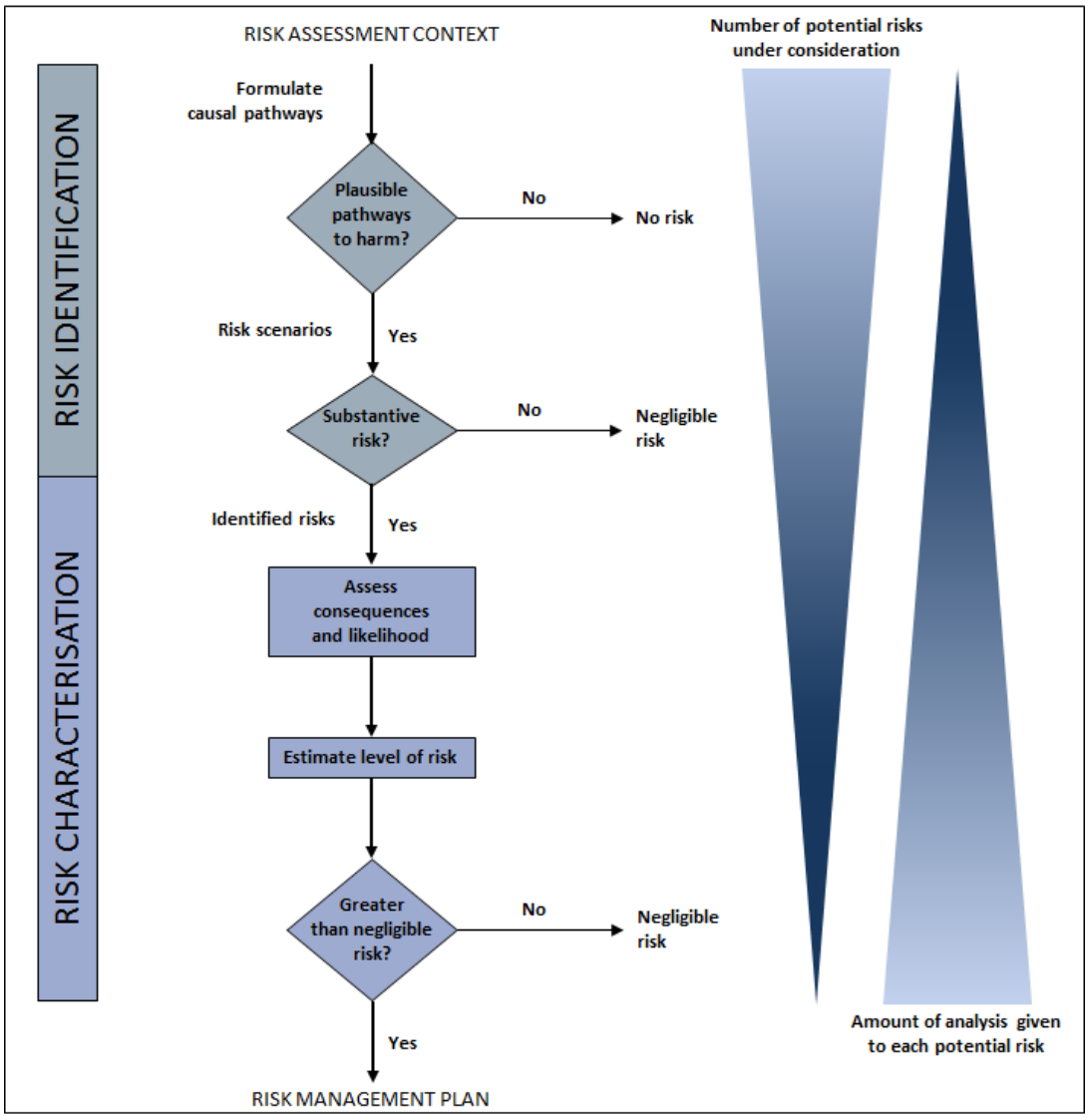

Figure 7: The risk assessment process

138. The Regulator uses a number of techniques to identify risks, including checklists, brainstorming, previous agency experience, reported international experience and consultation (OGTR, 2013).

139. Risk identification first considers a wide range of circumstances in which the GMO, or the introduced genetic material, could come into contact with people or the environment. This leads to postulating causal pathways that may give rise to harm for people or the environment from dealings with a GMO. These are called risk scenarios.

140. Risk scenarios are screened to identify substantive risks, which are risk scenarios that are considered to have some reasonable chance of causing harm. Risk scenarios that could not plausibly occur, or do not lead to harm in the short and long term, do not advance in the risk assessment process (Figure 6), i.e. the risk is considered no greater than negligible.

141. Risk scenarios identified as substantive risks are further characterised in terms of the potential seriousness of harm (Consequence assessment) and the likelihood of harm (Likelihood assessment). The consequence and likelihood assessments are combined to estimate the level of risk and determine whether risk treatment measures are required. The potential for interactions between risks is also considered.

Section 2 Risk identification

142. Postulated risk scenarios are comprised of three components (Figure 8):

i. The source of potential harm (risk source)

ii. A plausible causal linkage to potential harm (causal pathway), and

iii. Potential harm to people or the environment.

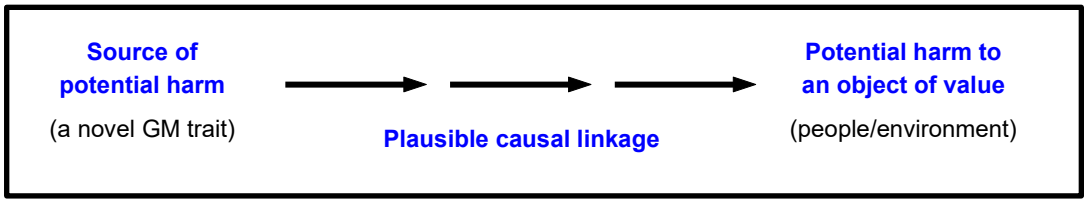

Figure 8: Components of a risk scenario

143. When postulating relevant risk scenarios, the risk context is taken into account, including the following factors detailed in Chapter 1:

- the proposed dealings
- the proposed limits including the extent and scale of the proposed dealings
- the proposed controls to limit the spread and persistence of the GMO and
- the characteristics of the parent organism(s).

2.1 Risk source

144. The parent organism is a chimeric human Ad11p/Ad3 (also known as EnAd) with the majority of the genetic material derived from Ad11p. Details of the pathogenicity and transmissibility of HAdV is discussed in Chapter 1. Infection is generally the result of inhalation of aerosolised droplets excreted from respiratory or ocular secretions containing the virus or mucosal exposure to the virus or via faecal-oral transmission. HAdV infects humans and causes common cold-like symptoms, eye infections or diarrhoea.

145. Toxicity and allergenicity of the introduced genes and their protein products have not been directly considered, but are taken into account in the context of their contribution to ill health.

146. As discussed in Chapter 1, Section 4.1, the GMO has been modified by insertion of genes encoding an agonist antibody to human CD40. These introduced genes and their encoded protein are considered further as a potential source of risk.

2.2 Causal pathway

147. The following factors are taken into account when postulating plausible causal pathways to potential harm:

- the proposed dealings, which are import, transport or disposal of the GMO and possession (including storage) in the course of any of these dealings;
- restrictions placed on the import, transport or disposal of the GMO by other regulatory agencies, the States and Territories;
- characteristics of the parent organism;
- routes of exposure to the GMO, the introduced gene(s) and gene product(s);
- potential effects of the introduced gene(s) and gene product(s) on the properties of the organism;
- potential exposure of other organisms to the introduced gene(s) and gene product(s) from other sources in the environment;
- potential exposure of other organisms to the GMs in the environment;
- the release environment;
- spread and persistence of the GMO (e.g. dispersal pathways and establishment potential);
- environmental stability of the organism (tolerance to temperature, UV irradiation and humidity);
- unauthorised activities; and
- practices before and after administration of the GMO.

148. As discussed in Chapter 1 Section 1.1, the TGA, the trial sponsor, the Investigators and HREC all have roles in ensuring the safety of trial participants under the *Therapeutic Goods Act 1989*, and human clinical trials must be conducted in accordance with the *National Statement on Ethical Conduct in Human Research* (National Health and Medical Research Council, 2023). Therefore, risk scenarios in the current assessment focus primarily on risks posed to people other than the intended GMO recipient, and to the environment, including long term persistence of the GMOs, which may arise from the import, transport, storage or disposal of the GMO.

149. The Act provides for substantial penalties for unauthorised dealings with GMOs or non-compliance with licence conditions, and also requires the Regulator to have regard to the suitability of an applicant to hold a licence prior to the issuing of the licence. These legislative provisions are considered sufficient to minimise risks from unauthorised activities. Therefore, unauthorised activities will not be considered further.

150. As mentioned in Chapter 1, Section 3.4, adenoviruses remain episomal throughout the infection and do not integrate into the host DNA. Similarly, the vectors derived from these adenoviruses are considered as non-integrating vectors which do not have a propensity to integrate or reactivate following latency in a host (EMEA, 2007; FDA, 2020). Further, adenoviral vectors (such as HAdV-C5) have been used extensively in clinical studies as a vaccine and as a gene therapy for almost 30 years (Crystal, 2014) and there is no evidence of integration of viral DNA into the host genome. Thus, the consequences of integration of viral DNA into a host cell genome will not be further discussed.

2.3 Potential harm

151. The following factors are taken into account when postulating relevant risk scenarios for this licence application:

- harm to the health of people or other organisms, including disease in humans or animals or adverse immune response to the GMO
- the potential for establishment of a novel virus that could cause harm to people or the environment.

2.4 Postulated risk scenarios

152. Three risk scenarios were postulated and screened to identify substantive risks. These hypothetical scenarios are summarised in Table 2 and discussed in depth in Sections 2.4.1-2.4.3 (this chapter).

153. In the context of the activities proposed by the applicant and considering both the short and long term, none of the 3 risk scenarios gave rise to any substantive risks that could be greater than negligible.

Table 2 Summary of hypothetical risk scenarios from dealings with the GMO

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
1	GMO	Exposure of people conducting dealings with the GMO to the GMO via needle-stick injury, aerosols, fomites, contact with abraded skin or mucous membranes through the following events: (a) Preparation and administration of the GMO (b) During import, transport or storage of the GMO (c) Handling of samples containing the GMO (d) Disposal of the GMO ⬇ Transduction of cells by GMO ⬇ Post infection immune response due to the presence of the virus and/or Expression of CD40 agonist by infected cells	Adverse immune reactions (e.g., cytokine storm), illness, local inflammation, flu-like symptoms	No	• Import and transport of the GMO would be in accordance with IATA 3373 and/or the Regulator's *Guidelines for Transport, Storage and Disposal of GMOs* • Only trained and experienced personnel would conduct dealings with the GMO, using personal protective equipment (PPE) to minimise potential exposure • GMO and contaminated waste would be disposed of as clinical waste • Serious adverse reactions attributed to administration of a full dose of the GMO (or parent organism) are not common in clinical trial participants • The dose received through accidental exposure during preparation or administration would be substantially less than that administered to trial participants and would not be sufficient to result in a serious adverse reaction in exposed persons • Persons dealing with the GMO must be informed of the risks, particularly to people who are immunosuppressed or pregnant, prior to dealing with the GMO

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
					• The GMO has limited replication potential in healthy cells • People are regularly exposed to HAdVs and the genetic modifications do not confer any pathogenic advantage over the wild type • The immune system is expected to clear the GMO quickly due to lack of E3 gene region
2	GMO	GMO release into the environment (e.g. sewerage, spills, shedding of the GMO from participants) ⬇ Exposure to people or animals ⬇ As per Risk Scenario 1	Adverse immune reactions (e.g. cytokine storm); Disease in people or animals	No	• As discussed in Risk Scenario 1 and: • Viral titres shed by trial participants decrease over time due to a smaller number of GMO permissive cells and immune response. • Trial participants will be asked to use barrier contraception for the duration of the trial and for at least 90 days after the last treatment with the GMO • Trial participants will be asked to avoid close contact with immunocompromised or pregnant individuals • Parent organism is not known to naturally infect non-human hosts and does not infect aquatic species • The GMO does not replicate outside a host
3	GMO	Exposure of other people and animals to the GMO as mentioned in Risk Scenarios 1 and 2 Or Exposure of trial participants during treatment ⬇ Transduction of cells by GMO ⬇	Adverse immune reactions (e.g., cytokine storm); Disease in people or animals	No	As for Risk Scenarios 1 and 2 and: • There is only a short temporal window when co-infection could occur, and the same cell has to be infected with both viruses at the same time. • Recombination among adenoviruses in natural setting is usually restricted to the same species and is a rare event, especially for HAdV-B.

Risk scenario	Risk source	Possible causal pathway	Potential harm	Substantive risk	Reason
		Transduced cells co-infected with AdV ⬇ (a) Complementation by AdV (b) Homologous recombination with AdV ⬇ Production of other recombinant GMOs including with increased virulence and/or host range			• Different tropism of the GMO and most frequently encountered species B HAdV (respiratory) further limits the likelihood of co-infection of the same cell as the administration is via IV • There is a low probability of continuous complementation of GMO by AdV because AdV infection is self-limiting • Exclusion of some individuals with exposure to adenovirus based oncolytic therapy or vaccines further reduces chances of recombination

2.4.1 Risk scenario 1

Risk source	GMO
Causal pathway	Exposure of people conducting dealings with the GMO to the GMO via needle-stick injury, aerosols, fomites, contact with abraded skin or mucous membranes through the following events: (a) Preparation and administration of the GMO (b) During import, transport or storage of the GMO (c) Handling of samples containing the GMO (d) Disposal of the GMO ⬇ Transduction of cells by GMO ⬇ Post-infection immune response due to the presence of the virus and/or Expression of CD40 agonist by infected cells
Potential harm	Adverse immune reactions (e.g. cytokine storm); illness, local inflammation, flu-like symptoms

Risk source

154. The source of potential harm for this postulated risk scenario is the GMO.

Causal Pathway

155. People (other than the intended recipient) conducting dealings with the GMO could be directly or indirectly exposed to the GMO in a number of ways. The GMO could be transmitted via aerosol droplets generated during an unintentional spill of the GMO or during preparation of the GMO. It could also be transmitted via sharps injury during preparation or administration. The collection of samples from trial participants could pose another route of exposure. These exposures could result in infection with the GMO that could lead to ill health.

Exposure during preparation and administration of the GMO

156. As discussed in Chapter 1, Section 2.3, preparation and administration of the GMO will be carried out in clinical trial sites. There is the potential for exposure of people involved in the preparation of the GMO by needle stick/sharps injury, preparation and/or due to breakage/spillage of GMO onto surfaces during preparation and administration The GMO will be prepared and administered by authorised, experienced and trained health professionals. Samples will also be taken, handled and analysed by trained professionals. Persons handling the GMO will be informed of the risks of handling the GMO particularly for those who are pregnant or immunocompromised. The risks of dealing with the GMO by persons who are not immunocompromised or pregnant are considered minimal. All personnel working in settings where healthcare is provided, including clinical trial services, are required to comply with the standard precautions for working with potentially infectious material, as described in the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (2019).

157. For a symptomatic infection to occur, individuals must be exposed to an infectious dose. Residual liquid in used vials and used syringes is unlikely to contain a sufficient titre to cause a symptomatic infection. The same would apply to secondary waste such as gloves that may be contaminated with the GMO. Thus, the dose received through accidental exposure would be far smaller than that administered during the clinical trial and likely to be lower than that required for symptomatic infection. Therefore, even if an individual is inadvertently exposed to the GMO during preparation and administration, they are unlikely to develop an adverse immune reaction.

158. A rare accidental exposure to oncolytic viruses in healthcare personnel during preparation, administration or care, have to date not resulted in illness (Kaufman et al., 2015).

159. The compliance with the *Australian Guidelines for the Prevention and Control of Infection in Healthcare* (2019) and existing work practices will minimise the potential exposure of people to the GMOs during preparation and administration of the GMO.

Exposure through the collection of samples

160. Clinical trial staff collecting samples from trial participants could also be exposed to the GMO in the samples. However, as via the shedding route, the exposure via clinical sample collection is expected to be very low. Furthermore, only trained staff will collect the majority of the samples and only trained staff will be involved in testing clinical samples. Additional information about sample collection and processing is CCI.

Exposure during import, transport and storage of the GMO

161. If the GMO was spilled during import, transport or storage, this could result in exposure to people via aerosol or liquid contact with eyes, mucous membranes or skin. Further, people could be inadvertently exposed to the GMO via contact with materials or surfaces contaminated with the GMO and subsequent hand to mouth transmission.

162. The GMO will be imported, stored, handled and transported according to the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs* (TSDs) (Chapter 1, Section 2.3). Biological samples that may contain GMO will be handled in the same manner. These practices will lower the likelihood of unintended dispersal of the GMOs.

163. Decontamination of surfaces will be performed after administration of the GMO or in the case of accidental spills of the GMO.

164. The import, transport and storage procedures discussed above would mitigate exposure occurring as a result of spills of the GMO during these dealings.

Exposure during disposal of the GMO and any contaminated waste

165. Individuals may be inadvertently exposed to the GMO while disposing of used, expired or unused vials of the GMO. The two locations where this is most likely to occur are at:

- locations where stocks of the GMO are stored
- locations where the GMO is administered.

166. As discussed in Chapter 1, Section 2.3, unused vials of the GMO and waste contaminated with the GMO would be treated as clinical waste and disposed of in accordance with the waste disposal methods approved by the Environmental Protection Agency or Health Department in the relevant State or Territory. Adherence to the disposal procedures would reduce the likelihood of accidental exposure of people or animals to the GMO.

167. Taken together, the disposal and decontamination procedures discussed above would minimise likelihood of exposure that could be associated with conducting these dealings with the GMOs.

Potential harm

168. If people are exposed to the GMO they could develop flu-like symptoms, or local inflammation for a short period of time before the virus is cleared by the immune system. The GMO capsid is derived from HAdV-11p which has tropism for the urinary tract and is therefore unlikely to lead to respiratory or gastrointestinal symptoms. It is plausible that exposed people could experience an adverse immune response or disease as a response to the viral proteins as these are considered foreign antigens by the immune system.

169. A productive infection is unlikely to occur in a healthy cell, or it may occur at very low level and is likely to be abortive because a body of literature from *in vitro* and *in vivo*, as well as clinical trial studies have indicated that EnAd and NG-350A are epithelial tumour cell specific and do not effectively replicate or produce infectious virus from normal cells (Garcia-Carbonero et al., 2017; Illingworth et al., 2017; Kuhn et al., 2008). Additional rationale is made from preclinical data which has been claimed as CCI. There have been no serious reported side effects in patients receiving these treatments and the dose received through accidental exposure would be a fraction of therapeutic dose. Exposure to few μL from residual liquid in used vials or used syringes would contain much less of the viral particles than therapeutic dose that is administered to patients. Patients will receive $1x10^{12}$ vp on Day 1 of the cycle and $3x10^{12}$ vp on Days 3 and 5 and the concentration of the GMO in the vials provided in $2x10^{12}$vp/mL. That means that exposure of few μL would result in a one-off exposure dose of ~$1x10^{9}$vp, which is a 100-fold lower dose from than what is received by participants on Day 1, and ~700-fold lower than cumulative exposure dose that will be received by trial participants during the first therapy cycle.

170. A very low volume of a highly attenuated virus is therefore unlikely to lead to an adverse immune reaction even if an individual was to inadvertently be exposed to the GMOs.

171. Effective expression of the transgene protein is only likely to occur during productive infection, and locally in the tumour. The transgene mRNA was noted in the blood of clinical trial participants receiving the GMO (Naing et al., 2024), however, there was no detectable antibody measured in the serum of these patients. If the expression is to occur upon accidental exposure, it is likely to facilitate clearance of the GMO. Systemic administration of selicrelumab (anti-CD40) carries a risk of toxicity (as discussed in Chapter 1, Section 4), however this is more likely to occur with a large dose. A small fraction of therapeutic dose is unlikely to induce expression of the antibody in any meaningful way from healthy cells. The transgene is highly unlikely to encode novel toxic or allergenic compound as it encodes a fully humanised antibody that has been administered in the clinical setting for many years.

172. A small dose exposure and a transient nature of the infection would be expected to result in very mild or negligible symptoms and would also minimise the potential for an adverse immune

response to the GMO. Therefore, exposure to the GMO is not expected to result in an infection and would not result in an increased disease burden in humans.

173. Immunocompromised or pregnant individuals are considered at higher risk of adverse events when exposed to the GMO. Although the attenuated nature of the GMO reduces likelihood of harm, the applicant has proposed that persons handling the GMO should be informed of the risks and persons who are immunocompromised or pregnant and these individuals, including children under the age of 12 months should avoid close contact with the trial participant.

Conclusion

174. The potential for an unintentional exposure of people to the GMO to cause harm via a serious adverse immune reaction in humans is not identified as a risk that could be greater than negligible. The main reasons are that that the GMO is not expected to infect or replicate in healthy people, and any infection resulting from potential exposure is expected to be rapidly cleared and unlikely to cause disease. Therefore, this risk scenario does not warrant further detailed assessment.

2.4.2 Risk Scenario 2

Risk source	GMO
Causal pathway	Release of GMO into the environment (e.g. sewerage, spills, shedding from trial participants) ⬇ Exposure of people or animals ⬇ As per Risk Scenario 1
Potential harm	Adverse immune reactions (e.g., cytokine storm) and/or disease in people or animals

Risk Source

175. The source of potential harm for this postulated risk scenario is the GMO.

Causal Pathway

176. The GMO could be released into the environment through a spill during transport, storage, or disposal. It is also possible that the GMO will be shed in saliva, urine and faeces from participants for up to 2 months post administration, potentially contaminating toilets, shared household items and exposing non-participants. This could result in exposure of people other than those conducting dealings with the GMO and exposure of animals (including marine or aquatic animals) to the GMO, and could potentially result in adverse immune reactions and/or disease in people and animals.

Exposure from shedding of the GMO

177. The previous clinical study with the GMO has found that trial participants could shed the GMO DNA for a few weeks in urine and saliva and 2 months in faeces and blood after IV administration.

178. Caregivers, household pets and healthcare personnel who are in close contact with people treated with the GMO may be inadvertently exposed to the GMO during administration via spillage or after patient use of bathrooms or sharing household items such as cutlery. Trial participants may also collect some samples at home. Caregivers, family members, pets and others exposed to the GMO in this way will only be expected to be exposed to very low levels of the GMO.

179. The trial participant will be informed to avoid close physical contact with individuals who are pregnant or immunocompromised for at least 15 days after administration of the GMO. This will further limit the exposure of vulnerable close contacts to the GMO.

180. There are no data on transmission of the GMO to babies via breastfeeding or to foetuses if pregnant, as pregnant and breastfeeding women were excluded from the trials. Therefore, the applicant has proposed that pregnant and breastfeeding women be excluded from this licence.

Exposure from spills and from the GMOs entering sewerage

181. As discussed in Risk Scenario 1, accidental spills associated with import, transport, storage, disposal have been considered, including the range of measures that are in place that would reduce the chances of GMO being released into the environment.

182. Accidental spills or unused vials, if not decontaminated appropriately, could result in the survival of the GMO and its presence in the sewerage and subsequently GMO dispersal in the aquatic environment. Without correct decontamination with suitable disinfectants, the GMO could potentially persist on surfaces for more than 12 weeks at low humidity (see Chapter 1, Section 3.5.4). In cold water or dark sediments, survival could be up to a few months (see Chapter 1, Section 3.5.4 and Section 4.2.2). As AdVs are resistant to UV treatment in wastewater and can survive for a long time, this could lead to the persistence of the GMO in the environment. However, due to its conditionally replicating nature, the GMO would be unable to maintain a stable presence in the environment for long periods and is unlikely to spread and would eventually degrade.

183. In the event that the GMO is released into sewage water, the sewage water is firstly treated, and secondly, it would be markedly diluted due to the small quantity of GMO present in a large volume of liquid waste or water. The number of individuals receiving this GMO is low and the virus does not replicate extensively outside of cancer tissue. Water quality studies have shown that sewerage treatment may not fully remove the adenovirus (Fong et al., 2010; Thompson et al., 2003), however the GMO is unlikely to be present in high enough amounts for an infectious dose. In Australia there have been no reported outbreaks with HAdV associated with drinking water supplies (Guidelines, 2011). Therefore, it is highly unlikely that infection of humans or animals could occur following exposure to an environmental source.

184. As mentioned in Chapter 1, Section 3 and 5.2, HAdV-11p is a member of the genus *Mastadenovirus* which infects a wide range of mammals including non-human primates, bats, felines, swine, canine, ovine and caprine (Borkenhagen et al., 2019; Hoppe et al., 2015; Roy et al., 2004). Therefore, hypothetically the GMO could infect other mammals including non-human primates. However, given that the GMO replicates poorly in healthy cells and the parent organism is not known to infect and replicate effectively in animals or animal models, the likelihood of infecting other mammals from exposure to the GMO is very low.

185. As mentioned above, HAdV infection is limited to mammals only and is not known to infect insects, birds and other non-mammalian aquatic organisms. Therefore, the likelihood of the GMO infecting other species in the Australian environment in highly unlikely.

Potential harm

186. Potential harms to people in this risk scenario would be the same as considered in Risk Scenario 1. As it is highly unlikely to infect or replicate in animals, animals are not expected to be harmed.

187. *In vitro* data has indicated that liver or kidney epithelial cells can be infected with the GMO upon administration, and these cells are likely to be exposed during accidental exposure. However, the exposure dose would be a very small fraction, and *in vitro* data has demonstrated that the infection is abortive in these cells. Any transgene is also unlikely to be expressed in sufficient quantities from accidental exposure. Although low transgene mRNA quantity was produced by healthy hepatocytes and proximal renal cells, when exposed to the GMO *in vitro*, this was a negligible fraction compared to a tumour cell line and there was no detectable transgenic antibody produced by these cells.

Conclusion

188. The potential for the GMO to be released into the environment and result in adverse immune reactions or disease in people or other animals is not identified as a risk that could be greater than negligible. The main reasons are that that the GMO is not expected to infect or replicate in healthy people or in animals, and any infection resulting from potential exposure is expected to be rapidly cleared and unlikely to cause disease. Therefore, this risk scenario does not warrant further assessment.

2.4.3 Risk Scenario 3

Risk source	GMO
Causal pathway	Exposure of other people and animals to the GMO as mentioned in Risk Scenarios 1 and 2 Or Exposure of trial participants during treatment ⬇ Transduction of cells by GMO ⬇ Transduced cells co-infected with AdV ↙ ↘ Complementation by AdV Homologous recombination with AdV ↘ ↙ Production of other recombinant GMOs including with increased virulence and or host range
Potential harm	Adverse immune reactions (e.g., cytokine storm) and/or disease in people or animals

Risk source

189. The source of potential harm for this postulated risk scenario is the GMO.

Causal Pathway

190. Transmission of GMO can occur by the pathways mentioned in Risk Scenarios 1 and 2 which could potentially result in transduction of host cells. If the person, or animal exposed to the GMO has an existing infection of AdVs at the time, or acquired an AdV infection while the GMO is present, this co-infection could potentially result in complementation and recombination of the GMO with wild-type AdVs and cause adverse immune reactions and/or disease in people or animals. The recombination and complementation between wild type (WT) AdV and GMO can also occur in a trial participant who can later shed this virus and infect other people or animals.

191. Recombination between different GMOs using adenovirus platforms is unlikely. NG-350A is of species B and is unlikely to recombine with adenovirus-based therapeutics belonging to AdV derived from other species. The applicant has proposed that participants who have previously received EnAd-based therapy will be excluded from the trial and those who have received adenovirus-based coronavirus disease 2019 (COVID-19) vaccine will be excluded for 30 days further limiting the possibility of co-infection. Whereas the target of the GMO is cancer cells, vaccines are likely to target muscle cells, limiting the likelihood of co-localisation. Treatment with a secondary oncolytic adenovirus while NG-350A is still present in the trial participant could lead to co-localisation to the same cell and provide an opportunity for recombination. These viruses are likely to be attenuated compared to the WT AdV but may still provide deleted genes during recombination.

Complementation of E3, E4 orf4 by AdV

192. Proteins encoded by E3 and E4orf4 can be provided in *trans* from a pre-existing or acquired WT HAdV infection in people accidentally exposed to the GMO if a co-infection in the same cell occurs.

Trial participants could also be exposed to WT AdV. This could result in complementation by the WT HAdV and spread of the GMO to healthy cells.

193. HAdV infections are self-limiting, which decreases the probability of continuous complementation of GMO by HAdV. Thus, the likelihood that a person has a HAdV infection that could complement the protein encoded by E3 and E4orf4 gene regions necessary for the GMO to spread to healthy cells is very low.

194. Replicating WT AdV would also compete for proteins with the GMO to form a mature viral particle, which would further limit the chances of complementation.

195. As mentioned in Chapter 1, Section 3.5.1, HAdVs are generally unable to replicate in animals (Ismail et al., 2019). Therefore, the likelihood that the GMO could replicate in animals as a result of complementation is highly unlikely.

Homologous recombination with AdV

196. Recombination is a major driver of diversity and evolution in circulating WT AdV. Like complementation, homologous recombination requires co-infection of the same cell with both, the GMO and WT AdV. Adenoviruses commonly infect a variety of tissues depending on the type. Therefore, it is plausible that a person or animal exposed to the GMO is co-infected with AdV. Co-infection could also occur from contact with GMO contaminated surfaces or spills. Licence conditions will be in place to limit and control the exposure of people or animals to the GMO via inhalation or contact with mucus tissue via requirements to use PPE and though transport and disposal procedures.

197. As mentioned in Chapter 1, Section 3.4, homologous recombination is restricted to members of the same species. However, homologous recombination with closely related adenoviruses species has been observed in regions of high sequence homology although it is much rarer. The DNA homology between HAdV species is less than 20% (Ghebremedhin, 2014). There is a potential for homologous recombination between the GMO and WT HAdV-B (e.g. highly prevalent HAdV-B3 and -B7) although different cellular tropisms are likely to reduce the opportunity for co-localisation and co-infection. If co-infection was to occur and recombination did take place, it could potentially result in the generation of different GM recombinants, as described in Table 3.

Table 3 Theoretical recombinants of GMO and wild-type (WT) Human Adenoviruses

Recombinant region	Resultant recombinant	Outcome	Likelihood
Transgene region • NG-350A	• Loss of transgenes	• Conditionally replicating GMO without anti-CD40 transgenes	Unlikely
• WT HAdV	• WT HAdV expressing anti-CD40 transgenes	• WT HAdV that produces anti-CD40 antibody in infected cells	Unlikely
E3 region • NG-350A	• GMO with intact E3 region	• GMO with some immune-evasion properties restored, but due to lack of E4orf4, preferentially localised in tumour cells	Unlikely

Recombinant region	Resultant recombinant	Outcome	Likelihood
• WT HAdV	• WT HAdV with deletion in E3 region	• Loss of immune evasion by WT HAdV	Unlikely
E4 between • NG-350A • WT HAdV	• GMO with intact E4 region • WT HAdV with partially deleted E4	• Replication-competent GMO with intact transgenes but without immune evasion properties • Conditionally replicating WT HAdV	Unlikely Unlikely
Capsid genes (hexon, penton, fiber) between • NG-350A • WT HAdV	• Conditionally replication competent GMO with altered tropism (e.g. respiratory cells) • Replication competent WT HAdV with acquired urinary system/GI tropism	• Altered tropism of GMO • Altered tropism of WT HAdV	Highly unlikely Highly unlikely

198. The transgene cassette contains anti-CD40 agonist antibody, and a recombination event could integrate the transgene into the WT HAdV genome. This would increase the overall genome size of WT HAdV by over 2000 bp. Previous studies have shown that the likelihood of recombination depends on the size of the potential inserted sequence (Kung et al., 2013). If recombination was to happen, the virus would be more immunogenic due to the nature of the transgene and is likely to be cleared faster by the immune system. Localised expression of the antibody is unlikely to have a systemic effect.

199. As discussed in Chapter 1, Section 3.2, the combination of E3 and E4orf4 deletion is thought to allow selective replication of EnAd in cancer cells. Recombination can also lead to loss of the transgenes from the GMO and transfer of the genomic region from WT AdV between the regions of homology. This could possibly lead to some E4 gene region exchange and acquisition of E4orf4 from WT AdV by the GMO which would enable the GMO to replicate in both healthy and cancer cells but would still lack immune evasion genes which would make it more attenuated than WT AdV and would lead to faster clearance of the virus.

200. A recombination event could also provide the GMO with a full sequence of the E3 region. This would enable the GMO to evade immune response which is a key component of virus being able to replicate in non-cancerous tissue. However, as the E4orf4 would still be missing, the virus would be expected to still be attenuated in healthy cells.

201. WT HAdV could also recombine with the GMO and lose E3 region. This would prevent its immune evasion properties and would likely enhance sensitivity to host's anti-viral immune response.

202. There could also be a recombination event in the E4 region. As noted above, this theoretical recombination could create GMO with full E4orf4 from WT HAdV. This GMO could be more

replication competent in normal cells, but would lack immune evasion genes which would still make the GMO more attenuated than the WT. Further, because the GMO would still have the transgene, this would further enhance viral clearance. Recombination could also lead to loss of E4orf4 from WT HAdV, which would attenuate the virus.

203. Recombination could also lead to a novel tropism for the GMO. For example, it could acquire respiratory tropism. However, this would not result in increased harm as the virus would still be conditionally replicating. On the other hand, WT HAdV could also acquire different cellular tropism, but this would not change the WT HAdV. As noted in Chapter 1, Section 3.4, a recombination event Between HAdV-B14 which resulted in acquisition of one of the capsid genes from HAdV-11p, still maintained respiratory tropism, indicating the low likelihood of tropism alteration due to a single capsid gene recombination event. The attachment of the virus to the cell is mediated by fiber protein, with penton base facilitating the internalisation of the virus; therefore at least 2 genes encoding for capsid proteins would need to be exchanged for tropism to be altered. Given that the GMO has low ability to replicate in healthy cells, acquisition of respiratory tropism would not provide an advantage.

204. In order for a full reversion of the GMO into WT virus, multiple recombination events would need to occur which is highly unlikely.

Potential harm

205. If complementation were to occur, the GMOs produced in the host cells may be able to infect cells other that tumour cells and possibly increase the persistence of the GMO in the host. Homologous recombination could have a similar effect. Replication competent GMO could produce more CD40 agonist antibody from infected cells which would result in enhanced anti-viral local immune response.

206. A person exposed to recombinant GMO could potentially experience mild respiratory, gastrointestinal or eye reactions or infection depending on the route of exposure as described in Chapter 1, Section 3.1. These infections are self-limiting and rarely need medical intervention. As the entire viral capsid components are derived from HAdV-11p which has tropism for urinary system, the portals of viral entry such as respiratory, gastrointestinal or ocular mucosa are unlikely to lead to infection. If needed, first line antiviral therapies could be used. Any anti-viral immune reaction would be minimal as the exposure dose would be much lower than therapeutic dose. Theoretically, homologous recombination could also lead to exchange of gene regions that encode for capsid proteins, which could alter viral tropism. For example, whereas HAdV-11 has tropism for urinary tract, HAdV-3 has tropism for the respiratory tract. Therefore, a GMO could acquire respiratory tropism. Since multiple recombination events would be required for a GMO to acquire the ability to replicate in normal cells in addition to acquiring novel tropism, the risk of increased harm is still negligible as adenoviruses do not typically cause severe disease, and the resultant recombinants would not be more pathogenic than the wild-type virus.

Conclusion

207. The exposure of people to a GMO or other recombinant viruses resulting in adverse immune responses or disease in people or animals is not identified as a risk that could be greater than negligible. The reasons for this are that the GMO is highly unlikely to co-infect the same cell as WT HAdV and resulting strains from any recombination will not produce disease more severe than wild type HAdV. Therefore, this risk scenario does not warrant further assessment.

Section 3 Uncertainty

208. Uncertainty is an intrinsic property of risk analysis and is present in all aspects of risk analysis. This is discussed in detail in the Regulator's Risk Analysis Framework document.

209. Uncertainty is addressed by approaches such as balance of evidence, conservative assumptions, and applying risk management measures that reduce the potential for risk scenarios involving uncertainty to lead to harm. If there is residual uncertainty that is important to estimating the level of risk, the Regulator will take this uncertainty into account in making decisions.

210. This is not a first in human clinical trial, and available clinical biodistribution and shedding data for this GMO and parent organism has been used in this risk assessment. The uncertainty regarding shedding data may be influenced by different types of cancers being treated and is reasonable to assume that the GMO replicating in rectal cancer is likely to shed more of the GMO from gastrointestinal (GI) tract compared to non-GI cancers.

211. A limitation of a PCR-based methods of detecting viral DNA is that they do not measure infectivity. It is possible that a DNA measure is an over-estimation of infectious virus shedding as fragmented DNA from damaged tissue could be shed from tumours without infectious virus particles being released. A conservative approach has been taken, and an assumption has been made that viral DNA may indicate infectious particle shedding.

212. Uncertainty may also arise due to the lack of information as to what types of healthy cells *in vivo* can be infected with the GMO. Although data presented thus far indicates high degree of selectivity towards cancer cells, a conservative approach and the possibility that the GMO can infect healthy cells has also been considered.

213. Overall, the level of uncertainty in this risk assessment is considered low and does not impact on the overall estimate of risk.

Section 4 Risk evaluation

214. Risk is evaluated against the objective of protecting the health and safety of people and the environment to determine the level of concern and, subsequently, the need for controls to mitigate or reduce risk. Risk evaluation may also aid consideration of whether the proposed dealings should be authorised, need further assessment, or require collection of additional information.

215. Factors used to determine which risks need treatment may include:

- risk criteria,
- level of risk,
- uncertainty associated with risk characterisation, and
- interactions between substantive risks.

216. Three risk scenarios were postulated whereby the proposed dealings might give rise to harm to people or the environment. This included consideration of whether people can be exposed to the GMO while conducting the dealings and whether there is a potential for complementation and recombination of the GMO with other adenoviruses both in the trial participants and in other people and animals. The potential for GMO to be released into the environment and its effects was also considered.

217. A risk is substantive only when the risk scenario may, because of gene technology, have some chance of causing harm. Risk scenarios that do not lead to harm, or could not reasonably occur, do not represent an identified risk and do not advance in the risk assessment process.

218. In the context of the range of measures already in place, including the operating guidelines and requirements of the other regulatory agencies, and considering both the short and long term, none of these scenarios were identified as representing a substantive risk requiring further assessment. The principal reasons for this include:

- the GMO is highly attenuated in normal cells and is unlikely to form meaningful number of mature viral particles in healthy cells, which will prevent it from multiplying in non-tumour cells;
- the GMO is unlikely to be shed from recipients in a meaningful way in saliva or urine after day 15 and in faeces after 2 months which limits the likelihood of exposure;
- the likelihood of accidental exposure to the GMO in people not being treated or animals would be minimised due to well-established import, transport, storage and disposal procedures; and
- complementation and recombination of GMO with other adenoviruses is highly unlikely to lead to adverse effects; and
- survival and persistence of any GMO that is to be released in the Australian aquatic and terrestrial environment is highly unlikely.

219. Therefore, any risks to the health and safety of people, or the environment, from the proposed clinical trial using the GMO are considered to be negligible. The *Risk Analysis Framework* (OGTR, 2013), which guides the risk assessment and risk management process, defines negligible risks as insubstantial with no present need to invoke actions for their mitigation. No controls are required to treat these negligible risks. Hence, the Regulator considers that the dealings involved in this proposed release do not pose a significant risk to either people or the environment.[1]

[1] As none of the proposed dealings are considered to pose a significant risk to people or the environment, Section 52(2)(d)(ii) of the Act mandates a minimum period of 30 days for consultation on the RARMP.

Chapter 3 Risk management plan

Section 1 Background

220. 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 addresses risks evaluated as requiring treatment and considers limits and controls proposed by the applicant, as well as general risk management measures. The risk management plan informs the Regulator's decision-making process and is given effect through proposed licence conditions.

221. Under section 56 of the Act, the Regulator must not issue a licence unless satisfied that any risks posed by the dealings proposed to be authorised by the licence are able to be managed in a way that protects the health and safety of people and the environment.

222. All licences are subject to 3 conditions prescribed in the Act. Section 63 of the Act requires that each licence holder inform relevant people of their obligations under the licence. The other statutory conditions allow the Regulator to maintain oversight of licensed dealings: Section 64 requires the licence holder to provide access to premises to OGTR inspectors and Section 65 requires the licence holder to report any information about risks or unintended effects of the dealing to the Regulator on becoming aware of them. Matters related to the ongoing suitability of the licence holder are also required to be reported to the Regulator.

223. The licence is also subject to any conditions imposed by the Regulator. Examples of the matters to which conditions may relate are listed in Section 62 of the Act. Licence conditions can be imposed to limit and control the scope of the dealings. In addition, the Regulator has extensive powers to monitor compliance with licence conditions under Section 152 of the Act.

Section 2 Risk treatment measures for substantive risks

224. The risk assessment of risk scenarios listed in Chapter 2 concluded that there are negligible risks to people and the environment from the proposed clinical trial with the GMO. These risk scenarios were considered in the context of the scale of the proposed clinical trial (Chapter 1, Section 2.1), the proposed controls (Chapter 1, Section 2.2), the proposed receiving environment (Chapter 1, Section 5), and considering both the short and long term effects of the GMO. Limits and controls proposed by the applicant and other general risk management measures are discussed below.

Section 3 General risk management

225. The limits and controls proposed in the application were important in establishing the context for the risk assessment and in reaching the conclusion that the risks posed to people and the environment are negligible. Therefore, to maintain the risk context, draft licence conditions have been imposed to limit the number of trial participants, location limited to hospitals and clinical trial sites, limits on the duration of the trial, as well as a range of controls to restrict the spread and persistence of the GMOs and their genetic material in the environment. The conditions are discussed and summarised in this Chapter and listed in detail in the draft licence.

3.1 Limits and controls on the clinical trial

226. Sections 2.1 and 2.2 in Chapter 1 list the limits and controls proposed by Novotech. Many of these are discussed in the 3 risk scenarios considered in Chapter 2. The appropriateness of the limits and controls is considered further in the following sections.

3.1.1 Consideration of limits and controls proposed by Novotech (Australia) Pty Ltd

227. The proposed clinical trial would involve approximately 40 participants within Australia, and dealings with the GMOs would take place in medical facilities such as clinical trial facilities or hospitals. Activities that would occur outside of medical facilities include transport, storage and disposal of the GMOs. The applicant has proposed to complete dealings with the GMO within 4 years of commencement. A proposed licence condition limits the period when the GMO may be administered under the licence to 4 years from the date of issue of the licence. Other conditions maintaining the risk context and proposed limits of the trial such as a maximum of 40 trial participants and requirements for dealings related to preparation and administration of the GMO to be conducted at a clinical trial site have been included in the draft licence.

228. The applicant advised that import and transport of the GMO and waste containing the GMO would be in accordance with the Regulator's *Guidelines for the Transport, Storage and Disposal of GMOs*. The applicant has proposed that importation will follow IATA 3373 suitable for this GMO. For flexibility, the draft licence states that importation must follow IATA 3245 or 3373 requirements as these are both suitable standards. Adenoviruses are normally considered to be Risk Group 2 organisms (Standards Australia/New Zealand, 2022). Although the applicant has indicated that the GMO can be considered RG1 and stored and handled as such, since the GMO is not replication incompetent, to maintain the risk context for a GM adenovirus, the draft licence proposes that all storage, and transport requirements are in accordance with the Regulator's *Guidelines for the Transport, Storage and Disposal* of RG2 GMOs. These are standard protocols for the handling and minimising exposure to the GMOs. Once at the clinical trial site, access to the GMO would be restricted to appropriately trained personnel. These transport conditions are suitable for the GMO. Therefore, the draft licence details the minimum requirements for packaging and labelling the GMO and waste contaminated with the GMO for transport and storage within a clinical trial site, as well as transport of the samples that may contain GMO for analysis.

229. There are proposed inclusion and exclusion criteria for trial participants as listed in Chapter 1, Section 2.3.5. The inclusion and exclusion criteria for trial participants would be subject to approval by a HREC, who would consider the safety of the individuals involved in the trial.

230. The relevant inclusion criteria proposed by the applicant include that the trial participants must:

- agree to use an acceptable method of effective contraception during treatment and for at least 6 months after the last treatment with the GMO;
- agree to abstain from donating blood, sperm, ova or organs during treatment and for at least 6 months following the last dose of the GMO;
- agree to avoid close contact with pregnant individuals, children under 1 year old, those who have significant immunodeficiency because of underlying illness and/or medication.

231. The relevant exclusion criteria proposed by the applicant include pregnant and breastfeeding women and immunocompromised individuals.

232. As stated in Chapter 1, Section 4.2.4, shedding of infectious viral particles from trial participants who have received oncolytic adenovirus is expected to be minimal. Shedding in semen has not been assessed for this GMO. Due to the conditionally replicative nature of the GMO, sexual transmission of the GMO from the trial participants in the semen is unlikely. However, to prevent possible transfer of the GMO during sexual activities, a licence condition specifies the use of barrier methods during sexual activity, aimed at minimising physical contact with bodily fluids during sexual activity in addition to preventing conception. Using a conservative timeframe of 90 days, the criteria included in the draft licence are that the licence holder must obtain written agreement from the trial participant

that for the duration of the trial and 90 days after the last dose of the GMO they will not donate blood, sperm, ova, tissues or organs and will use condoms as effective barrier contraception.

233. The GMO was shown to be shed in faeces for approximately 2 months in one clinical trial. It was shown to be shed in saliva at 3 days after the last dose of the GMO, reducing dramatically by day 10 after the last dose of the GMO. As the shedding of the GMO is expected to be minimal and the GMO will be diluted in a large volume of water, for urine and faeces, treatment of urine and faeces does not require special precautions. Any home collection is unlikely to expose other individuals to the GMO and therefore special precautions beyond good hygiene practice are not required. Shedding of the virus in saliva may pose risk during close contact especially with individuals who may be immunocompromised. Although likely to be low level and transient, to maintain the context of the risk assessment, a condition in the draft licence proposes that the trial participant agrees to avoid close contact (e.g. close physical contact, sharing of cutlery) with children under 12 months of age, pregnant women or those who have significant immunodeficiency because of underlying illness or medication for at least 15 days after each administration of the GMO.

234. As the HAdV is passed between individuals frequently via faecal-oral route, the cancer is rectal and the virus is likely to shed in the faeces, and the GMO was detected in faeces in some studies for close to 2 months, the trial participants will be instructed to follow good hand hygiene practices to limit transmission both during the clinical trial, and as a precaution for 90 days after the last dose of the GMO. Although this measure was not specified by the applicant, it would limit the exposure to the GMO.

235. For the context of this RARMP, persons who have immunosuppressive disorders or who are pregnant are considered persons at higher risk of a serious adverse event when exposed to the GMO. To manage risk and to maintain the context of the risk assessment, a condition in the draft licence requires persons preparing or administering the GMO must be informed of the risks associated with the GMO (including risks in people suffering from immunosuppressive disorder or pregnant individuals).

236. The applicant has proposed exclusion of patients who have received prior treatment with EnAd-based oncolytic therapy. While recombination between the GMO and WT AdVs is considered unlikely and the risks are considered to be negligible, since oncolytic therapy can target the therapy towards cancer cell and can include a broad set of transgenes and modifications to the virus not considered in this risk assessment, to maintain the risk context, a precautionary licence condition is introduced that limits participants who have received oncolytic adenovirus-based therapy in the 90 days prior from participating in the trial. Similarly, trial participants must agree not to undergo treatment with oncolytic adenovirus therapy for 90 days following the last treatment with the GMO.

237. The risk context is maintained provided the GMO can be cleared by the immune system, therefore a precautionary condition is included in the licence to exclude participants with an immunosuppressive disorder or an illness that impairs immune function.

238. There are no data on transmission of the GMO to babies via breastfeeding and to foetuses if pregnant, as pregnant and breastfeeding women were excluded from the trials. Therefore, the applicant has proposed that pregnant and breastfeeding women be excluded from this licence. Given the absence of data, this is considered to be an acceptable measure.

239. The clinical staff handling the GMO would wear PPE including gown, gloves, mask and eye protection/face shield. These practices would minimise exposure of people handling and administering the GMOs (Risk scenario 1) and have been included in the draft licence conditions.

240. The applicant has indicated that the preparation of the GMO will be conducted in Class I BSC. As this type of BSC protects the operator, the licence condition requires preparation of the GMO to be conducted in BSC or similar cabinet, due to the RG2 nature of the GMO. Furthermore, as AdV can

be transmitted via aerosols, the draft licence condition requires the person administering the GMO to wear a P2 facemask.

241. Conditions are included in the draft licence requiring the licence holder to ensure that all GMOs, including material or waste that has been in contact with the GMO, within the clinical trial site, are decontaminated by autoclaving, chemical treatment or by high-temperature incineration. Draft licence conditions require that the licence holder must ensure that the GMO, or material or waste that has been in contact with the GMO, that is to be destroyed by external service providers, is through a clinical waste stream.

242. The Industry Code of Practice for the Management of Clinical and Related Wastes details requirements for clinical waste including waste segregation, packaging, labelling, storage, transport and accountability ((BWI), 2010). The clinical waste stream typically involves destruction of infectious waste by incineration or autoclaving, which are considered appropriate for disposal of the GMO. Given that AdV can persist in the environment, disposal measures such as burial or maceration would not ensure containment. Therefore, the draft licence requires waste disposal by external service providers to be by autoclaving or high-temperature incineration. These measures would limit the exposure of people or other animals to the GMOs.

243. A standard condition is included in the draft licence requiring the licence holder to ensure that dealings are conducted so as to ensure containment of the GMO, not compromise the health and safety of people and minimise unintentional exposure to the GMO. A note to the condition explains that compliance may be achieved by only engaging persons who are required to adhere to appropriate standards to conduct the dealings.

244. Other standard conditions included in the draft licence state that only people authorised by the licence holder are covered by the licence, and that the licence holder must inform all people dealing with the GMOs, other than external service providers, of applicable licence conditions.

245. Further conditions to be implemented in the draft licence is to ensure that a compliance management plan is in place for each clinical trial site before administration of the GMOs commences at that site. The compliance management plan must detail how the licence holder intends to comply with the licence conditions, including listing persons responsible for site management, proposed reporting structures, staff training procedures and transport and disposal processes.

3.1.2 Summary of licence conditions to be implemented to limit and control the clinical trial

246. A number of licence conditions have been drafted to limit and control the proposed clinical trial, based on the above considerations. These include requirements to:

- limit the trial to 40 trial participants;
- conduct the trial at suitable clinical trial sites;
- limit the time when the GMO can be administered to 4 years from issue of the licence;
- restrict access to the GMO;
- ensure personnel involved in the trial are appropriately trained and follow appropriate behavioural requirements;
- ensure appropriate PPE is used;
- restrict personnel permitted to administer the GMO;
- requirement for appropriate decontamination of the GMO and materials and equipment that have been in contact with the GMO;
- transport and store the GMO and samples from GMO-treated participants in accordance with IATA shipping classification UN3245 or UN 3373 or the minimum requirements for packaging, and labelling as detailed in the draft licence;
- clinical waste stream to be used by external service providers to destroy untreated GMO and GMO-related waste.

3.2 Other risk management considerations

247. All DIR licences issued by the Regulator contain a number of conditions that relate to general risk management. These include conditions relating to:

- applicant suitability
- contingency plans
- identification of the persons or classes of persons covered by the licence
- reporting requirements
- access for the purpose of monitoring for compliance.

3.2.1 Applicant suitability

248. In making a decision whether or not to issue a licence, the Regulator must have regard to the suitability of the applicant to hold a licence. Under Section 58 of the Act, matters that the Regulator must take into account include:

- any relevant convictions of the applicant
- any revocation or suspension of a relevant licence or permit held by the applicant under a law of the Commonwealth, a State or a foreign country
- the capacity of the applicant to meet the conditions of the licence.

249. If a licence were issued, the conditions would include a requirement for the licence holder to inform the Regulator of any information that would affect their suitability.

250. In addition, the applicant organisation must have access to an IBC and be an accredited organisation under the Act.

3.2.2 Contingency plans

251. Should a licence be issued, Novotech is required to submit a contingency plan to the Regulator before commencing dealings with the GMOs. This plan will detail measures to be undertaken in the event of:

- the unintended release of the GMOs, including spills
- exposure of, or transmission to persons other than trial participants
- a person exposed to the GMOs developing a serious adverse response.

3.2.3 Identification of the persons or classes of persons covered by the licence

252. If issued, the persons covered by the licence would be the licence holder and employees, agents or contractors of the licence holder and other persons who are, or have been, engaged or otherwise authorised by the licence holder to undertake any activity in connection with the dealings authorised by the licence. Prior to dealings with the GMOs, Novotech is required to provide a list of people and organisations that are covered by the licence, or the function or position where names are not known at the time.

3.2.4 Reporting requirements

253. If issued, the licence would require the licence holder to immediately report any of the following to the Regulator:

- any additional information regarding risks to the health and safety of people or the environment associated with the dealings
- any contraventions of the licence by persons covered by the licence
- any unintended effects of the clinical trial.

254. A number of written notices are also required under the licence regarding dealings with the GMO, to assist the Regulator in designing and implementing a monitoring program for all licensed dealings. The notices include:

- identification of the clinical trial sites where administration of the GMO to trial participants would take place
- expected date of administration with the GMOs for each clinical trial site
- cease of administration with the GMOs for each clinical trial site.

3.2.5 Monitoring for compliance

255. The Act stipulates, as a condition of every licence, that a person who is authorised by the licence to deal with a GMO, and who is required to comply with a condition of the licence, must allow inspectors and other persons authorised by the Regulator to enter premises where a dealing is being undertaken for the purpose of monitoring or auditing the dealing.

256. If monitoring activities identify changes in the risks associated with the authorised dealings, the Regulator may also vary licence conditions, or if necessary, suspend or cancel the licence.

257. In cases of non-compliance with licence conditions, the Regulator may instigate an investigation to determine the nature and extent of non-compliance. The Act provides for criminal sanctions of large fines and/or imprisonment for failing to abide by the legislation, conditions of the licence or directions from the Regulator, especially where significant damage to the health and safety of people or the environment could result.

Section 4 Issues to be addressed for future releases

258. Additional information has been identified that may be required to assess an application for a commercial release of the GMO, or to justify a reduction in limits and controls. This includes:

- information and data that would address the uncertainties noted in Chapter 2, Section 3. Specifically, information obtained on the shedding of the GMO and the infectivity of the shed GMO in trial participants with locally advanced rectal cancer.

Section 5 Conclusions of the consultation RARMP

259. The risk assessment concludes that the proposed clinical trial of the GMOs poses negligible risks to the health and safety of people or the environment as a result of gene technology. These negligible risks do not require specific risk treatment measures.

260. If a licence is issued, conditions are imposed to limit the trial to the proposed scale, location and duration, and to restrict the spread and persistence of the GMOs and its genetic material in the environment, as these were important considerations in establishing the context for assessing the risks.

Chapter 4 Draft licence conditions

Section 1 Interpretations and Definitions

1. In this licence:

   (a) unless defined otherwise in this licence, words and phrases used in this licence have the same meaning as they do in the Act and the Regulations;

   (b) words importing a gender include every other gender;

   (c) words in the singular number include the plural and words in the plural number include the singular;

   (d) expressions used to denote persons generally (such as “person”, “party”, “someone”, “anyone”, “no one”, “one”, “another” and “whoever”), include a body politic or corporate as well as an individual;

   (e) references to any statute or other legislation (whether primary or subordinate) are a reference to a statute or other legislation of the Commonwealth of Australia as amended or replaced from time to time and equivalent provisions, if any, in corresponding State law, unless the contrary intention appears;

   (f) where a word or phrase is given a particular meaning, other grammatical forms of that word or phrase have corresponding meanings;

   (g) specific conditions prevail over general conditions to the extent of any inconsistency.

2. In this licence:

   ‘Act’ means the *Gene Technology Act 2000* (Commonwealth) or the corresponding State law under which this licence is issued.

   ‘Analytical facility’ means a laboratory in Australia accredited to undertake testing of human diagnostic Samples, such as a medical testing laboratory accredited by the National Pathology Accreditation Advisory Council (NPAAC).

   ‘Clinical trial site’ means a medical facility in Australia such as a clinical trial facility and associated Pharmacy, which are notified in writing to the Regulator for the purposes of conducting this clinical trial.

   ‘Decontaminate’ (or ***‘Decontamination’***) means, as the case requires, kill the GMOs by one or more of the following methods:

   (a) chemical treatment;

   (b) autoclaving;

   (c) high-temperature incineration; or

   (d) a method approved in writing by the Regulator.

   Note: 'As the case requires' has the effect that, depending on the circumstances, one or more of these techniques may not be appropriate.

   ‘External service provider’ means a person engaged by the licence holder solely in relation to transport, storage and/or disposal of the GMOs, and who is not undertaking any dealings with the GMOs that are not for those purposes.

   ‘GM’ means genetically modified.

   ‘*GMO’* means the genetically modified organisms that are the subject of the dealings authorised by this licence.

'Immunosuppressive disorder' means a condition characterised by a weakened immune system due to underlying disease (e.g. HIV), medications (excluding anti-cancer medications) or treatment (e.g. organ transplant).

'NLRD' is a Notifiable low risk dealing. Dealings conducted as an NLRD must be assessed by an institutional biosafety committee (IBC) before commencement and must comply with the requirements of the Regulations.

'OGTR' means the Office of the Gene Technology Regulator.

'Personal information' has the same meaning as in the *Privacy Act 1988*. Personal information means information or an opinion about an identified individual, or an individual who is reasonably identifiable:

(a) whether the information or opinion is true or not; and

(b) whether the information or opinion is recorded in a material form or not.

'Pharmacy' means a location within the Clinical trial site, where authorised staff store, prepare, and dispense medications in a medical environment.

'Regulations' means the Gene Technology Regulations 2001 (Commonwealth) or the corresponding State law under which this licence is issued.

'Regulator' means the Gene Technology Regulator.

'Sample' means any biological material collected from a treated trial participant for analysis as part of the trial

'Storage facility' means a third-party facility offering logistical services and distribution of clinical supplies.

Section 2 General conditions and obligations

Holder of licence

3. The licence holder is Novotech (Australia) Pty Ltd.

Remaining an Accredited Organisation

4. The licence holder must, at all times, remain an accredited organisation.

Validity of licence

5. This licence remains in force until it is suspended, cancelled or surrendered. No dealings with the GMO are authorised during any period of suspension, or after the licence has been cancelled or surrendered.

Note: Although this licence has no expiry date, the duration of preparation and administration of the GMOs is restricted in accordance with Condition 23.

Persons covered by this licence

6. The persons covered by this licence are:

   (a) the licence holder, and any employees, agents or External service providers engaged by the licence holder; and

   (b) the project supervisor(s); and

   (c) other persons who are, or have been, engaged or otherwise authorised by the licence holder or the project supervisor to conduct any of the dealings authorised by this licence.

7. To the extent that any activity by a trial participant may be considered to be a dealing with the GMO as described in **Attachment A** for purposes of the Act, that dealing is authorised by this licence.

8. The licence holder must keep a record of all persons covered by this licence, and must keep a record of the contact details of the project supervisor(s) for the licence.

Note: Where External service providers are used, it is sufficient to record the company name and the position or job title of the person(s) conducting the dealing.

9. The licence holder must provide information related to the persons covered by the licence when requested to do so in writing by the Regulator and must provide the information within a time period stipulated by the Regulator.

Description of GMOs covered

10. The licence authorises specified dealings in respect of the GMOs identified and described in **Attachment A**.

Dealings authorised by this licence

11. The licence holder and persons covered by this licence may conduct the following dealings with the GMOs:

    (a) import the GMO;

    (b) conduct the following experiments with the GMOs:

        i) prepare the GMO for administration to trial participants;

        ii) administer the GMO to trial participants by intra-venous (IV) administration;

        iii) collect Samples from trial participants;

        iv) prepare and/or analyse the Samples described in 11(b)iii);

    (c) transport the GMOs;

    (d) dispose of the GMOs;

    and may possess, supply, use or store the GMO for the purposes of, or in the course of, any of these dealings.

12. Supply of the GMOs for the purposes of dealings by a person or organisation not covered by this licence is only authorised by this licence if the Regulator provides prior written approval to the licence holder.

Note: For approval to be granted, the receiving person or organisation must have an appropriate authorisation to conduct dealings with the GMOs. This is likely to be a NLRD or a licence issued by the Regulator.

Conditions imposed by the Act

Note: The Act mandates the following 3 conditions.

Informing people of licence conditions (section 63)

13. The licence holder must inform any person covered by the licence, to whom a particular condition of the licence applies, of the following:

    (a) the particular condition, including any variations of it; and

    (b) the cancellation or suspension of the licence; and

    (c) the surrender of the licence.

Note: No particular conditions of this licence apply to trial participants; therefore, Condition 13 does not apply to trial participants.

Monitoring and audits (section 64)

14. If a person is authorised by this licence to deal with the GMOs and a particular condition of this licence applies to the dealing by that person, the person must allow the Regulator, or a person authorised by the Regulator, to enter premises where the dealing is being undertaken, for the purposes of auditing or monitoring the dealing.

Additional information to be given to the Regulator (section 65)

15. The licence holder must immediately inform the Regulator, if they become aware of:

    (a) additional information about any risks to the health and safety of people, or to the environment, associated with the dealings authorised by the licence; or

    (b) any contraventions of the licence by a person covered by the licence; or

    (c) any unintended effects of the dealings authorised by the licence.

Note 1: For the purposes of this condition:

(a) The licence holder is taken to have become aware of additional information if they were reckless as to whether such information existed; and

(b) The licence holder is taken to have become aware of contraventions, or unintended effects, if they were reckless as to whether such contraventions had occurred, or such unintended effects existed.

Note 2: Contraventions of the licence may occur through the action or inaction of a person.
Note 3: Additional information includes any changes at a Clinical trial site, which might increase the likelihood of unintentional exposure of people or release of the GMO into the environment.
Note 4: An example of informing immediately is contact made at the time of the incident via the OGTR free call phone number 1800 181 030 or email to OGTR.M&C@health.gov.au.

Informing the Regulator of any material changes of circumstance

16. The licence holder must immediately, by notice in writing, inform the Regulator of:

    (a) any relevant conviction of the licence holder occurring after the commencement of this licence;

    (b) any revocation or suspension after the commencement of this licence, of a licence or permit held by the licence holder under a law of the Commonwealth, a State or a foreign country, being a law relating to the health and safety of people or the environment;

    (c) any event or circumstances occurring after the commencement of this licence that would affect the capacity of the licence holder to meet the conditions in it.

17. The licence holder must provide information related to the licence holder's ongoing suitability to hold a licence when requested to do so in writing by the Regulator, and must provide the information within a time period stipulated by the Regulator.

Further conditions with respect to informing persons covered by the licence

18. If a particular condition, including any variation of it, applies to an External service provider covered by this licence, the licence holder must not permit that person to conduct any dealings unless the person has been informed of the condition, including any variation of it.

Note: Information required under Condition 18 may be provided to External service providers who are engaged solely for storage and transport of the GMO through labelling of the outermost container of the GMOs in accordance with Condition 37(a).

19. If a particular condition, including any variation of it, applies to a person with respect to any dealing, other than to an External service provider, the licence holder must not permit a person covered by this licence to conduct that dealing unless:

    (a) the licence holder has obtained from the person a signed and dated statement that the person:

        i) has been informed by the licence holder of the condition and, when applicable, its variation; and

        ii) has understood and agreed to be bound by the condition, or its variation; and

        iii) has been trained in accordance with sub-condition 19(b) below; and

    (b) the licence holder has trained that person in a manner which enables them to conduct the dealings in accordance with the conditions of this licence.

20. The licence holder must notify all persons covered by the licence, from whom Personal information relevant to the administration and/or enforcement of the licence is collected by the licence holder, that such Personal information may be disclosed to the Regulator.

21. The licence holder must ensure that a copy of the licence is readily available to all persons covered by the licence, other than External service providers, who are conducting dealings with the GMO.

Note: The licence may be made available electronically.

Section 3 Limits and control measures

Limits on clinical trials conducted under this licence

22. The GMO may be administered to a maximum of 40 trial participants.

23. The preparation and administration of the GMO must be completed within 4 years from the date of issuing of the licence.

Preparation and administration of the GMOs

24. Administration of the GMO to trial participants must not commence prior to approval by a Human Research Ethics Committee.

25. The following activities must occur within a Clinical trial site:

    (a) preparation of the GMO for administration to trial participants; and

    (b) administration of the GMO to trial participants.

    Note: Before any of these activities take place, the details of each Clinical trial site must have been notified to the Regulator in accordance with Condition 43(a).

Conditions relating to trial participants

26. The licence holder must notify each trial participant, from whom Personal information relevant to the administration and/or enforcement of the licence is collected by the licence holder, that such Personal information may be disclosed to the Regulator.

27. The licence holder must ensure that exclusion criteria used in selecting trial participants include (though are not limited to) the following persons:

    (a) pregnant and breastfeeding women;

    (b) any people suffering from Immunosuppressive disorder;

    (c) those having received a prior treatment with a different adenovirus based oncolytic therapy within 90 days of participating in the trial; and

(d) those intending to become pregnant during the first 90 days following the last treatment with the GMO.

28. Before inoculating any trial participant with the GMOs, the licence holder must obtain written agreement from the trial participant that they would:

(a) forgo any treatment with a different adenovirus based oncolytic therapy for 90 days following the last treatment with the GMO;

(b) use barrier method(s) to prevent pregnancy and exposure to the GMO during sexual activities for at least 90 days after each treatment with the GMO; and

(c) not donate blood, sperm, ova, tissues or organs while participating in the trial and for 90 days after their last treatment with the GMO.

Note: Condition 28(b) is intended to minimise physical contact with bodily fluids during sexual activity in addition to preventing conception.

Preventive practices required post-administration

29. Before inoculating a trial participant with the GMOs, the licence holder must also obtain the trial participant's written agreement that they will:

(a) avoid close contact (e.g. close physical contact, sharing of cutlery) with individuals who are pregnant, children under 12 months of age and those who suffer from Immunosuppressive disorder for 15 days after the administration of the GMO; and

(b) implement hygiene measures including hand washing intended to prevent transmission of the GMO to other people and to animals for at least 90 days after the administration of the GMO.

Conditions related to the conduct of the dealings

30. Conditions that apply to dealings with GMOs do not apply to Samples collected from trial participants, or other materials or waste, that are reasonably expected not to contain the GMO. The licence holder must provide to the Regulator upon request, a written justification for this expectation.

31. The licence holder must ensure that dealings are only conducted in a manner which:

(a) does not compromise the health and safety of people; and

(b) minimises the exposure of persons conducting the dealings to the GMO, other than intended exposure of trial participants.

Note: The licence holder may achieve this by only engaging or otherwise authorising persons to conduct dealings who are required to adhere to appropriate standards and guidelines. For example, standards developed by the National Pathology Accreditation Advisory Council for pathology practices, the Australian Guidelines for the Prevention and Control of Infection in Healthcare, Guidelines for Good Clinical Practice and the National Safety and Quality Health Service (NSQHS) Standards.

32. The licence holder must ensure that procedures are in place to account for the GMO from import to destruction/export, and records must be made available to the Regulator on request.

Work practices at Clinical trial sites

33. For the purposes of Condition 31 , work practices and behaviours within a Clinical trial site must include, but are not limited to, the following:

(a) preparation of the GMO must be conducted in a biosafety cabinet (BSC), a negative pressure pharmaceutical isolator, or alternative containment equipment approved in writing by the Regulator;

(b) persons preparing the GMOs must wear personal protective equipment (PPE), including gowns, gloves, and eye protection. In addition to this, persons administering the GMO must also wear a P2 facemask.

(c) persons preparing or administering the GMO must be informed of the risks associated with the GMO (including risks in people suffering from Immunosuppressive disorder or pregnant individuals) and have provided a signed statement to that effect in accordance with Condition 19;

(d) any broken skin (e.g. cuts, scratches, dermatitis) of persons conducting dealings not covered by PPE or clothing must be covered with a waterproof dressing;

(e) all work surfaces must be Decontaminated after they have been used for conducting dealings authorised by this licence;

(f) equipment used for dealings with the GMOs must be Decontaminated after use;

(g) preparation and administration of the GMO must be conducted by suitably qualified and trained staff.

(h) the administration site must be covered with an occlusive dressing following administration of the GMO; and

(i) the dressing applied to the administration site must be removed and the administration site cleaned prior to the trial participant leaving the Clinical trial site.

Transport, storage and disposal of the GMOs

34. The licence holder must ensure that transport of the GMOs is conducted only for the purposes of, or in the course of, another dealing permitted by this licence.

35. For the purposes of import or export, and transport between the border and either a Storage facility or a Clinical trial site, the licence holder must ensure the GMO is packaged, labelled, stored and transported consistent with International Air Transport Association (IATA) shipping classification UN 3245 or UN 3373.

36. Transport between a Storage facility and the clinical trial site can also be done consistent with IATA shipping classification UN 3245 or UN 3373 if the GMO is not repackaged at the Storage facility.

37. The licence holder must ensure that transport and storage of the GMO, unless conducted according to Condition 35 or 36, follows these sub-conditions:

(a) GMOs must be contained within sealed, unbreakable primary and secondary containers, with the outer packaging labelled to indicate at least:

i) that it contains GMOs; and

ii) that it contains biohazardous material as designated by a biohazard label; and

iii) the contact details for the licence holder; and

iv) instructions to notify the licence holder in case of loss or spill of the GMOs; and

(b) the external surface of the primary and secondary container must be Decontaminated prior to transport; and

(c) procedures must be in place to ensure that GMOs can be accounted for and that a loss of GMOs during transport or storage or failure of delivery can be detected; and

(d) access to the GMOs is restricted to authorised persons for whom Condition 18 or Condition 19 has been met (i.e. the GMOs are within a locked unit or an area which has restricted access). This includes situations where containers are left for collection in a holding area, or left unattended prior to Decontamination; and

Note: All stored GMOs remain the responsibility of the licence holder.

(e) if the GMO is being transported or stored with a coolant (e.g. dry ice, liquid nitrogen or any other coolant) which will release a gas, a mechanism to allow the escape of the gas must be included. If water ice is used as a coolant then the outer packaging should be constructed so as to prevent any leakage. All containers must be able to withstand the temperatures to which they will be subjected; and

Note: When transporting and storing with coolants, it is preferable for coolants to be used outside of the secondary container.

(f) a consolidated record of all GMOs being stored under this condition is maintained and made available to the Regulator upon request; and

(g) for the purposes of transport entirely within a building, where the GMOs are accompanied by an authorised person for whom Condition 19 has been met, Conditions 37(a)iii), 37(a)iv) and 37(c) do not apply.

38. The licence holder must ensure that all GMOs and waste reasonably expected to contain the GMOs are Decontaminated:

(a) prior to disposal, unless the method of disposal is also a method of Decontamination; and

(b) before or upon suspension, cancellation, expiration or surrender of the licence, unless covered by another authorisation under the Act, or exported; and

(c) by autoclaving, chemical treatment, high-temperature incineration or any other method approved in writing by the Regulator.

39. Where transport is conducted by External service providers for the purpose of destruction, the licence holder must ensure that the GMO, or waste reasonably expected to contain the GMO, enters the clinical waste stream for Decontamination via autoclaving or high-temperature incineration.

Note: In the event of a spill during transport by an External service provider, compliance with relevant State or Territory legislation and regulations to manage clinical or biohazardous spills is sufficient.

Contingency plans

40. The licence holder must ensure that any person (other than a trial participant) exposed to the GMOs is offered prompt medical attention by a medical practitioner. The medical practitioner must be provided with any relevant information about the GMO.

41. If there is a spill or an unintentional release of the GMOs at a Storage facility or Clinical trial site, the following measures must be implemented:

(a) the GMOs must be contained to prevent further dispersal; and

(b) persons cleaning up the GMO must wear appropriate PPE as specified in condition 33(b); and

(c) the exposed area must be Decontaminated with an appropriate chemical disinfectant effective against the GMOs; and

(d) any material used to clean up the spill or PPE worn during clean-up of the spill must be Decontaminated; and

(e) the licence holder must be notified as soon as reasonably practicable.

Section 4 Reporting and Documentation

Note: The following licence conditions are imposed to demonstrate compliance with other conditions and facilitate monitoring of compliance by staff of the OGTR. Notices and reports may be emailed to OGTR.M&C@health.gov.au. A summary of notification and reporting requirements is provided at ***Attachment B****.*

42. The licence holder must notify the Regulator, in writing, of the name and address of each Storage facility before commencement of dealings at that location.

43. At least 14 days prior to first administering the GMO at each Clinical trial site, or a timeframe agreed to in writing by the Regulator, the licence holder must provide the Regulator with a Compliance Management Plan for that Clinical trial site, specifying:

    (a) the name, address and description of the Clinical trial site, including any associated Pharmacies/storage areas/Analytical facilities/hospitals;

    (b) the role and contact details for key persons responsible for the management of the trial at the site;

    (c) that the Institutional Biosafety Committee (IBC) associated with the site (if any) has been notified of the trial and have been consulted regarding site specific procedures;

    (d) the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of all reportable events including but not limited to Conditions 15, 16, 44 and 45;

    (e) details of how the persons covered by the licence (for that type of dealing) will be informed of licence conditions applicable to them and how they will be trained to safely conduct the dealings;

    (f) the person(s) or class of persons administering the GMO;

    (g) where, within the site, the GMO is expected to be administered;

    (h) the expected date of first administration;

    (i) how compliance with Condition 31 will be achieved in relation to preparation of participant Samples for analysis subsequent to administering the GMO.

    Note: For the purpose of finding out whether the Act has been complied with, an OGTR inspector may, if entry is at a reasonable time, enter a facility occupied by the licence holder or a person covered by the licence and exercise monitoring powers.

44. For each Clinical trial site, the licence holder must notify the Regulator, in writing, of the end of the clinical trial, no later than 30 days after:

    (a) the final dose being administered; or

    (b) the decision that no further participants will be treated at that site.

45. The licence holder must inform the Regulator as soon as reasonably possible:

    (a) in the event of a loss or spill of the GMO;

    (b) in the event of the exposure of a person other than a trial participant, or animals, to the GMO; and

    (c) if a trial participant has not followed the agreements under Conditions 28 and 29.

46. Upon request from the Regulator, the licence holder must provide any signed records or documentation collected under a condition of this licence, within a time period stipulated by the Regulator.

Attachment A

DIR No: 222

Title: Clinical trial of GM adenovirus for treatment of locally advanced rectal cancer

Licence holder Novotech (Australia) Pty Ltd

GMO Description

GMOs covered by this licence:

Human chimeric adenovirus type 11p (Ad11p)/Ad3, with deletions in E3 and E4 gene regions modified by placement of heavy and light chain genes for antibody against CD40

Parent Organisms:

Common Name: *Human adenovirus*

Scientific Name: *Chimeric human adenovirus 11p/3 (Enadenotucirev, ColoAd1)*

Modified traits:

Categories: Human therapeutic

Description: The GMO, known as NG-350A, is a live *Human adenovirus* treatment derived from the sequence of chimeric human adenovirus 11p/3, which selectively replicates in cancer cells. The transgene encodes for a human antibody to CD40 to enhance the human immune response to the target cancerous tumour cells. The plasmid encoding the whole genome of the GMO is transfected into cell line to produce viable virus particles. Modified genes are listed in Table 1.

Table 1. Nucleic acid responsible for conferring the modified traits

Genetic modifications	
Source, identity, nature of modification	**Modified trait description**
Insertion of an expression cassette consisting of: • heavy chain of IgG2 antibody to CD40 • Light chain of IgG2 antibody to CD40 • Additional non-coding sequences such as regulatory elements, introns and/or spacers	Expression of human IgG2 antibody against human CD40

Trial participants and route of administration of the GMOs

Intravenous administration to adult humans with locally advanced rectal cancer.

Attachment B Summary of reporting requirements*

Prior to the commencement of the trial	Condition	Timeframe for reporting
The name and address of each Storage facility	42	Before commencement of dealings at that location
A written Compliance Management Plan for each Clinical trial site: (a) the name, address and description of the Clinical trial site, including any associated Pharmacies/storage areas/Analytical facilities; (b) the role and contact details for key persons responsible for the management of the trial at the site; (c) that the Institutional Biosafety Committee (IBC) associated with the site (if any) has been notified of the trial and have been consulted regarding site specific procedures; (d) the proposed reporting structure for the trial at the site and how the reporting structure enables the licence holder to become aware of all reportable events including but not limited to Conditions 15, 16, 44 and 45; (e) details of how the persons covered by the licence (for that type of dealing) will be informed of licence conditions applicable to them and how they will be trained to safely conduct the dealings; (f) the person(s) or class of persons administering the GMO; (g) where, within the site, the GMO is expected to be administered; (h) expected date of first administration; (i) how compliance with Condition 31 will be achieved in relation to preparation of participant Samples for analysis subsequent to administering the GMO	43	At least 14 days prior to the first administration of the GMO at each Clinical trial site, or a timeframe agreed to in writing by the Regulator
Information to be provided at any time during the clinical trial	**Condition**	**Timeframe for reporting**
Any additional information related to the health and safety of people and the environment associated with the dealings covered by the licence, or any unintended effects of the dealings authorised by the licence	15(a)(c)	Immediately
Information related to any contravention of the licence by a person covered by the licence	15(b)	Immediately
Any relevant conviction of the licence holder	16(a)	Immediately

Any revocation or suspension of a licence or permit held by the licence holder under a law of the Commonwealth, a State or a foreign country	16(b)	Immediately
Any event or circumstances that would impact the licence holder capacity to meet the licence conditions	16(c)	Immediately
Provide notification to the Regulator, in writing, of the final GMO administration of the last trial participant at each Clinical trial site	44(a)	Within 30 days of the decision to cease GMO administration at that particular Clinical trial site.
Any loss or spill of the GMO, or exposure of a person other than the trial participant to the GMO	45(a)(b)	As soon as reasonably possible
Any event where a trial participant has not followed the procedures described in the instruction provided by the licence holder	45(c)	As soon as reasonably possible
Information to be provided on request by the Regulator		
Information related to the persons covered by the licence	9	Within a timeframe stipulated by the Regulator
Information related to the licence holder's ongoing suitability to hold a licence	17	Within a timeframe stipulated by the Regulator
Copies of signed and dated statements and training records	19	Within a timeframe stipulated by the Regulator
A consolidated record of all GMOs being stored	37(f)	Within a timeframe stipulated by the Regulator
Any signed records or documentation collected under a condition of this licence	46	Within a timeframe stipulated by the Regulator

***** Notifications and documents to be sent to OGTR.M&C@health.gov.au

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