# CLINICAL PROTOCOL

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| TITLE: | A multicentre, open-label, non-randomised first in human study of NG-350A in patients with metastatic or advanced epithelial tumours (FORTITUDE) |
| STUDY TREATMENT: | NG-350A |
| INDICATION STUDIED: | Metastatic or advanced epithelial tumours |
| PROTOCOL NUMBER: | NG-350A-01 |
| VERSION NUMBER: | Version 1.0 |
| VERSION DATE: | 08 October 2018 |
| EudraCT NUMBER: | To be obtained |
| IND NUMBER: | To be obtained |
| SPONSOR: | PsiOxus Therapeutics Ltd.<br>PsiOxus House<br>4-10 The Quadrant<br>Abingdon Science Park<br>Abingdon<br>Oxfordshire, OX14 3YS<br>United Kingdom |
| SPONSOR APPROVAL: | Dr Hilary McElwaine-Johnn |

[redacted]

## ADMINISTRATIVE AND CONTACT INFORMATION

| | |
|---|---|
| Co-ordinating Investigator: | Dr Aung Naing [redacted] |
| Sponsor: | PsiOxus Therapeutics Ltd. [redacted] |
| Sponsor's Medical Expert/ Medical Monitor: | Dr Hilary McElwaine-Johnn<br>Chief Medical Officer [redacted] |
| 24 hour Safety Hotline: | [redacted] |
| SAE/Pregnancy Reporting: | [redacted] |
| Contract Research Organisation: | [redacted] |
| Analytical Laboratory: | [redacted] |

A list of study centres will be held in the Trial Master File.

## INVESTIGATOR AGREEMENT

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|---|---|
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| SPONSOR: | PsiOxus Therapeutics Ltd. |

I have read the protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this protocol as outlined therein, including all statements regarding confidentiality. I will make a reasonable effort to complete the study within the time designated. I will provide copies of the protocol and access to all information furnished by the Sponsor to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study treatment and the study. I understand that the study may be terminated, or enrolment suspended at any time by the Sponsor, with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

| | |
|---|---|
| Principal Investigator's Name (print) | |
| Principal Investigator's Signature | Date<br>(DD Month YYYY) |

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## PROTOCOL AMENDMENT

| Version Number | Summary of Amendments |
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| 1.0 | New document |
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This is the first version of the protocol, therefore there are no amendments included.

# PROTOCOL SYNOPSIS

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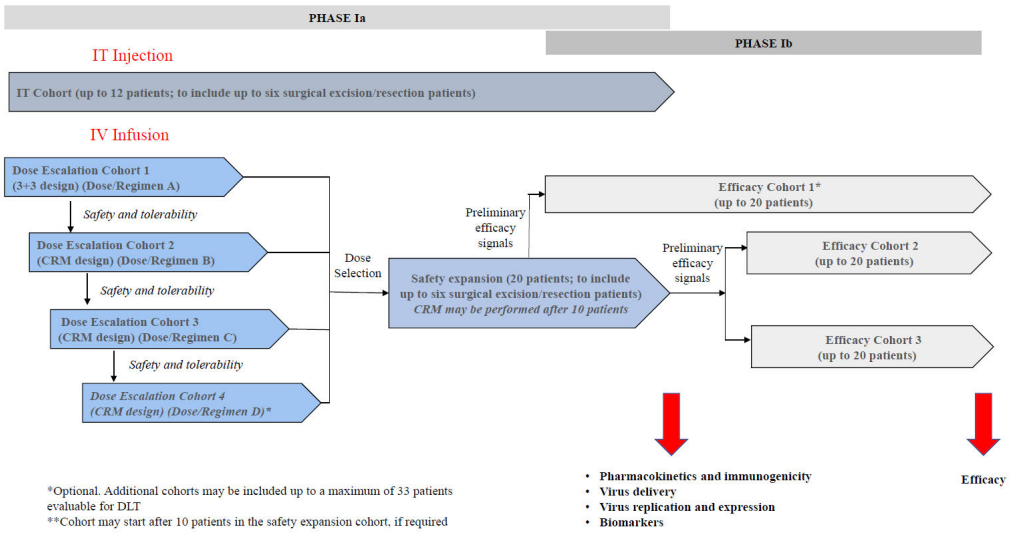
| Title of Study: | A multicentre, open-label, non-randomised first in human study of NG-350A in patients with metastatic or advanced epithelial tumours (FORTITUDE) |
| Short Title: | First in human study of NG-350A (an oncolytic adenoviral vector which expresses a full length anti-CD40 antibody at the site of virus replication) |
| Sponsor: | PsiOxus Therapeutics Ltd |
| Protocol Number: | NG-350A-01 |
| Objectives: | **Primary Objectives**<br>To characterise the safety and tolerability of NG-350A in patients with metastatic or advanced epithelial tumours.<br>**Secondary Objectives**<br>• To determine the recommended dose of NG-350A for further development in patients with metastatic or advanced epithelial tumours<br>• To explore the preliminary anti-tumour activity of NG-350A in patients with metastatic or advanced epithelial tumours using Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 and immune Response Evaluation Criteria in Solid Tumours (iRECIST)<br>• To assess the pharmacokinetics and immunogenicity of NG-350A<br>**Exploratory Objectives**<br>• To assess levels of anti-CD40 antibody in the blood<br>• To assess cytokine responses to NG-350A treatment<br>• To explore NG-350A virus delivery to the tumour<br>• To assess viral shedding in buccal swabs, rectal swabs and urine samples<br>• To assess levels of infectious virus in blood<br>• To explore effect on tumour specific serum biomarkers<br>• To explore methodologies to detect virus replication, anti-CD40 antibody transgene expression in tumour samples and potential immune/inflammatory responses to those activities of NG-350A |
| Study Design: | This is a Phase Ia/Ib, multicentre, open-label, non-randomised first in human study of NG-350A in patients with metastatic or advanced epithelial tumours. The study design is shown in Figure S1.<br>**Figure S1 Study Schematic for NG-350A-01**<br>  <br><br>Abbreviations: CRM=continual reassessment method; DLT=dose limiting toxicity; IT=intratumoural; IV=intravenous |

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| | **Phase Ia**<br>The Phase Ia part of the study is a dose escalation and safety expansion phase investigating NG-350A administration by intratumoural (IT) injection and intravenous (IV) infusion. The two routes of administration will be investigated in parallel.<br>• IT Injection<br>Patients will receive a single dose of NG-350A by IT injection on Day 1. The dose will be determined by the size of the tumour lesion to be injected. Patients will provide blood samples and tumour tissue samples to evaluate NG-350A activity parameters following IT injection. It is anticipated that up to six patients dosed in this cohort who are candidates for surgical excision/resection of the injected tumour lesion will undergo planned endoscopic or open surgery between Days 8 and 29 which will provide tumour tissue from the treated lesion. The remaining patients will undergo tumour core biopsies of the treated lesion (see Study Procedures and Frequency section) with the option for any other tumour samples to be collected in the event a patient undergoes any surgical procedure whilst taking part in the study.<br>• IV Infusion<br>Patients will receive one cycle of study treatment, with three single doses of NG-350A on Days 1, 3 and 5 by IV infusion.<br>A dose escalation (three dose escalation cohorts of NG-350A with an optional fourth dose escalation cohort are planned) will be performed to investigate the safety and tolerability of NG-350A. Further cohorts may be included to optimise the dose and dosing regimen for safety expansion if required, up to a maximum of 33 patients evaluable for a dose limiting toxicity (DLT). The first cohort will follow a standard "3+3" design; thereafter a continual reassessment method (CRM) will be implemented, with dose recommendations guided by the escalation with overdose control (EWOC) principle, will be implemented to guide subsequent doses and dose regimens, with the CRM run after each set of three evaluable patients and the total number of patients evaluable for DLT capped at nine per cohort. Assessments will be performed to determine the safety and tolerability of administration following IV infusion.<br>A Safety Review Committee (SRC), made up of Principal Investigators (or their deputies), an Independent Reviewer and a representative of the Sponsor with a medical background, will be ultimately responsible for dose escalation decisions and for selecting the optimal dose and dosing regimen to be further investigated in a safety expansion cohort of up to 20 patients to confirm the dose of NG-350A for Phase Ib and to determine the recommended dose of NG-350A for future development. The SRC will meet after Dose Escalation Cohort 1 and after each three patients evaluable for DLT in the rest of the Dose Escalation Cohorts, guided by the CRM. The CRM may also be implemented after 10 patients in the safety expansion cohort, followed by SRC review, to optimise the dose and dosing regimen in the final 10 patients prior to Phase Ib.<br>Patients in the dose escalation and safety expansion cohorts will provide blood samples and tumour tissue samples to evaluate NG-350A activity parameters following IV infusion. All patients will have tumour biopsies at baseline. It is anticipated that up to six of the patients in the safety expansion cohort who are candidates for surgical tumour excision/resection will undergo planned endoscopic or open surgery between Days 10 and 29 which will provide tumour tissue. The remaining patients will undergo tumour core biopsies (see Study Procedures and Frequency section) with the option for any other tumour samples to be collected in the event a patient undergoes any surgical procedure whilst taking part in the study.<br>**Phase Ib**<br>The Phase Ib part of the study is to investigate efficacy in separate efficacy cohorts of patients with specific epithelial tumour types. It is anticipated that up to three cohorts of up to 20 patients will be included. An appropriately constituted committee (including representatives from the Sponsor and Investigators) will review any emerging signals and, considering also (1) previous clinical experience with enadenotucirev (the platform virus of NG-350A), (2) availability of eligible patients, (3) emerging data with other classes of therapies and (4) unmet need in the particular indication to make a recommendation as to which tumour types might be studied in the efficacy cohorts on the basis of overall assessment of risk: benefit.<br>If appropriate, one efficacy cohort may start after 10 patients in total have been treated in the safety expansion cohort. The remaining cohorts will start after the safety expansion cohort. |

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| | Patients will receive one cycle of treatment by IV infusion at the dose and dosing regimen selected for the safety expansion phase (after optimisation by the CRM if applicable).<br>**Phase Ia and Phase Ib**<br>In all parts of the study, patients will be screened in the 30 days before study treatment. Written informed consent for the study will be obtained before any study specific procedures are performed.<br>Eligible patients will then enter the study treatment period consisting of:<br>• For IT injection: a single dose of NG-350A monotherapy by IT injection and an end of study treatment visit on Day 57<br>• For IV infusion: one cycle of NG-350A monotherapy by IV infusion and an end of study treatment visit on Day 57<br>Tumour imaging using Magnetic Resonance Imaging (MRI) or computed tomography (CT) scans will be performed every 8 weeks (±3 days for the first scan, ±7 days thereafter) (and whenever disease progression is suspected) until disease progression, starting at the end of study treatment visit. Disease progression should be confirmed by a repeat scan after at least 4 weeks (and up to 8 weeks).<br>Patients will be followed-up at 8 week intervals until disease progression is confirmed. Patients will then be followed-up for overall survival, further cancer therapy and its best response and the date of disease progression on further cancer therapy (unless death or one of the criteria for study discontinuation is met, or the end of the study is reached, whichever occurs first). Follow-up after disease progression may be performed by telephone calls or at routine visits to the study centre. |
| Dose Escalation Procedures (Phase Ia dose escalation phase, IV only): | The DLT assessment period is defined as the time from the first dose until 28 days after the first dose of study treatment.<br>Note: to be evaluable for DLT, patients must have:<br>• Experienced a DLT during the DLT assessment period or<br>• Received all three planned doses of study treatment as required by the protocol and within the 7 day window<br>Patients who are not evaluable for DLT may be replaced.<br>In each dose escalation cohort, three patients will be initially enrolled and followed during the DLT assessment period. The first patient in each dose escalation cohort must be assessed for 14 days (until Day 15) before the next patient receives the first dose of study treatment in the same dose escalation cohort. The second and third patients should not start study treatment on the same day. Increasing to the next dose escalation cohort will depend on the safety findings of the previous dose escalation cohorts following either the "3+3" or CRM recommendations, as applicable. If a cohort has to expand to three more patients, then there must be a minimum of 7 days between each additional patient receiving their first dose.<br>**Definition of a DLT:**<br>A DLT is defined by any of the following adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 5 unless clearly related to the underlying disease:<br>• Grade 3 cytokine release syndrome lasting >12 hours with appropriate treatment or any ≥Grade 4 cytokine release syndrome<br>• Grade ≥3 non-haematological toxicity with the exception of: nausea, fatigue, headache and chills<br>• Grade ≥3 nausea, fatigue, headache and chills lasting >3 days*<br>• Grade 3 haematologic toxicities lasting >3 days* and Grade 4 haematological toxicities<br>*These events must be followed-up for up to 4 days after their onset for appropriate interpretation of their duration. In the absence of adequate follow-up, these toxicities will be reviewed by the SRC to ascertain if they are DLTs. |
| Duration of Study: | The end of the study is defined as the last patient last visit. The estimated duration of the study is 36 months.<br>Patients will participate until one of the pre-defined criteria for study treatment discontinuation or study discontinuation is met. A patient's minimum participation will be for 56 days (plus up |

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| | to 30 days for screening), they will then be followed-up until disease progression is confirmed and then further for overall survival, long-term well-being, further cancer therapy and the best response and date of disease progression on further cancer therapy. |
| Patient Numbers: | Up to 125 patients are expected to participate in the study (variations are possible if additional cohorts of patients are required or if patients not evaluable for DLT are replaced):<br>• Phase Ia:<br>– Up to 12 patients receiving NG-350A by IT injection (to include up to six patients undergoing surgical excision/resection)<br>– Up to 53 patients receiving NG-350A by IV infusion (up to 33 patients evaluable for DLT in the dose escalation cohorts and up to 20 patients in the safety expansion cohort to include up to six patients undergoing surgical excision/resection)<br>• Phase Ib: Up to 60 patients (up to three efficacy cohorts of up to 20 patients each, based upon tumour type) |
| Inclusion and Exclusion Criteria: | **Inclusion Criteria**<br>1. Provide written informed consent to participate<br>2. Males or females aged 18 years or over<br>3. Histologically or cytologically documented metastatic or advanced epithelial cancer (carcinoma or adenocarcinoma) that has relapsed from, or is refractory to, standard treatment, or for which no standard treatment is available<br>4. a) For patients undergoing surgical excision/resection:<br>• Excisable tumour/tumour lesion accessible for baseline biopsies and biopsies deemed safe by the Investigator<br>• Willing to consent for baseline biopsies and surgical procedure<br>• Patient able to undergo surgical procedure and appropriate anaesthesia<br>b) For patients not undergoing surgical excision/resection:<br>• Tumour accessible for biopsy and biopsies deemed safe by the Investigator<br>• Willing to consent to tumour biopsies at baseline and during the study<br>5. Safety expansion and efficacy cohorts only: at least one measurable site of disease according to RECIST criteria; this lesion must be either (i) outside a previously irradiated area or (ii) progressive if it is in a previously irradiated area (not applicable in patients undergoing surgical excision/resection if the lesion to be resected is the target lesion)<br>6. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1<br>7. Predicted life expectancy of 3 months or more<br>8. Ability to comply with study procedures in the Investigator's opinion<br>9. Recovered to Grade 1 from the effects (excluding alopecia) of any prior therapy for their malignancies<br>10. Non-impaired renal function<br>• Creatinine ≤1.5 mg/dL and estimated glomerular filtration rate (eGFR) using the Cockroft-Gault formula ≥60 mL/min/1.73m$^2$ (or measured creatinine clearance ≥60 mL/min)<br>• Urine dipstick for proteinuria at screening and baseline negative or trace. Patients may be included with results of 1+ if they have a spot urinary albumin: creatinine ratio (ACR) of either (i) ≤3 mg/mmol or (ii) >3 mg to <70 mg/mmol with a 24 hour urinary protein <0.2 g/24hours<br>• Serum complement components C3 and C4 above the lower limit of normal range<br>11. Adequate hepatic function:<br>• Serum bilirubin <1.5 mg/dL (except patients with Gilbert's syndrome who may have total bilirubin <3.0 mg/mL)<br>• Aspartate aminotransferase and alanine aminotransferase ≤3 x upper limit of normal<br>• Albumin ≥3 g/dL |

12. Adequate bone marrow function:
    - Absolute neutrophil count ≥1.5 x $10^9$/L
    - Platelets ≥100 x $10^9$/L
    - Haemoglobin ≥90 g/L (9 g/dL)
13. Prothrombin time and activated partial thromboplastin time within normal range or international normalised ratio ≤1.5, as appropriate
14. Meeting reproductive status requirements:
    - Females must not be pregnant or breastfeeding
    - Females of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotrophin [hCG]) within 24 hours before the first dose of study treatment
    - Females of childbearing potential must agree to use a highly effective method of contraception, for the duration of study treatment with NG-350A and 6 months following the last dose of study treatment. Females of childbearing potential who are continuously not heterosexually active are exempt from contraceptive requirements, but must still undergo pregnancy testing
    - Fertile males who are sexually active with females of childbearing potential must agree to follow instructions for method(s) of contraception, for the duration of study treatment with NG-350A and 6 months following the last dose of study treatment. In addition, males must be willing to refrain from sperm donation during this time. Azoospermic males are exempt from contraceptive requirements

**Exclusion Criteria**

1. Known history or evidence of significant immunodeficiency due to underlying illness (e.g. human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS]) and/or medication (e.g. systemic corticosteroids or other immunosuppressive medications, including cyclosporine, azathioprine, interferons in the 4 weeks before the first dose of study treatment). Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisolone equivalent) or other immunosuppressive medications within 14 days of the first dose of study treatment. Inhaled or topical steroids and adrenal replacement steroid doses are permitted in the absence of autoimmune disease
2. Splenectomy
3. Prior allogeneic or autologous bone marrow or organ transplantation
4. Active infections requiring antibiotics, physician monitoring or recurrent fevers (>38.0˚C) associated with a clinical diagnosis of active infection
5. Active viral disease or positive test for hepatitis B virus using hepatitis B surface antigen test or positive test for hepatitis C virus (HCV) using HCV ribonucleic acid (RNA) or HCV antibody test indicating acute or chronic infection. Positive test for HIV or AIDS; testing is not required in the absence of history
6. Use of the following antiviral agents: ribavirin, adefovir, lamivudine or cidofovir within 7 days prior to the first dose of study treatment; or pegylated interferon in the 14 days before the first dose of study treatment
7. Administration of an investigational drug in the 28 days, or six half-lives (whichever is longer) before the first dose of study treatment
8. Major surgery or treatment with any chemotherapy, radiation therapy, biologics for cancer or investigational therapy in the 28 days before the first dose of study treatment. All toxicities attributed to prior anti-cancer therapy other than alopecia must have resolved to Grade 1 or baseline before the first dose of study treatment. Patients with toxicities (other than renal toxicities) attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enrol
9. Other prior malignancy active within the previous 3 years except for local or organ confined early stage cancer that has been definitively treated with curative intent, does not require ongoing treatment, has no evidence of residual disease and has a negligible

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| | risk of recurrence and is therefore unlikely to interfere with the primary and secondary endpoints of the study, including response rate and safety<br>10. Symptomatic brain metastases or any leptomeningeal metastasis that is symptomatic and/or requires treatment. Patients with brain metastases are eligible if these have been locally treated (surgery, radiotherapy). There must also be no requirement for immunosuppressive doses of systemic corticosteroids (>10 mg/day prednisone equivalent) for at least 2 weeks before the first dose of study treatment<br>11. Any history of renal disease or renal injury or autoimmune disease. Patients with active, known or suspected auto-immune disease or a syndrome that requires systemic or immunosuppressive agents; patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune disease only requiring hormone replacement, psoriasis not requiring systemic treatment or conditions not expected to recur in the absence of an external trigger are permitted to enrol providing they comply with the other eligibility criteria relating to renal function<br>12. Any serious or uncontrolled medical disorder that, in the opinion of the Investigator or the Medical Monitor, may increase the risk associated with study participation or study treatment administration, impair the ability of the patient to receive protocol therapy or interfere with the interpretation of study results<br>13. History of coagulopathy, transient ischaemic attacks, cerebrovascular accidents or venous thromboembolism<br>14. Previous treatment with enadenotucirev or an anti-CD40 antibody<br>15. Known allergy to NG-350A transgene products or formulation<br>16. Any other medical or psychological condition that would preclude participation in the study or compromise ability to give informed consent |
| Study Treatments: | NG-350A is oncolytic adenoviral vector which, following replication in permissive tissues, expresses the Heavy and Light chain genes encoding a full length agonist anti-CD40 antibody of the immunoglobulin G2 (IgG2) isotype at the site of virus replication [redacted] NG-350A is derived from the Group B oncolytic platform virus enadenotucirev.<br>It is supplied frozen in stock vials containing 0.7 mL solution at a concentration of $2.0 \times 10^{12}$ viral particles (vp)/mL that is thawed and diluted to the required concentration prior to administration.<br>NG-350A will be administered by IT injection or IV infusion:<br>**IT Injection:**<br>Patients will receive a single dose of NG-350A by IT injection on Day 1. The dose given to each patient will be dependent on the size of the tumour lesion to be injected.<br>A 2 mL volume of the virus diluted to a concentration of $5 \times 10^{11}$ vp/mL will be loaded into a syringe or other injection device and repeated insertions of 100 µL to 200 µL made into injection sites approximately 0.5 cm to 1 cm apart, up to a total volume of 2 mL, depending on the size of the tumour lesion to be injected. Within each injection site there may be a single track or multiple tracks.<br>In patients with several lesions suitable for IT injection, the total volume of the diluted virus to be injected (2 mL) can be distributed over several lesions. The volume per lesion will depend on the individual lesion size e.g. a lesion of 2.5 cm longest diameter would allow up to five injections of 200 µL, approximately 0.5 cm apart, to a maximum of 1 mL for that lesion.<br>**IV Infusion:**<br>Patients will receive one cycle of study treatment with three IV infusions of NG-350A on Days 1, 3 and 5.<br>In Phase Ia, three dose escalation cohorts are planned, with an optional fourth dose escalation cohort. The starting dose in Dose Escalation Cohort 1 will be $1 \times 10^{11}$ vp infused over 5 minutes. It is anticipated the dose in Dose Escalation Cohort 2 will be escalated to $1 \times 10^{12}$ vp infused over 5 minutes. This will be confirmed by the SRC after Dose Escalation Cohort 1. The dose selected for Dose Escalation Cohort 3 and Dose Escalation Cohort 4 (optional) will be determined by the SRC based upon the results from the first two cohorts using the CRM model. |

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| | This may include investigation of a lower dose of NG-350A on Day 1 to that on Days 3 and 5 (e.g. a "Low-High-High" dosing regimen). The Day 1 dose will not exceed 3 x $10^{12}$ vp. The infusion duration will be altered in Dose Escalation Cohorts 3 and 4 to standardise the infusion rate of NG-350A to that in Dose Escalation Cohort 2 (2 x $10^{11}$ vp/min).<br>The results from the dose escalation cohorts will be used to determine the dose and dosing regimen for the safety expansion cohort.<br>The results from the safety expansion cohort will be used to determine the dose and dosing regimen for Phase Ib.<br>**All Patients:**<br>Patients will receive the following standard antipyretic prophylaxis pre-dose and post-dose on each NG-350A dosing day:<br>• ~1 hour pre-dose: 650 mg or 1 g oral acetaminophen/paracetamol (depending on local prescribing information). 100 mg IV hydrocortisone will also be given for IV patients only. Non-steroidal anti-inflammatory drugs (NSAIDs) may also be given to IT patients, if required<br>• 3 hours post-dose: 650 mg or 1 g oral acetaminophen/paracetamol. 100 mg IV hydrocortisone will also be given for IV patients only. NSAIDs may also be given to IT patients, if required<br>• Thereafter, paracetamol/acetaminophen (with NSAIDs if required) every 4 to 6 hours as indicated and following the prescribing information for the product(s)<br>Other medications, including diphenhydramine, may be used in line with the study centre's standard practice providing they are not excluded concomitant medications. |
| Study Procedures and Frequency: | Tumour assessments will be made using RECIST Version 1.1 and iRECIST. Depending on responses seen, a central review of all images may also be performed by an Independent Reviewer in addition to the local review by the Investigator.<br>Patients will be monitored for adverse events from informed consent until the end of study treatment visit (or 28 days after the last dose of study treatment, whichever is later). New study treatment related adverse events only will be recorded during the follow-up period. All serious or study treatment-related adverse events must be followed-up until they are resolved or until patient contact discontinues. Other safety assessments (physical examination and weight, vital signs, laboratory safety tests, 12-lead electrocardiograms [ECG] and ECOG performance status) will be performed at screening and on Days 1, 8, 15, 22 and 29 (plus Days 3 and 5 for IV treated patients only). Urinalysis will be performed weekly during the study treatment period. Urinalysis and assessment of ECOG will be further performed in the follow-up period until disease progression. Concomitant medications will be recorded throughout the study.<br>Blood samples for analysis of NG-350A concentration will be taken on Day 1 (pre-dose and post-dose), Day 15 and the end of study treatment visit for all patients and Days 3 and 5 (pre-dose and post-dose) for IV treated patients only. Blood samples for measurement of serum anti-NG-350A and anti-CD40 antibody titres will also be taken pre-dose on Day 1, Days 8, 15, 22 and 29 and the end of study treatment visit; additional, voluntary samples may also be taken in the follow-up period. Blood samples for analysis of plasma cytokine responses will be taken on Day 1 (pre-dose and 6 to 8 hours post-dose) and Days 8, 15, 22 and 29 and the end of study treatment visit for all patients and Days 3 and 5 (pre-dose and 6 to 8 hours post-dose) for IV treated patients only.<br>Tumour tissue samples will be taken to explore methodologies to detect virus replication, transgene expression and potential immune/inflammatory responses to those activities of NG-350A. Tumour core biopsies will be taken at baseline (any time between screening and pre-dose on Day 1) for all patients. For patients undergoing surgical excision/resection, excised/resected tumour tissue will then be collected either between Days 8 and 29 for IT treated patients or between Days 10 and 29 for IV treated patients. For patients not undergoing surgical excision/resection, further tumour core biopsies will be taken on Day 15 (required), Day 29 (optional) and the end of study treatment visit (required) (unless the patient has disease progression before the end of study treatment visit, then these biopsies should be taken at the time of progression).<br>In appropriate tumour types, samples will be taken for tumour specific serum biomarkers pre-dose on Day 1, Day 29 and the end of study treatment visit (unless the patient has disease |

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| | progression before the end of study treatment visit, then this sample should be taken at the time of progression); additional, voluntary samples may also be taken in the follow-up period.<br>Blood samples for immunophenotyping analysis will be taken pre-dose on Day 1, Day 15 and the end of study treatment visit from patients at selected centres. In addition, residual plasma, serum, blood, tissue or tumour samples used for the assessment of primary, secondary and exploratory objectives may be retained for additional research, except where prohibited by local laws or regulations.<br>Buccal and rectal swabs and urine samples to detect viral shedding will be taken pre-dose on Day 1, on Days 8, 15 and 29 and the end of study treatment visit. |
| Endpoints: | **Primary Endpoints**<br>Incidence of: adverse events, serious adverse events (SAEs), adverse events meeting protocol-defined DLT criteria, severe adverse events, adverse events leading to study treatment or study discontinuation, and adverse events resulting in death.<br>**Secondary Endpoints**<br>• Incidence of safety laboratory assessment abnormalities<br>• Incidence of abnormalities in vital signs or other clinical safety assessments<br>• Overall response rate, disease control rate, median duration of response, median progression free survival (PFS) and PFS rate at 8, 16 and 24 weeks (depending on indication) assessed by RECIST Version 1.1 and iRECIST<br>• Overall survival<br>• Blood concentrations of NG-350A<br>• Anti-NG-350A antibody titres<br>**Exploratory Endpoints**<br>• Anti-CD40 antibody titres<br>• Measurement of cytokine levels in blood<br>• Measurement of virus genomes in the tumour<br>• Measurement of virus genomes in buccal swabs, rectal swabs and urine samples<br>• Measurement of infectious virus in blood<br>• Summary measures of: prostate specific antigen (PSA), PSA doubling time, carcinoembryonic antigen, cancer antigen (CA)-125, CA19-9 (as appropriate)<br>• Identification of methods for future use |
| Statistical Methods and Analysis: | The CRM, guided by the escalation with the EWOC principle, will be implemented after the first three patients evaluable for DLT have been dosed in Dose Escalation Cohort 2. The CRM may also be implemented after 10 patients in the safety expansion cohort. The CRM will provide recommendations to the SRC who will make the ultimate decisions regarding dosing. A 2-parameter logistic regression model will be fitted to DLTs observed during the DLT assessment period (i.e. absence or presence of DLT) to model the dose-toxicity relationship combined with a prior to make dose recommendations. The prior used in the study is based on DLT data previously observed with enadenotucirev. The EWOC principle recommends that the next dose is the one with the highest posterior probability of DLT in the target interval (20%, 33%) among the doses fulfilling the overdose criterion that there is a 25% or lower chance of a ≥33% DLT rate.<br>Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA dictionary) and summarised by System Organ Class and preferred term and further by severity (according to NCI CTCAE Version 5.0) and relationship to study treatment using incidence tables for number of patients and number of events.<br>Other safety parameters will be analysed using descriptive statistics and shift tables. Laboratory safety test parameters will be converted to standard units and graded according to NCI CTCAE Version 5.<br>Time to event efficacy endpoints will be analysed using Kaplan-Meier survival models. Other endpoints will be summarised using incidence tables. Response-based endpoints (and the derived PFS endpoint) will be based on the Investigator's assessments (and also on the |

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| | Independent Reviewer's assessments if applicable). Efficacy analysis will be performed on the full analysis set and a per protocol set analysis may also be performed.<br>Pharmacokinetic, pharmacodynamic and exploratory data will be analysed descriptively. |

# ABBREVIATIONS AND DEFINITIONS OF TERMS

## List of Abbreviations

| ABBREVIATION | DEFINITION |
|---|---|
| ACR | Albumin: Creatinine Ratio |
| Ad11p/Ad3 | Adenovirus 11p/3 |
| AIDS | Acquired Immunodeficiency Syndrome |
| ALT | Alanine Aminotransferase |
| AST | Aspartate Aminotransferase |
| CA | Cancer Antigen |
| CD | Cluster of Differentiation |
| CEA | Carcinoembryonic Antigen |
| CFR | Code of Federal Regulations |
| iCPD | Confirmed Progression assigned using iRECIST |
| CRM | Continual Reassessment Method |
| CT | Computed Tomography (scan) |
| DCR | Disease Control Rate |
| DOR | Duration of Response |
| DLT | Dose Limiting Toxicity |
| DNA | Deoxyribonucleic Acid |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| eCRF | Electronic Case Report Form |
| eGFR | Estimated Glomerular Filtration Rate |
| EU | European Union |
| EWOC | Overdose Control |
| FDA | Food and Drug Administration |
| FSH | Follicle Stimulating Hormone |
| GCP | Good Clinical Practice |
| hCG | human Chorionic Gonadotrophin |
| HCV | Hepatitis C Virus |
| HIV | Human Immunodeficiency Virus |
| ICH | International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IEC | Independent Ethics Committee |
| IL | Interleukin |
| IND | Investigational New Drug |
| IP | Intraperitoneal |
| IRB | Institutional Review Board |
| iRECIST | immune Response Evaluation Criteria in Solid Tumours |
| IT | Intratumoural |
| iUPD | Unconfirmed progression assigned using iRECIST |
| IV | Intravenous |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic Resonance Imaging |
| MTD | Maximum Tolerated Dose |
| NCI CTCAE | National Cancer Institute Common Terminology Criteria for Adverse Events |

| ABBREVIATION | DEFINITION |
|---|---|
| NSAID | Non-steroidal Anti-inflammatory Drug |
| ORR | Overall Response Rate |
| PD-1 | Programmed Death 1 |
| PET | Positron Emission Tomography |
| PFS | Progression Free Survival |
| PSA | Prostate Specific Antigen |
| qPCR | quantitative Polymerase Chain Reaction |
| RECIST | Response Evaluation Criteria in Solid Tumours |
| RNA | Ribonucleic Acid |
| SAE | Serious Adverse Event |
| SAS | Statistical Analysis Software |
| SOC | System Organ Class |
| SRC | Safety Review Committee |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TEAE | Treatment Emergent Adverse Event |
| US | United States |
| vp | Viral Particles |

**Definition of Terms**

Adverse event related terms are defined in Section 9.1.1. Efficacy-related definitions are provided in Section 11.2.3.3, Appendix 1 and Appendix 2.

# 1 SCHEDULES OF ASSESSMENTS

The schedule of assessments at each visit are shown in Table 1 for patients receiving intratumoural (IT) injection and in Table 2 for patients receiving intravenous (IV) infusion.

## Table 1 Overall Schedule of Assessments at Each Study Visit: IT Injection

| | Screen | Study Treatment Period | | | | | | | | | Follow-Up Period[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | <30 days | Day 1 | | | Day 8 (±1 day) | Day 15 (±1 day) | Day 22 (±1 day) | Day 29 (±1 day) | Days 36, 43, 50 (±1 day) | End of Study Treatment Visit Day 57 (±3) days | Every 8 weeks (±7 days) |
| | | Pre-dose | Dose | Post-dose[b] | | | | | | | |
| **Baseline documentation** | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | |
| Demographic data, including height | X | | | | | | | | | | |
| Cancer history and therapies | X | | | | | | | | | | |
| Medical history and prior medications | X | | | | | | | | | | |
| Urine/serum pregnancy test | | X[c] | | | | | | | | X | |
| Eligibility criteria check | X | X | | | | | | | | | |
| **Treatment administration** | | | | | | | | | | | |
| Prophylactic treatment | | X[d] | | X[d] | | | | | | | |
| Dose NG-350A | | | X | | | | | | | | |
| **Safety assessments** | | | | | | | | | | | |
| *Clinical safety assessments:* | | | | | | | | | | | |
| Adverse events | Continuous[e] | | | | | | | | | | |
| Vital signs | X | X | | X[f] | X | X | X | X | | X | |
| Physical examination and weight | X | X | | | X | X | X | X | | X | |
| 12-lead ECG | X | X | | | X | X | X | X | | X | |
| ECOG performance status | X | X | | | X | X | X | X | | X | X (until DP) |
| *Laboratory safety assessments:* | | | | | | | | | | | |
| Serum chemistry | X | X[g] | | | X | X | X | X | | X | |
| Haematology | X | X[g] | | | X | X | X | X | | X | |
| Coagulation profile | X | X[g] | | | X | X | X | X | | X | |
| Urinalysis[h] | X | X[g] | | | X | X | X | X | X[i] | X | X (until DP) |
| Complement C3/C4 | X | X[g] | | | X | X | X | X | | X | |
| Thyroid function test | | X[g] | | | | | | | | X | |
| **Efficacy assessments** | | | | | | | | | | | |
| Tumour imaging (RECIST, iRECIST)[j] | X | | | | | | | | | X | X (until DP) |
| OS and further therapies | | | | | | | | | | | X (after DP) |
| **Pharmacodynamic and exploratory assessments** | | | | | | | | | | | |
| NG-350A pharmacokinetics | | X | | X | | X | | | | X | |
| Anti-NG-350A and anti-CD40 antibodies | | X | | | X | X | X | X | | X | (X)[k] (until DP) |
| Immunophenotyping (at selected centres) | | X | | | | X | | | | X | |

| | Screen | Study Treatment Period | | | | | | | | | Follow-Up Period[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | <30 days | Day 1 | | | Day 8 (±1 day) | Day 15 (±1 day) | Day 22 (±1 day) | Day 29 (±1 day) | Days 36, 43, 50 (±1 day) | End of Study Treatment Visit Day 57 (±3) days | Every 8 weeks (±7 days) |
| | | Pre-dose | Dose | Post-dose[b] | | | | | | | |
| Cytokines | | X | | X[l] | X | X | X | X | | X | |
| Buccal, rectal and urine shedding | | X | | | X | X | | X | | X | |
| Tumour biopsies[m] | X (baseline)[n] | | | | | X[o] | | X[o] | | X[o] | |
| Surgical excision/resection of tumour | | | | | X[p] | | | | | | |
| Tumour specific serum biomarkers[q] | | X | | | | | | X | | X | (X)[k] (until DP) |
| **Other Clinical Assessments** | | | | | | | | | | | |
| Concomitant Medications | | Continuous[r] | | | | | | | | | |

Abbreviations: ACR=albumin: creatinine ratio; CA=cancer antigen; CD=cluster of differentiation; CEA=carcinoembryonic antigen; DP=disease progression; ECG=electrocardiogram; ECOG=Eastern Co-operative Oncology Group; eGFR=estimated glomerular filtration rate; NSAID=non-steroidal anti-inflammatory drugs; iRECIST= immune Response Evaluation Criteria in Solid Tumours; IT=intratumoural; OS=overall survival; PSA=prostate specific antigen

Note: Clinical progression/deterioration of disease will be assessed throughout the study.

[a] Patients will be followed-up until disease progression is confirmed. Patients will then be followed-up for overall survival, further cancer therapy and its best response and the date of disease progression on further cancer therapy (unless death or one of the criteria for study discontinuation is met, or the end of the study is reached, whichever occurs first). Follow-up after disease progression may be performed by telephone calls or at routine visits to the hospital.

[b] Post-dose assessments times are in relation to the end time of dosing. Assessments are immediately after the end of IT injection (±5 minutes), unless stated otherwise.

[c] In women of childbearing potential in the 24 hours before the first dose of study treatment.

[d] Patients will receive 650 mg or 1 g oral acetaminophen/paracetamol (depending on local prescribing information), with NSAIDs if required, 1 hour pre-dose and 3 hours post-dose for antipyretic prophylaxis. Thereafter paracetamol/acetaminophen (with NSAIDs if required) after every 4 to 6 hours as indicated and following the prescribing information for the product(s).

[e] Patients will be monitored for adverse events from informed consent until the end of study treatment visit or 28 days after the last dose of study treatment, whichever is later. New study treatment-related adverse events only will be recorded during the follow-up period. All serious or study treatment-related adverse events must be followed-up until they are resolved or until patient contact discontinues.

[f] Performed immediately after the end of the injection (± 5 minutes) and 30 minutes (± 5 minutes), 1 hour (±10 minutes), 4 hours (±30 minutes) and 8 hours (± 1 hour) post-dose.

[g] All results must be available before study treatment is started. A window of 24 hours is permitted on these samples to allow availability of results before dosing.

[h] Urinalysis: dipstick for leukocytes, blood, protein to be performed within 24 hours before study treatment administration on Day 1 and weekly thereafter. Any urinalysis results that are positive for proteinuria must be confirmed by repeat testing and further quantification by ACR of either (i) ≤3 mg/mmol or (ii) >3 mg and <70 mg/mmol with a 24 hour urinary protein <0.2 g/24hours. Positive results that have not worsened since the previous visit do not need to be confirmed and quantified. If ACR >3 mg/mmol or 24 hour urinary protein ≥0.2gm/24 hours or there is a decline in eGFR or consumption of complement (C3/C4 proteins) then the Sponsor must be contacted and the following two step process should be performed: Full renal work-up, including examination of urine sediment, then commence high dose corticosteroids and then, if further decline, renal biopsy, followed by plasmapheresis. The use of anti-viral agents in this scenario is not recommended. Cases of treatment-emergent positive proteinuria (≥1+ when negative or trace at baseline) or worsening treatment-emergent proteinuria (when positive at baseline) must be followed until resolution if still present at the end of study treatment visit.

[i] May be performed in the clinic or at home and the results reported to the study centre. **Results positive for proteinuria should be followed-up as above.**

[j] Post-dose scans will be performed every 8 weeks (±3 days for the first scan, ±7 days thereafter) from the first dose of NG-350A. Local assessments will be performed by the Investigator (central assessments by an Independent Reviewer may be performed). Suspected disease progression must be confirmed by a second scan performed at least 4 weeks (and up to 8 weeks) later. Post-excision scans will only be performed in patients undergoing surgical excision/resection where this is appropriate.

[k] Additional, voluntary samples may be taken during the follow-up period.

[l] At 6 to 8 hours post-dose.

| | Screen | Study Treatment Period | | | | | | | | Follow-Up Period[a] |
|---|---|---|---|---|---|---|---|---|---|---|
| | <30 days | Day 1 | | | Day 8 (±1 day) | Day 15 (±1 day) | Day 22 (±1 day) | Day 29 (±1 day) | Days 36, 43, 50 (±1 day) | End of Study Treatment Visit Day 57 (±3) days | Every 8 weeks (±7 days) |
| | | Pre-dose | Dose | Post-dose[b] | | | | | | | |

[m] All biopsies will only be taken if the clinical risk is deemed acceptable (as judged by the Investigator based upon the patient's health at the time of the visit). At each timepoint, every effort should be made to obtain five cores; at least two cores must be obtained.

[n] Taken for all patients (required). May be taken at any time between screening (after eligibility has been confirmed) and Day 1 pre-dose. For patients undergoing surgical excision/resection, the baseline biopsies must be taken from the tumour to be excised.

[o] For patients not undergoing non-surgical excision/resection only: Post-dose biopsies will be taken on Day 15 (required), Day 29 (optional) and the end of study treatment visit (required). If the patient has disease progression before the end of study treatment visit, then the end of treatment visit biopsies should instead be taken at the time of progression. Biopsies should be taken from the same regions of tumour that were IT injected where feasible.

[p] For patients undergoing surgical excision/resection only - may be performed any time between Days 8 and 29.

[q] PSA for prostate cancer, CEA for colorectal cancer, CA-125 for ovarian cancer and CA19-9 for pancreatic cancer. If the patient has disease progression before the end of study treatment visit, then the end of treatment visit samples should instead be taken at the time of progression.

[r] Only medications administered to treat study treatment-related-adverse events should be recorded during the follow-up period. This information may be collected by telephone.

## Table 2 Overall Schedule of Assessments at Each Study Visit: IV Infusion

| | Screen | Study Treatment Period | | | | | | | | | | Days 36, 43, 50 (±1 day) | End of Study Treatment Visit Day 57 (±3) days | Follow-Up Period[a] Every 8 weeks (±7 days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <30 days | Day 1 | | | Days 3 and 5 (±1 day) | | | Day 8 (±1 day) | Day 15 (±1 day) | Day 22 (±1 day) | Day 29 (±1 day) | | | |
| | | Pre-dose | Dose | Post-dose[b] | Pre-dose | Dose | Post-dose[b] | | | | | | | |
| **Baseline documentation** | | | | | | | | | | | | | | |
| Informed consent | X | | | | | | | | | | | | | |
| Demographic data including height | X | | | | | | | | | | | | | |
| Cancer history and therapies | X | | | | | | | | | | | | | |
| Medical history and prior medications | X | | | | | | | | | | | | | |
| Urine/serum pregnancy test | | X[c] | | | | | | | | | | | X | |
| Eligibility criteria check | X | X | | | | | | | | | | | | |
| **Treatment administration** | | | | | | | | | | | | | | |
| Prophylactic treatment | | X[d] | | X[d] | X[d] | | X[d] | | | | | | | |
| Dose NG-350A | | | X | | | X[e] | | | | | | | | |
| **Safety assessments** | | | | | | | | | | | | | | |
| *Clinical safety assessments:* | | | | | | | | | | | | | | |
| Adverse events | Continuous[f] | | | | | | | | | | | | | |
| Vital signs | X | X | | X[g] | X | | X[g] | X | X | X | X | | X | |
| Physical examination and weight | X | X | | | X | | | X | X | X | X | | X | |
| 12-lead ECG | X | X | | | X | | | X | X | X | X | | X | |
| ECOG performance status | X | X | | | X | | | X | X | X | X | | X | X (until DP) |
| *Laboratory safety assessments:* | | | | | | | | | | | | | | |
| Serum chemistry | X | X[h] | | | X[i] | | | X | X | X | X | | X | |
| Haematology | X | X[h] | | | X | | | X | X | X | X | | X | |
| Coagulation profile | X | X[h] | | | X | | | X | X | X | X | | X | |
| Urinalysis[j] | X | X[h] | | | X[i] | | | X | X | X | X | X[k] | X | X (until DP) |
| Complement C3/C4 | X | X[h] | | | X | | | X | X | X | X | | X | |
| Thyroid function test | | X[h] | | | | | | | | | | | X | |
| **Efficacy assessments** | | | | | | | | | | | | | | |
| Tumour imaging (RECIST, iRECIST)[k] | X | | | | | | | | | | | | X | X |
| OS and further therapies | | | | | | | | | | | | | | X (after DP) |
| **Pharmacodynamic and exploratory assessments** | | | | | | | | | | | | | | |
| NG-350A pharmacokinetics | | X | | X | X | | X | | X | | | | X | |
| Anti-NG-350A and anti-CD40 | | X | | | | | | X | X | X | X | | X | (X)[m] (until DP) |

| | Screen | Study Treatment Period | | | | | | | | | | Days 36, 43, 50 (±1 day) | End of Study Treatment Visit Day 57 (±3) days | Follow-Up Period[a] Every 8 weeks (±7 days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <30 days | Day 1 | | | Days 3 and 5 (±1 day) | | | Day 8 (±1 day) | Day 15 (±1 day) | Day 22 (±1 day) | Day 29 (±1 day) | | | |
| | | Pre-dose | Dose | Post-dose[b] | Pre-dose | Dose | Post-dose[b] | | | | | | | |
| antibodies | | | | | | | | | | | | | | |
| Immunophenotyping (at selected centres) | | X | | | | | | | X | | | | X | |
| Cytokines | | X | | X[n] | X | | X[n] | X | X | X | X | | X | |
| Buccal, rectal and urine shedding | | X | | | | | | X | X | | X | | X | |
| Tumour biopsies[o] | X (baseline)[p] | | | | | | | | X[q] | | X | | | X [q] |
| Surgical excision/resection of tumour | | | | | | | | X[r] | | | | | | |
| Tumour specific serum biomarkers[s] | | X | | | | | | | | | X | | X | (X)[m] (until DP) |
| **Other Clinical Assessments** | | | | | | | | | | | | | | |
| Concomitant Medications | | Continuous[t] | | | | | | | | | | | | |

Abbreviations: ACR=albumin: creatinine ratio; CA=cancer antigen; CD=cluster of differentiation; CEA=carcinoembryonic antigen; DP=disease progression; ECG=electrocardiogram; ECOG=Eastern Co-operative Oncology Group; eGFR=estimated glomerular filtration rate; NSAID=non-steroidal anti-inflammatory drugs; RECIST=Response Evaluation Criteria in Solid Tumours; iRECIST=immune Response Evaluation Criteria in Solid Tumours; IV=intravenous; OS=overall survival; PSA=prostate specific antigen

Note: Clinical progression/deterioration of disease will be assessed throughout the study.

[a] Patients will be followed-up until disease progression is confirmed. Patients will then be followed-up for overall survival, further cancer therapy and its best response and the date of disease progression on further cancer therapy (unless death or one of the criteria for study discontinuation is met, or the end of the study is reached, whichever occurs first). Follow-up after disease progression may be performed by telephone calls or at routine visits to the hospital.

[b] Post-dose assessments times are in relation to the end time of the infusion. Assessments are immediately after the end of infusion (±5 minutes), unless stated otherwise.

[c] In women of childbearing potential in the 24 hours before the first dose of study treatment.

[d] Patients will receive 650 mg or 1 g oral acetaminophen/paracetamol (depending on local prescribing information) and 100 mg IV hydrocortisone 1 hour pre-dose and 3 hours post-dose as antipyretic prophylaxis. Thereafter, paracetamol/acetaminophen (with NSAIDs if required) every 4 to 6 hours as indicated and following the prescribing information for the product(s). Other medications, including diphenhydramine, may be used in line with the study centre's standard practice providing they are not excluded concomitant medications.

[e] The second and third doses of NG-350A on Day 3 and Day 5 must be administered within 7 days of Day 1, doses may not be given on consecutive days. Some cohorts may have a higher dose at these time points than on Day 1.

[f] Patients will be monitored for adverse events from informed consent until the end of study treatment visit or 28 days after the last dose of study treatment, whichever is later. New study treatment related adverse events only will be recorded during the follow-up period. All serious or study treatment-related adverse events must be followed-up until they are resolved or until patient contact discontinues.

[g] Performed immediately after the end of the infusion and 30 minutes (± 5 minutes), 1 hour (±10 minutes), 4 hours (±30 minutes) and 8 hours (± 1 hour) post-dose. The 8 hour assessment is required on Day 1 but is optional on Days 3 and 5 providing the patient is well (otherwise it is still required).

[h] All results for the Day 1 pre-dose samples must be available before study treatment in that cycle is started. A window of 24 hours is permitted on these samples to allow availability of results before dosing.

[i] The urinalysis and serum creatinine results must be available before study treatment administration on Days 3 and 5. A window of -24 hours is permitted on these samples to allow availability of results before dosing.

[j] Urinalysis: dipstick for leukocytes, blood, protein to be performed within 24 hours before study treatment administration on Day 1 and weekly thereafter. Any urinalysis results that are positive for proteinuria must be confirmed by repeat testing and further quantification by ACR of either (i) ≤3 mg/mmol or (ii) >3 mg and <70 mg/mmol with a 24 hour urinary protein <0.2 g/24hours. Positive results that have not worsened

| | Screen | Study Treatment Period | | | | | | | | | Days 36, 43, 50 (±1 day) | End of Study Treatment Visit Day 57 (±3) days | Follow-Up Period[a] Every 8 weeks (±7 days) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | <30 days | Day 1 | | | Days 3 and 5 (±1 day) | | | Day 8 (±1 day) | Day 15 (±1 day) | Day 22 (±1 day) | Day 29 (±1 day) | | | |
| | | Pre-dose | Dose | Post-dose[b] | Pre-dose | Dose | Post-dose[b] | | | | | | | |

since the previous visit do not need to be confirmed and quantified. If ACR >3 mg/mmol or 24 hour urinary protein ≥0.2gm/24 hours or there is a decline in eGFR or consumption of complement (C3/C4 proteins) then the Sponsor must be contacted and the following two step process should be performed: Full renal work-up, including examination of urine sediment, then commence high dose corticosteroids and then, if further decline, renal biopsy, followed by plasmapheresis. The use of anti-viral agents in this scenario is not recommended. Cases of treatment-emergent positive proteinuria (≥1+ when negative or trace at baseline) or worsening treatment-emergent proteinuria (when positive at baseline) must be followed until resolution if still present at the end of study treatment visit.

[k] May be performed in the clinic or at home and the results reported to the study centre. **Results positive for proteinuria should be followed-up as above.**

[l] The screening scan may be performed any time in the 30 days before the first dose of NG-350A. Post-dose scans will be performed every 8 weeks (±3 days for the first scan, ±7 days thereafter) from the first dose of NG-350A. Local assessments by the Investigator will be performed (and central assessments by an Independent Reviewer may also be performed). Suspected disease progression must be confirmed by a second scan performed at least 4 weeks (and up to 8 weeks) later. Post-excision scans will only be performed in patients undergoing surgical excision/resection where this is appropriate.

[m] Additional, voluntary samples may be taken during the follow-up period.

[n] At 6 to 8 hours post-dose.

[o] All biopsies will only be taken if the clinical risk is deemed acceptable (as judged by the Investigator based upon the patient's health at the time of the visit). At each timepoint, every effort should be made to obtain five cores; at least two cores must be obtained.

[p] Taken for all patients (required). May be taken at any time between screening (after eligibility has been confirmed) and Day 1 pre-dose. For patients undergoing surgical excision/resection, the baseline biopsies must be taken from the tumour to be excised.

[q] For patients not undergoing-surgical excision/resection only: Post-dose biopsies will be taken on Day 15 (required), Day 29 (optional) and the end of study treatment visit (required). If the patient has disease progression before the end of study treatment visit, then the end of treatment visit biopsies should instead be taken at the time of progression.

[r] For patients undergoing surgical excision/resection only - may be performed any time between Days 10 and 29.

[s] PSA for prostate cancer, CEA for colorectal cancer, CA-125 for ovarian cancer and CA19-9 for pancreatic cancer. If the patient has disease progression before the end of study treatment visit, then the end of study treatment visit samples should instead be taken at the time of progression.

[t] Only medications administered to treat study treatment-related-adverse events should be recorded during the follow-up period. This information may be collected by telephone.

# 2 BACKGROUND

There were an estimated 18 million cancer cases worldwide in 2018[1]. There is therefore a clinical need for new and improved therapies. Understanding of tumour immunology has increased dramatically over recent years, which has led to the development of immunotherapy agents meeting areas of previously unmet need.

Oncolytic viruses are a form of immunotherapy that kill tumour cells by a direct lysis that stimulates the immune system which can, in turn, directly kill uninfected tumour cells and stimulate immune inflammation within the tumour microenvironment. Oncolytic viruses can also be genetically modified to encode therapeutic proteins that complement the viruses' oncolytic and immune-stimulatory mechanisms of action.

PsiOxus Therapeutics has developed the oncolytic platform virus enadenotucirev. Humans are the only permissive species for enadenotucirev. Enadenotucirev is active against cell lines derived from a range of epithelial tumours but shows limited activity on normal cells and is inactive against cell lines derived from non-epithelial origins including glioblastoma, leukaemia, melanoma and neuroendocrine tumours.

Enadenotucirev is an adenovirus type 11p/adenovirus type 3 (Ad11p/Ad3) chimeric Group B adenovirus with deletions in the E3 and E4 regions. The loss of genes in the E3 region has been shown in Group B adenoviruses to enhance viral induced cell lysis and virus replication. E3 genes are often removed as a safety feature and to make space for transgenes in gene therapy vectors. The enadenotucirev virus itself does not contain transgenes, however modified variants of enadenotucirev are now being developed with transgenes inserted in a non-coding region located downstream of the virus major late promoter. This design allows the functional properties of enadenotucirev to be fully retained (e.g. replication, tumour selectivity, oncolytic potency) and ensures that the transgene-encoded proteins are only expressed after virus replication has begun. The transgene proteins do not form part of the external virus particle structure.

Cluster of Differentiation (CD)40 is a tumour necrosis factor superfamily member expressed on antigen presenting cells, including dendritic cells, B cells, and monocytes, as well as on a wide range of tumours [2, 3, 4]. CD40 targeting may directly and indirectly affect tumour growth, therefore it has become a promising therapeutic target for cancer immunotherapy. NG-350A is an oncolytic adenoviral vector that has a transgene for an agonist anti-CD40 antibody inserted in the non-coding region of enadenotucirev. In summary, NG-350A is designed to promote anti-tumour responses selectively within tumour tissues via two distinct mechanisms:

- Firstly, the oncolytic properties of the virus lead to direct immunogenic death of tumour cells, providing tumour cell antigens and activation of innate immune cell responses within the tumour and associated lymphoid tissues. Enadenotucirev itself can also directly activate such innate responses via its binding to CD46 in innate immune cells such as dendritic cells
- Secondly, the transgene encoded antibody can interact with its target protein on multiple immune cells within the tumour microenvironment enhancing their activation and subsequent tumoricidal responses.

The mechanism of action is more fully described in the Investigator's Brochure [5].

The relative structures of Ad11, enadenotucirev and NG-350A are shown in Figure 1.

[redacted]

While NG-350A has not been administered to humans, prior clinical experience has been obtained for both enadenotucirev and multiple agonistic anti-CD40 antibodies including selicrelumab. [redacted]

- Enadenotucirev is currently in clinical development. A total of 135 patients have received enadenotucirev either as a monotherapy or in combination with a Programmed Death 1 (PD-1) inhibitor or paclitaxel, including 113 by IV infusion. An IV dose and dosing regimen and has been established that is tolerated. Since NG-350A is identical in virus structure and has the same method of delivery as enadenotucirev, it is anticipated that potential adverse events related directly to the viral particle infusion and the oncolytic effects on tumour or normal tissues would be similar with enadenotucirev and NG 350A. Findings with IV infusion of enadenotucirev can be summarised as follows:
  - IV administration is feasible and delivers replicating virus to tumours [6]
  - CD8+ cells have been demonstrated in microsatellite instability-low tumours post-dose
  - Viral kinetic data suggest enadenotucirev has a half-life of 17 minutes. No infectious virus was detected in blood samples later than 48 hours after dosing
  - Anti-virus antibodies have been measured in the majority of patients and levels increase over ~21 days after the first dose then plateau irrespective of whether a patient receives one or repeated cycles of treatment
  - Live virus is still detectable in blood in the presence of antibodies at plateau level (Day 1 of Cycle 2)

- Shedding data has indicated a positive signal by quantitative polymerase chain reaction (qPCR) analysis from rectal and buccal swabs and urine samples with little evidence for long-term shedding after dosing. However, the analysis cannot discriminate between infectious virus and inactive virus or fragments of viral deoxyribonucleic acid (DNA)
- Monotherapy anti-tumour efficacy has not been established
- Cytokine studies are consistent with initial activation of, and removal of virus by, Kupffer cells. Tolerability is primarily determined by dosing on Day 1 of Cycle 1 [7]. The maximum tolerated dose (MTD) was considered to be $3 \times 10^{12}$ viral particles (vp). At this dose, the majority of patients experience adverse events of an inflammatory nature particularly pyrexia and chills which have onset within 24 hours of dosing. The frequency of these type of events is lower after subsequent doses and appear to reflect the cytokine responses to treatment. The initial doses of virus may down-regulate the Kupffer cell clearance, decreasing toxicity and improving circulation for the subsequent doses [7]. This is supported by recent non-clinical data (see Section 6.8.1.2). Alternative dosing regimens, whereby a lower dose is given on Day 1 compared to subsequent doses are being included in ongoing study ColoAd1-1003 and, based on the outcome, may be included in the current study
- Serious adverse events (SAEs) were reported in about a third of patients. The majority of the SAEs were single cases
- There were seven patients with of obstruction of the intestines (reported as intestinal obstruction, small intestinal obstruction and gastrointestinal obstruction), six of which were SAEs. These events were considered unrelated to treatment in five patients. The other two patients had early event onset after dosing but also had other pre-disposing conditions, such as a history of abdominal surgery, although the obstruction could also be explained by tumour flare
- Other SAEs occurring in more than one patient were hypoxia, pyrexia and dyspnoea in three, three and two patients, respectively
- Two SAEs relating to renal injury were reported in Study ColoAd1-1001: National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) Grade 2 glomerulonephritis membranoproliferative at a dose of $6 \times 10^{12}$ vp and CTCAE Grade 3 nephrotic syndrome at a dose of $3 \times 10^{12}$ vp. Review of the available data from the 61 patients treated in this study appears to indicate two separate time periods following enadenotucirev administration when there are discernible effects on renal function (although the majority of these are noted to not have been considered of clinical significance or reported as adverse events). The first period follows dosing (on Days 1, 3 and 5) where proteinuria, reduction in albumin, reduction in blood pressure and reduced renal function are likely to be related to cytokine-mediated vascular leakage, in turn recovering over time. In the second period, similar findings occur around Day 21 onwards, again, in most cases, resolving over time. The latter do not to appear to be related to dose or dosing regimen

A further Dose Limiting Toxicity (DLT) of Grade 4 acute renal injury has also been seen in a single patient with Stage IV colon cancer in the ongoing study with enadenotucirev and nivolumab (Study ColoAd1-1003). The patient presented with clinical symptoms from around Day 21 with marked decline in renal function by Day 28 and required long term dialysis; the patient subsequently died from disease progression. Although the patient met the eligibility criteria for study entry (with adequate renal function), he had a past history of

methotrexate-related renal injury and chronic kidney disease that was not documented at study entry.

Selicrelumab has been administered to over 100 patients in clinical studies either as a monotherapy or in combination with chemotherapy, with some encouraging efficacy [8, 9]. To date, systemic toxicity associated with broad CD40 activation has limited dosing with anti-CD40 antibodies [10, 11]. A range of dose-dependent non-clinical and clinical toxicities have been observed, including cytokine release syndrome, autoimmune reactions, thromboembolic syndromes, hyperimmune stimulation leading to activation-induced cell death or tolerance, proangiogenesis, hepatotoxicity, ocular inflammation, acute renal failure and immunosuppression. Since the NG-350A anti-CD40 antibody is expressed at the site of virus replication within the tumour, it is expected that this would avoid many of the adverse events associated with systemic exposure seen with anti CD40 antibody therapies to date. Projections based on data from human tumour xenograft studies of NG-350A dosing in mice indicate that levels are likely to be at least 100-fold lower than those achieved by systemic dosing of agonist anti-CD40 antibodies (at MTD levels) to patients (PsiOxus, data on file). While there may be some drainage of anti-CD40 antibody into the systemic circulation, it is expected that this will be minimal and systemic exposure will be significantly lower than the established maximum tolerated dose for selicrelumab when administered by IV infusion that selectively replicates in human carcinoma cells with only very limited or no replication in normal (non-cancerous) human cells. In preclinical models, anti-CD40 antibodies used as a locally-delivered monotherapy [12, 13, 14] can have improved efficacy with fewer side effects compared to systemic administration.

Further information is provided in the Investigator's Brochure [5].

## 2.1 Rationale for the Study

Oncolytic viruses encoding immunomodulatory transgenes represent a unique single agent approach to the targeted delivery of immunomodulatory drugs to tumours. NG-350A is oncolytic adenoviral vector which expresses a full length agonist anti-CD40 antibody. NG-350A is derived from the Group B oncolytic platform virus enadenotucirev.

In preclinical studies, NG-350A was indistinguishable compared to enadenotucirev, in regard to virus related activities, including viral particle and virus replication mediated effects. Anti-CD40 antibody expression was demonstrated in tumour cells and antibody could also be detected in tumour cell supernatants post-inoculation. Elevated levels of activation markers and cytokine release was demonstrated in monocyte-derived dendritic cells treated with the supernatant in a dose dependent manner. Both single and repeat dose in vivo studies were conducted which demonstrated that the induction of inflammatory cytokines, and elevation of alanine aminotransferase (ALT) levels were indistinguishable between NG-350A and enadenotucirev which were attenuated with doses after the first dose. When human primary cells isolated from healthy tissue were inoculated with NG-350A and enadenotucirev, no biologically significant change in NG-350A selectivity was observed compared to enadenotucirev. NG-350A transgene messenger ribonucleic acid (RNA) was not detected in the majority of primary cells evaluated and where low levels were observed, these did not translate to the production of detectable transgene protein. In summary, the nonclinical efficacy and safety data demonstrated that NG-350A has a favourable safety profile that can support evaluation in this first clinical study.

Since NG-350A has identical virus structure to enadenotucirev, the clinical safety and tolerability experience with enadenotucirev to date is relevant and supports this first clinical

study with NG-350A. Given the similarity of the virus and the method of delivery it is anticipated that the acute tolerability of NG-350A will be similar to that of enadenotucirev.

Since NG-350A drives anti-CD40 antibody production in the tumour it is unlikely to generate circulating levels as high as achieved by systemic administration and it is expected that this would avoid many of the adverse events associated with systemic exposure seen with anti-CD40 antibody therapies to date.

The current study will evaluate the safety, tolerability and preliminary efficacy and also pharmacokinetics, immunogenicity and other pharmacodynamic effects to elucidate the mechanism of action of NG-350A in patients with advanced or metastatic epithelial tumours.

# 3 STUDY OBJECTIVES

## 3.1 Primary Objective

- To characterise the safety and tolerability of NG-350A in patients with metastatic or advanced epithelial tumours.

## 3.2 Secondary Objectives

- To determine the recommended dose of NG-350A for further development in patients with metastatic or advanced epithelial tumours
- To explore the preliminary anti-tumour activity of NG-350A in patients with metastatic or advanced epithelial tumours using Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1 and immune Response Evaluation Criteria in Solid Tumours (iRECIST)
- To assess the pharmacokinetics and immunogenicity of NG-350A

## 3.3 Exploratory Objectives

- To assess levels of anti-CD40 antibody in the blood
- To assess cytokine responses to NG-350A treatment
- To explore NG-350A virus delivery to the tumour
- To assess viral shedding in buccal swabs, rectal swabs and urine samples
- To assess levels of infectious virus in blood
- To explore effect on tumour specific serum biomarkers
- To explore methodologies to detect virus replication, anti-CD40 antibody transgene expression in tumour samples and potential immune/inflammatory responses to those activities of NG-350A

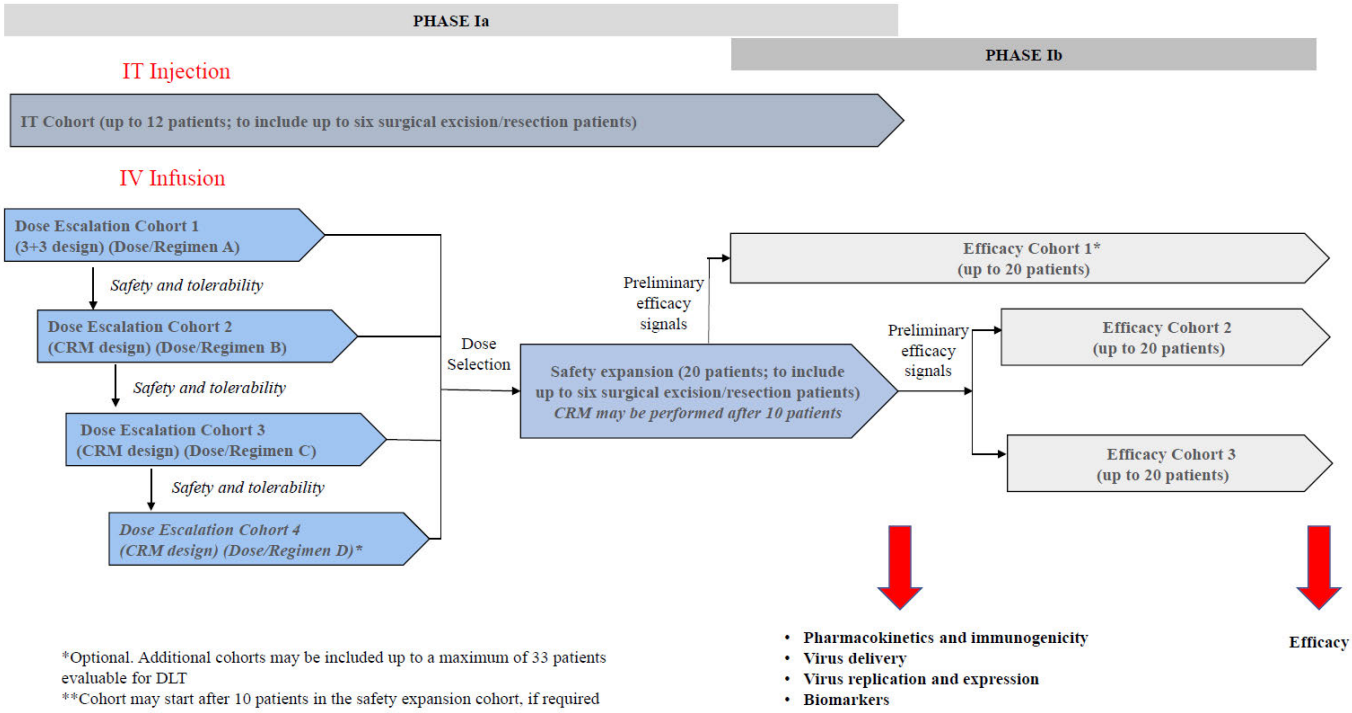
# 4 STUDY OVERVIEW

## 4.1 Overall Study Design and Methodology

### *4.1.1 Study Overview*

This is a Phase Ia/Ib, multicentre, open-label, non-randomised first in human study of NG-350A in patients with metastatic or advanced epithelial tumours. The study design is shown in Figure 2.

**Figure 2 Study Schematic for NG-350A-01**




Abbreviations: CRM=continual reassessment method; DLT=dose limiting toxicity; IT=intratumoural; IV=intravenous

#### *4.1.1.1 Phase Ia*

The Phase Ia part of the study is a dose escalation and safety expansion phase investigating NG-350A administration by IT injection and IV infusion. The two routes of administration will be investigated in parallel.

- IT Injection

  Patients will receive a single dose of NG-350A by IT injection on Day 1. The dose will be determined by the size of the tumour lesion to be injected. Patients will provide blood samples and tumour tissue samples to evaluate NG-350A activity parameters following IT injection. It is anticipated that up to six patients dosed in this cohort who are candidates for surgical excision/resection of the injected tumour lesion will undergo planned endoscopic or open surgery between Days 8 and 29 which will provide tumour tissue from the treated lesion. The remaining patients will undergo tumour core biopsies of the treated lesion as described in Section 4.1.2 with the option for any other tumour samples to be collected in the event a patient undergoes any surgical procedure whilst taking part in the study.

- IV Infusion

  Patients will receive one cycle of treatment, with three single doses of NG-350A on Days 1, 3 and 5 by IV infusion.

  A dose escalation (three dose escalation cohorts of NG-350A with an optional fourth dose escalation cohort are planned) will be performed to investigate safety and tolerability of NG-350A. Further cohorts may be included to optimise the dose and dosing regimen for safety expansion if required, up to a maximum of 33 patients evaluable for DLT. The first dose escalation cohort will follow a standard "3+3" design; thereafter a continual reassessment method (CRM) will be implemented with dose recommendations guided by the escalation with overdose control (EWOC) principle, to guide subsequent doses and dose regimens (see Section 4.1.5), with the CRM run after each set of three evaluable patients with the total number of patients evaluable for DLT capped at nine per cohort. Assessments will be performed to determine safety and tolerability of administration following IV infusion.

  A Safety Review Committee (SRC), made up of Principal Investigators (or their deputies), an Independent Reviewer and a representative of the Sponsor with a medical background, will be ultimately responsible for dose escalation decisions and for selecting the optimal dose and dosing regimen to be further investigated in a safety expansion cohort of up to 20 patients to confirm the dose of NG-350A for Phase Ib and to determine the recommended dose of NG-350A for future development. The SRC will meet after Dose Escalation Cohort 1 and after each three patients evaluable for DLT in the rest of the Dose Escalation Cohorts, guided by the CRM. The CRM may also be implemented after 10 patients in the safety expansion cohort, followed by SRC review, to optimise the dose and dosing regimen in the final 10 patients prior to Phase Ib.

  Patients in the dose escalation and safety expansion will provide blood samples and tumour tissue samples to evaluate NG-350A activity parameters following IV infusion. All patients will have tumour biopsies at baseline. It is anticipated that up to six of the patients in the safety expansion cohort who are candidates for surgical tumour excision/resection will undergo planned endoscopic or open surgery between Days 10 and 29 which will provide tumour tissue. The remaining patients will undergo tumour core biopsies as described in Section 4.1.2 with the option for any other tumour samples to be collected in the event a patient undergoes any surgical procedure whilst taking part in the study.

#### *4.1.1.2 Phase Ib*

The Phase Ib part of the study is to investigate efficacy in separate efficacy cohorts of patients with specific epithelial tumour types. It is anticipated that up to three cohorts of up to 20 patients will be included. An appropriately constituted committee (including representatives from the Sponsor and Investigators) will review any emerging signals and, considering also (1) previous clinical experience with enadenotucirev (the platform virus of NG-350A), (2) availability of eligible patients, (3) emerging data with other classes of therapies and (4) unmet need in the particular indication to make a recommendation as to which tumour types might be studied in the efficacy cohorts on the basis of overall assessment of risk: benefit.

If appropriate, one efficacy cohort may start after 10 patients in total have been treated in the safety expansion cohort. The remaining cohorts will start after the safety expansion cohort.

Patients will receive one cycle of treatment by IV infusion at the dose and dosing regimen selected for the safety expansion phase (after optimisation by the CRM if applicable).

### *4.1.2 Phase Ia and Phase Ib*

In all parts of the study, patients will be screened in the 30 days before study treatment. Written informed consent for the study will be obtained before any study specific procedures are performed.

Eligible patients will then enter the study treatment period consisting of:

- For IT injection: a single dose of NG-350A monotherapy by IT injection and an end of study treatment visit on Day 57
- For IV infusion: one cycle of NG-350A monotherapy by IV infusion and an end of study treatment visit on Day 57

Tumour imaging using Magnetic Resonance Imaging (MRI) or computed tomography (CT) scans will be performed every 8 weeks (±3 days for the first scan, ±7 days thereafter) (and whenever disease progression is suspected) until disease progression, starting at the end of study treatment visit. Disease progression should be confirmed by a repeat scan after at least 4 weeks (and up to 8 weeks). Tumour assessments will be made using RECIST Version 1.1 and iRECIST. Depending on responses seen, a central review of all images may also be performed by an Independent Reviewer in addition to the local review by the Investigator.

Patients will be followed-up at 8 week intervals until disease progression is confirmed. Patients will then be followed-up for overall survival, further cancer therapy and its best response and the date of disease progression on further cancer therapy and the date of disease progression on further cancer therapy (unless death or one of the criteria for study discontinuation is met, see Section 5.4.1, or the end of the study is reached, whichever occurs first). Follow-up after disease progression may be performed by telephone calls or at routine visits to the study centre.

Patients will be monitored for adverse events from informed consent until the end of study treatment visit (or 28 days after the last dose of study treatment, whichever is later). New study treatment related adverse events only will be recorded during the follow-up period. All serious or study treatment-related adverse events must be followed-up until they are resolved or until patient contact discontinues. Other safety assessments (physical examination and weight, vital signs, laboratory safety tests, 12-lead electrocardiograms [ECG] and Eastern Co-operative Oncology Group [ECOG] performance status) will be performed at screening and on Days 1, 8, 15, 22 and 29 (plus Days 3 and 5 for IV treated patients only). Urinalysis will be performed weekly during the study treatment period. Urinalysis and assessment of ECOG will be further performed in the follow-up period until disease progression. Concomitant medications will be recorded throughout the study.

Blood samples for analysis of NG-350A concentration will be taken on Day 1 (pre-dose and post-dose), Day 15 and the end of study visit for all patients and Days 3 and 5 (pre-dose and post-dose) for IV treated patients only. Blood samples for measurement of serum anti-NG-350A and anti-CD40 antibody titres will also be taken pre-dose on Day 1, Days 8, 15 22 and 29 and the end of study treatment visit; additional, voluntary samples may also be taken in the follow-up period. Blood samples for analysis of plasma cytokine responses be will be taken on Day 1 (pre-dose and 6 to 8 hours post-dose), Days 8, 15, 22 and 29 and the end of study treatment visit for all patients and Days 3 and 5 (pre-dose and 6 to 8 hours post-dose) for IV treated patients only.

Tumour tissue samples will be taken to explore methodologies to detect virus replication, transgene expression and potential immune/inflammatory responses to activities of NG-350A. Tumour core biopsies will be taken at baseline any time between screening and pre-dose on Day 1) for all patients. For patients undergoing surgical excision/resection, excised/resected

tumour tissue will then be collected either between Days 8 and 29 for IT treated patients or between Days 10 and 29 for IV treated patients. For patients not undergoing surgical excision/resection, further tumour core biopsies will be taken on Day 15 (required), Day 29 (optional) and the end of study treatment visit (required) (unless the patient has disease progression before the end of study treatment visit, then these biopsies should be taken at the time of progression).

In appropriate tumour types, samples will be taken for tumour specific serum biomarkers pre-dose on Day 1, Day 29 and the end of study treatment visit (unless the patient has disease progression before the end of study treatment visit, then these samples should be taken at the time of progression); additional, voluntary samples may also be taken in the follow-up period.

Blood samples for immunophenotyping analysis will be taken pre-dose on Day 1, Day 15 and the end of study treatment visit from patients at selected centres. In addition, residual plasma, serum, blood, tissue or tumour samples used for the assessment of primary, secondary and exploratory objectives may be retained for additional research, except where prohibited by local laws or regulations.

Buccal and rectal swabs and urine samples to detect viral shedding will be taken pre-dose on Day 1, on Days 8, 15 and Day 29 and the end of study treatment visit.

#### *4.1.3 Duration of Study*

The end of the study is defined as the last patient last visit. The estimated duration of the study is 36 months.

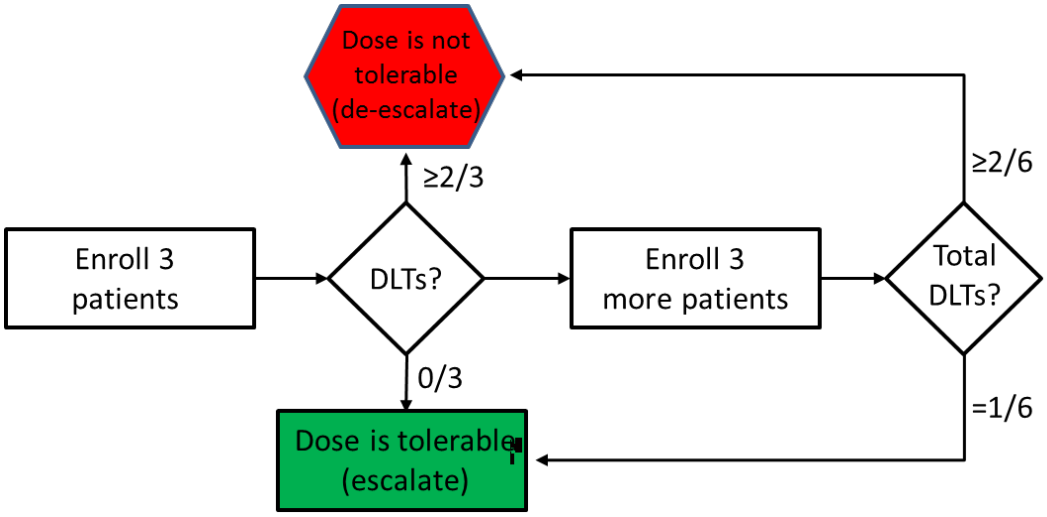
#### *4.1.4 Duration of Patient Participation*

Patients will participate until one of the pre-defined criteria for study treatment discontinuation (see Section 5.4.1) or study discontinuation (see Section 5.4.2) is met. A patient's minimum participation will be for 56 days (plus up to 30 days for screening), they will then be followed-up until disease progression is confirmed and then further for overall survival, long-term well-being, further cancer therapy and the best response and date of disease progression on further cancer therapy.

#### *4.1.5 Dose Escalation Process*

Dose Escalation Cohort 1 will be performed using the standard 3+3 design shown in Figure 3.

**Figure 3 Dose Escalation Schematic (3+3 Design)**




Abbreviations: DLT=dose-limiting toxicity

After Dose Escalation Cohort 1, a CRM, with dose recommendations guided by the escalation with EWOC principle, will be implemented to guide subsequent dose levels.

After enrollment and completion of the DLT monitoring period for the first three patients in Dose Escalation Cohort 2, dosing of subsequent patients will be guided by the CRM. Subsequent dose escalation cohorts will enroll in increments of three patients and decisions, up to nine patients per dose escalation cohort, will be guided by the CRM.

This study will use a modified version of EWOC applied to the CRM using a weakly informative prior based on DLT data observed with enadenotucirev. The data and output of the CRM analyses will be reviewed by the SRC. Emerging data of relevance in ongoing clinical studies with enadenotucirev may also be taken into account by the SRC when making decisions relating to NG-350A.

The DLT assessment period is defined as the time from the first dose until 28 days after the first dose of study treatment.

Note: to be evaluable for DLT, patients must have:

- Experienced a DLT during the DLT assessment period or
- Received all three planned doses of study treatment as required by the protocol and within the 7 day window

Patients who are not evaluable for DLT may be replaced.

In each dose escalation cohort, three patients will be initially enrolled and followed during the DLT assessment period. The first patient in each dose escalation cohort must be assessed for 14 days (until Day 15) before the next patient receives the first dose of study treatment in the same dose escalation cohort. The second and third patients should not start study treatment on the same day. Increasing to the next dose escalation cohort will depend on the safety findings of the previous dose escalation cohorts following either the “3+3” or CRM recommendations, as applicable. If a cohort has to expand to three more patients, then there must be a minimum of 7 days between each additional patient receiving their first dose.

**Definition of a DLT:**

A DLT is defined by any of the following adverse events according to NCI CTCAE Version 5 unless clearly related to the underlying disease:

- Grade 3 cytokine release syndrome lasting >12 hours with appropriate treatment or any ≥Grade 4 cytokine release syndrome as defined in Table 3
- Grade ≥3 non-haematological toxicity with the exception of: nausea, fatigue, headache and chills
- Grade ≥3 nausea, fatigue, headache and chills lasting >3 days*
- Grade 3 haematologic toxicities lasting >3 days* and Grade 4 haematological toxicities

*These events must be followed-up for up to 4 days after their onset for appropriate interpretation of their duration. In the absence of adequate follow-up, these toxicities will be reviewed by the SRC to ascertain if they are DLTs.

**Table 3 Cytokine Release Syndrome Definitions**

| Grade | Definition |
|---|---|
| 1 | Fever with or without constitutional symptoms |
| 2 | Hypotension responding to fluids; hypoxia responding to <40% oxygen |
| 3 | Hypotension managed with one pressor; hypoxia requiring ≥ 40% oxygen |
| 4 | Life-threatening consequences; urgent intervention indicated |
| 5 | Death |
| **Definition:** A disorder characterized by fever, tachypnoea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.<br>Abbreviations: IV=intravenous; NSAID=non-steroidal anti-inflammatory drug | |

The SRC will review data at each point of treatment adjustment in the dose escalation to determine the dose and dosing regimen for the next dose escalation cohort. A further SRC review of all appropriate data will then be performed at the end of the dose escalation to confirm the dose and dosing regimen for the safety expansion cohort.

Decisions for treatment adjustment will be made by the SRC. The nature of the DLTs that occurred at one dose level together with all safety data, including any patterns of toxicity emerging outside of the DLT observation period (including late immune related events) or emerging safety data from other clinical studies with enadenotucirev (and other available supporting non-safety data as required) will be considered when making decisions. The SRC may recommend one or more of the following:

1. The dose is increased
2. A lower or intermediate dose level is investigated
3. A different dosing schedule of NG-350A is investigated (e.g. a "Low-High-High schedule, see Section 6.8.1.2)
4. The infusion duration of NG-350A is altered
5. Modified prophylactic measures are required
6. That caution is exercised in patients presenting with conditions that may exacerbate any adverse events
7. That patients are replaced if not evaluable for DLT

### *4.1.6 Safety Expansion Process*

The CRM may also be re-run after 10 patients have been treated in the safety expansion phase in order to optimise the dose and/or dosing regimen prior to Phase Ib. All safety data (and other available supporting non-safety data as required) will then be reviewed by the SRC as described in Section 4.1.5.

## 4.2 Discussion of Study Design, Including the Choice of Control Groups

### *4.2.1 Study Design and Assessments*

A design involving open label, non-randomised dose escalation in sequential groups of patients with treatment of an expanded group of patients at the MTD is standard practice in Phase I oncology studies. The dose escalation phase starts with a standard "3+3" design and then a CRM of dose escalation. It is a well-established design for selecting a dose suitable for further investigation. The CRM was first proposed in 1990 [15] and was developed so that dose recommendations were based on the totality of data from all doses, acknowledging the existence of an underlying dose/toxicity model and prior data that gave some indication of where toxicity was likely to occur. Further simulation studies of these methods showed that they were more successful in identifying the MTD compared to the standard 3+3 design. However, as further experience with the CRM was gained, its application was modified. In particular, the escalation with EWOC principle was developed to minimise the chance of exposing subjects to toxic doses [16]. When the EWOC principle is applied to the CRM, the recommended dose has a low probability (e.g. ≤25%) of exposing patients to a dose with excessive toxicity (e.g.≥33% DLT). Furthermore, practical experience showed that the CRM could be used successfully with weakly or non-informative priors. In this study the prior is informed by previous DLT observed in 61 patients dosed with enadenotucirev by IV infusion. The acute tolerability is believed to be driven by response to viral particles mediated effects of IV delivered virus resulting in cytokine release by the Kupffer cells in the liver. As a viral particle, NG-350A is essentially the same as enadenotucirev. Data relating to the acute tolerability of enadenotucirev are therefore relevant to the same phase of dosing with NG-350A. The CRM provides recommendations to the SRC who will make the ultimate decisions regarding dose escalation.

The safety expansion phase is a continuation of the dose escalation phase to further evaluate the safety and tolerability of the selected dose in a larger group of patients.

The Phase Ia part of the study will investigate administration of NG-350A by two methods of administration - IT injection and IV infusion. IT injection of virus ensures delivery of relatively high concentration of virus directly to the tumour and allows assessment of the mechanism of action of NG-350A. When injected directly into tumours, oncolytic viruses are expected to infect only cells near the injection site hence minimising the potential for systemic adverse events. However, direct IT injection results in release along a relatively narrow needle track and may end in a non-viable region of necrotic tumour. Tumour access for IT injection may be a challenge and there may be specific associated morbidity depending upon the site of administration. Systemic IV delivery means that the virus has the potential for diffuse delivery throughout the vascularised regions of the tumour and may possibly be more efficient than local IT injection. Systemic delivery also potentially means that the virus can reach all metastatic sites in the body. However, systemic delivery may result in inefficient delivery of virus to tumour sites due to a number of reasons, including:

- Loss of virus to natural viral sinks including the liver

- Neutralisation of virus by antibodies and other blood factors
- Poor vascularisation of parts of the tumour

The dose escalation part of the study will be conducted in cancer centres with considerable experience of novel therapeutic agents in Phase I oncology studies and by experienced Investigators. Patients will be closely monitored during the study.

Throughout the study, ongoing review of data will be conducted by the SRC made up of Principal Investigators (or their deputies), an Independent Reviewer and a representative of the Sponsor with a medical background. Principal Investigators (or their deputies) who have enrolled patients must be involved in decision making; those who have not enrolled patients will be optional. Specific points of data review will be:

- After sets of three patients in each dose escalation cohort during the dose escalation phase to determine the dose and dosing regimen (and other parameters as applicable) for the next dose escalation cohort
- After 10 patients in the safety expansion phase to optimise the dose and dosing regimen (and other parameters as applicable) (optional)
- At the end of the dose escalation phase to determine the dose and dosing regimen (and other parameters as applicable) to be selected for the safety expansion phase

The efficacy assessments used in the study (overall response rate [ORR], disease control rate (DCR), duration of response [DOR] and progression free survival [PFS]) are standard measures assessed in oncology studies. In addition to RECIST Version 1.1 criteria (for other solid tumour patients) for efficacy assessments, the study will use iRECIST criteria as it is specifically designed for describing additional response patterns observed with immunotherapies that cannot be assessed by RECIST criteria.

NG-350A is designed to act selectively within tumour tissues to promote anti-tumour immune responses. The biomarker sampling and assessments in the study are therefore designed to investigate these responses, before and after dosing, both systemically in the blood as well as locally within the tumour.

There is no information on the teratogenic potential of NG-350A. Clear instructions on contraceptive methods have been included to avoid pregnancy (see Appendix 3).

In addition, symptoms caused by study conduct (e.g. due to blood sampling, biopsies) are possible. These risks are deemed acceptable as they are routinely used in clinical studies or clinical practice.

Vital signs, physical examinations, 12-lead ECGs, adverse event recording and laboratory safety tests are standard assessments of safety and tolerability. The range of assessments performed is deemed appropriate to detect any safety signals. Assessment of performance using the ECOG score is a standard means of determining a patients' level of functioning (in terms of their ability to care for themselves, daily activity and physical ability) used in the assessment of disease status.

Given the three SAEs relating to significant renal injury in the enadenotucirev clinical programme (see Section 2), patients potentially at higher risk of renal injury will be excluded, and patients included will have weekly urinalysis assessment. Patients with positive dipstick results for proteinuria (confirmed by repeat testing) will have a spot albumin: creatinine ratio (ACR) and 24 hour urinary protein measured with a view to early specialist intervention for investigation and treatment if decline in renal function is detected.

Prophylactic treatment, including paracetamol/acetaminophen for all patients and non-steroidal anti-inflammatory drugs (NSAIDs) (for IT injection only and if required) or hydrocortisone (for IV infusion only) or (see Section 6.8.2.5) has also been included on all dosing days to minimise any potential for renal damage as a result of cytokine-release mediated vascular leak syndrome and to manage adverse reactions including influenza-like symptoms (typically occurring between 6 and 24 hours after virus administration) that have been reported with enadenotucirev. Patients will also receive post-dose hydration following IV infusion of NG-350A (see Section 6.8.2.3.2) as a precaution.

### *4.2.2 Patient Population*

Carcinomas are malignancies of epithelial origin which are categorised as either squamous cell carcinomas or adenocarcinomas. Carcinomas can originate in any epithelial tissue and this group comprises some of the most common cancer types including bladder, breast, cervical, colorectal, lung, pancreatic, prostate and ovarian cancer. As of 2012, lung (13.0%), breast (11.9%) and colorectal (7.9%) were the most common forms of cancer worldwide [1].

In vitro studies with human tumour cell lines have shown that enadenotucirev is active against cell lines derived from a range of epithelial tumours but shows limited activity on normal cells. Further studies have shown that enadenotucirev is not effective against cell lines derived from non-epithelial origins including glioblastoma, leukaemia, melanoma and neuroendocrine tumours. These data indicate that enadenotucirev is selective for carcinoma cells which represent the vast majority of clinical disease. The study will therefore be performed in patients with metastatic or advanced epithelial tumours, with Phase Ib performed in specific epithelial tumour types based upon emerging efficacy signals from Phase Ia. Patients will be eligible when they have recovered to ≤Grade 1 from the effects (excluding alopecia) of any prior therapy for their malignancy to minimise the risk of study treatment exacerbating these effects.

## 4.3 Benefit-Risk Assessment

While NG-350A has not been administered to humans, prior clinical experience has been obtained for both enadenotucirev and multiple agonistic anti-CD40 antibodies including selicrelumab. The NG-350A transgene sequence encodes an amino acid sequence homologous to that of selicrelumab.

Enadenotucirev is currently being investigated for the treatment of epithelial solid tumours and has been administered to 135 patients to date either as a monotherapy or in combination with a PD-1 inhibitor or paclitaxel, including 113 by IV infusion. An IV dose and dosing regimen and has been established that is tolerated, with acute tolerability managed prophylactically with corticosteroids and paracetamol/acetaminophen and IV hydration. The risk of renal injury, most due to idiosyncratic post infectious glomerulonephritis, reported with enadenotucirev, can be also be managed by these prophylactic measures in addition to weekly monitoring for proteinuria and early intervention with high dose corticosteroids and plasmapheresis should proteinuria and a decline in renal function be detected. Since NG-350A has identical virus physiochemical structure and method of delivery as enadenotucirev, it is anticipated that potential adverse events related directly to the viral particle infusion and the oncolytic effects on tumour or normal tissues would be similar with enadenotucirev and NG-350A.

Systemic administration of other agonistic anti-CD40 antibodies in clinical studies has been associated with adverse events including cytokine release syndrome, autoimmune reactions, thromboembolic syndromes, hyperimmune stimulation leading to activation-induced cell death or tolerance, proangiogenesis, hepatotoxicity, ocular inflammation, acute renal failure and immunosuppression. However, it is unlikely that NG-350A will produce the same systemic

levels of antibodies seen in clinical studies with systemically dosed anti-CD40 antibodies because it will drive antibody production within the tumour.

The benefit/risk profile appears acceptable to proceed with the proposed clinical study in patients with metastatic or advanced epithelial tumours. The patient population and dose management recommendations and safety monitoring methods described in this protocol (based upon previous experience with enadenotucirev) have been chosen to minimise potential risk and should ensure appropriate safety measures are in place for the patients participating in the clinical study.

# 5 STUDY POPULATION

## 5.1 Number of Patients

Up to 125 patients are expected to participate in the study (variations are possible if additional cohorts of patients are required or if patients not evaluable for DLT are replaced):

- Phase Ia:
  - Up to 12 patients receiving NG-350A by IT injection (to include up to six patients undergoing surgical excision/resection)
  - Up to 53 patients receiving NG-350A by IV infusion (up to 33 patients evaluable for DLT in the dose escalation cohorts and up to 20 patients in the safety expansion phase to include up to six patients undergoing surgical excision/resection)
- Phase Ib: Up to 60 patients (up to three efficacy cohorts of up to 20 patients each, based upon tumour type)

The statistical considerations used to determine the number of patients planned and evaluable are presented in Section 11.1.

## 5.2 Inclusion Criteria

Patients must meet *all* the following criteria to be eligible for the study:

1. Provide written informed consent to participate
2. Males or females aged 18 years or over
3. Histologically or cytologically documented metastatic or advanced epithelial cancer (carcinoma or adenocarcinoma) that has relapsed from, or is refractory to, standard treatment, or for which no standard treatment is available
4. a) For patients undergoing surgical excision/resection:
   - Excisable tumour/tumour lesion accessible for baseline biopsies and biopsies deemed safe by the Investigator
   - Willing to consent for baseline biopsies and surgical procedure
   - Patient able to undergo surgical procedure and appropriate anaesthesia

   b) For patients not undergoing surgical excision/resection:
   - Tumour accessible for biopsy and biopsies deemed safe by the Investigator
   - Willing to consent to tumour biopsies at baseline and during the study
5. Safety expansion and efficacy cohorts only: at least one measurable site of disease according to RECIST criteria; this lesion must be either (i) outside a previously irradiated area or (ii) progressive if it is in a previously irradiated area (not applicable in patients undergoing surgical excision/resection if the lesion to be resected is the target lesion)
6. ECOG performance status 0 or 1
7. Predicted life expectancy of 3 months or more
8. Ability to comply with study procedures in the Investigator's opinion
9. Recovered to Grade 1 from the effects (excluding alopecia) of any prior therapy for their malignancies

10. Non-impaired renal function
    - Creatinine ≤1.5 mg/dL and estimated glomerular filtration rate (eGFR) using the Cockroft-Gault formula ≥60 mL/min/1.73m$^2$ (or measured creatinine clearance ≥60 mL/min)
    - Urine dipstick for proteinuria at screening and baseline negative or trace. Patients may be included with results of 1+ if they have a spot urinary ACR of either (i) ≤3 mg/mmol or (ii) >3 mg to <70 mg/mmol with a 24 hour urinary protein <0.2 g/24hours
    - Serum complement components C3 and C4 above the lower limit of normal range
11. Adequate hepatic function:
    - Serum bilirubin <1.5 mg/dL (except patients with Gilbert's syndrome who may have total bilirubin <3.0 mg/mL)
    - Aspartate aminotransferase (AST) and ALT ≤3 x upper limit of normal
    - Albumin ≥3 g/dL
12. Adequate bone marrow function:
    - Absolute neutrophil count ≥1.5 x 10$^9$/L
    - Platelets ≥100 x 10$^9$/L
    - Haemoglobin ≥90 g/L (9 g/dL)
13. Prothrombin time and activated partial thromboplastin time within normal range or international normalised ratio ≤1.5, as appropriate
14. Meeting reproductive status requirements:
    - Females must not be pregnant or breastfeeding
    - Females of childbearing potential, as defined in Appendix 3, must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotrophin [hCG]) within 24 hours before the first dose of study treatment
    - Females of childbearing potential must agree to use a highly effective method of contraception, as defined in Appendix 3, for the duration of study treatment with NG-350A and 6 months following the last dose of study treatment. Females of childbearing potential who are continuously not heterosexually active are exempt from contraceptive requirements, but must still undergo pregnancy testing
    - Fertile males who are sexually active with females of childbearing potential must agree to follow instructions for method(s) of contraception, as defined in Appendix 3, for the duration of study treatment with NG-350A and 6 months following the last dose of study treatment. In addition, males must be willing to refrain from sperm donation during this time. Azoospermic males are exempt from contraceptive requirements

## 5.3 Exclusion Criteria

Patients who meet *any* of the following criteria are not eligible for the study:

1. Known history or evidence of significant immunodeficiency due to underlying illness (e.g. human immunodeficiency virus [HIV]/acquired immunodeficiency syndrome [AIDS]) and/or medication (e.g. systemic corticosteroids or other immunosuppressive medications, including cyclosporine, azathioprine, interferons in the 4 weeks before the first dose of study treatment). Patients with a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisolone equivalent) or other immunosuppressive medications within 14 days of the first dose of study treatment. Inhaled or topical steroids and adrenal replacement steroid doses are permitted in the absence of autoimmune disease
2. Splenectomy
3. Prior allogeneic or autologous bone marrow or organ transplantation
4. Active infections requiring antibiotics, physician monitoring or recurrent fevers (>38.0˚C) associated with a clinical diagnosis of active infection
5. Active viral disease or positive test for hepatitis B virus using hepatitis B surface antigen test or positive test for hepatitis C virus (HCV) using HCV RNA or HCV antibody test indicating acute or chronic infection. Positive test for HIV or AIDS; testing is not required in the absence of history
6. Use of the following antiviral agents: ribavirin, adefovir, lamivudine or cidofovir within 7 days prior to the first dose of study treatment; or pegylated interferon in the 14 days before the first dose of study treatment
7. Administration of an investigational drug in the 28 days, or six half-lives (whichever is longer) before the first dose of study treatment
8. Major surgery or treatment with any chemotherapy, radiation therapy, biologics for cancer or investigational therapy in the 28 days before the first dose of study treatment. All toxicities attributed to prior anti-cancer therapy other than alopecia must have resolved to Grade 1 or baseline before the first dose of study treatment. Patients with toxicities (other than renal toxicities) attributed to prior anti-cancer therapy which are not expected to resolve and result in long lasting sequelae, such as neuropathy after platinum based therapy, are permitted to enrol
9. Other prior malignancy active within the previous 3 years except for local or organ confined early stage cancer that has been definitively treated with curative intent, does not require ongoing treatment, has no evidence of residual disease and has a negligible risk of recurrence and is therefore unlikely to interfere with the primary and secondary endpoints of the study, including response rate and safety
10. Symptomatic brain metastases or any leptomeningeal metastasis that is symptomatic and/or requires treatment. Patients with brain metastases are eligible if these have been locally treated (surgery, radiotherapy). There must also be no requirement for immunosuppressive doses of systemic corticosteroids (>10 mg/day prednisone equivalent) for at least 2 weeks before the first dose of study treatment
11. Any history of renal disease or renal injury or autoimmune disease. Patients with active, known or suspected auto-immune disease or a syndrome that requires systemic or immunosuppressive agents; patients with vitiligo, type I diabetes mellitus, residual

hypothyroidism due to autoimmune disease only requiring hormone replacement, psoriasis not requiring systemic treatment or conditions not expected to recur in the absence of an external trigger are permitted to enrol providing they comply with the other eligibility criteria relating to renal function

12. Any serious or uncontrolled medical disorder that, in the opinion of the Investigator or the Medical Monitor, may increase the risk associated with study participation or study treatment administration, impair the ability of the patient to receive protocol therapy or interfere with the interpretation of study results
13. History of coagulopathy, transient ischaemic attacks, cerebrovascular accidents or venous thromboembolism
14. Previous treatment with enadenotucirev or an anti-CD40 antibody
15. Known allergy to NG-350A transgene products or formulation
16. Any other medical or psychological condition that would preclude participation in the study or compromise ability to give informed consent

## 5.4 Removal of Patients from Therapy or Assessment

### *5.4.1 Study Treatment Discontinuation*

Study treatment will be permanently discontinued for the following reasons:

- Clinical deterioration, as assessed by the Investigator
- Confirmed radiographic disease progression
- Adverse events meeting the criteria for a DLT
- Any adverse event, laboratory abnormality or intercurrent illness, which presents a substantial clinical risk to the patient with continued treatment, as assessed by the Investigator
- Proteinuria 1+ on urinalysis and confirmed by repeat testing, spot ACR and 24 hour urinary protein (see Section 8.5.2)
- Pregnancy (female patients only)
- Significant deviation from the protocol or eligibility criteria or significant protocol non-compliance in the opinion of the Investigator and/or Medical Monitor
- Start of an additional anti-cancer therapy
- Withdrawal of consent from study treatment only
- Investigator's decision to discontinue study treatment for any other reason

Patients discontinuing study treatment and continuing the study should attend the end of study treatment visit on Day 57 for the procedures specified in Section 7.2.2.

### *5.4.2 Study Discontinuation*

A patient will be discontinued from the study for the following reasons:

- Confirmed radiographic disease progression
- Withdrawal of consent from the study

- Significant deviation from the protocol or eligibility criteria or significant protocol non-compliance in the opinion of the Investigator and/or Medical Monitor
- Lost to follow-up
- Termination of the study
- Investigator's decision to withdraw the patient from the study for any other reason

Patients discontinuing the study during the study treatment period should, wherever possible, have the end of study treatment visit procedures specified in Section 7.2.2.

### *5.4.3 Study Termination*

The study may be terminated, either at one centre or all centres for the following reasons:

- The discovery of an unexpected, serious or unacceptable risk to patients enrolled in the study
- The decision on the part of the Sponsor to suspend or discontinue testing, evaluation or development of NG-350A. In the event of the Sponsor's decision to no longer supply study treatment, ample notification will be provided so that appropriate adjustments to treatment can be made
- Serious failure of the Investigator to comply with International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP) [17] or local regulations
- Submission of knowingly false information from the study centre to the Sponsor, the independent ethics committee (IEC)/institutional review board (IRB) or regulatory authorities
- Major, repeated, non-adherence to the protocol

The Sponsor must be informed immediately in the event of any major protocol violation or serious breach of ICH GCP.

# 6 STUDY TREATMENT

Full details are provided in the Pharmacy Manual.

The Investigator must ensure that study treatment is handled only by study centre personnel who have been appropriately trained for the conduct of this clinical study and that dosing is only performed by study centre personnel who fully understand the procedures outlined in this section, the Investigator's Brochure and the Pharmacy Manual.

## 6.1 Identity of Study Treatments

NG-350A is oncolytic adenoviral vector which, following replication in permissive tissues, expresses the Heavy and Light chain genes encoding a full length agonist anti-CD40 antibody of the Immunoglobulin G2 (IgG2) isotype at the site of virus replication (using a transgene DNA sequence encoding an amino acid sequence homologous to that of selicrelumab but with a non-functional sequence modification to the Heavy chain C-terminus). NG-350A is derived from the Group B oncolytic platform virus enadenotucirev.

It is a colourless solution that is clear to slightly opalescent.

NG-350A will be manufactured according to Good Manufacturing Practice and released by a qualified person. NG-350A will be provided by the Sponsor.

NG-350A solution will be provided frozen as single doses in glass vials that are sealed with a rubber stopper and aluminium crimp. Each vial contains 0.7 mL NG-350A solution at a concentration of $2 \times 10^{12}$ vp/mL formulated in 5 mM HEPES, 20% glycerol and buffer to pH 7.8.

The NG-350A solution is dispensed when thawed from storage and made up to suitable dilutions and quantities for IT injection or IV infusion. The dilution preparation is carried out using varying quantities of sterile saline for injection. This allows the administration of the required dose of NG-350A. Full details are provided in the Pharmacy Manual.

## 6.2 Study Treatments Administered

### *6.2.1 IT Injection*

In the IT cohort, patients will receive a single dose of NG-350A by IT injection on Day 1. The dose given to each patient will be dependent on the size of the tumour lesion to be injected. The total injection volume should be up to a maximum of 2 mL of diluted virus.

The 2 mL volume of the virus diluted to a concentration of $5 \times 10^{11}$ vp/mL will be loaded into a syringe or other injection device and repeated insertions of 100 µL to 200 µL made into injection sites approximately 0.5 cm to 1 cm apart, up to a total volume of 2 mL, depending on the size of the tumour lesion. Within each injection site there may be a single track or multiple tracks.

In patients with several lesions suitable for IT injection, the total volume of the diluted virus to be injected (2 mL) can be distributed over several lesions. The volume per lesion will depend on the individual lesion size e.g. a lesion of 2.5 cm longest diameter would allow up to five injections of 200 µL, approximately 0.5 cm apart, to a maximum of 1 mL for that lesion.

### *6.2.2 IV Infusion*

NG-350A will be administered by IV infusion to all other patients. All patients will receive a single cycle of study treatment, with three single doses of NG-350A on Days 1, 3 and 5 by IV infusion.

In the Phase Ia part of the study, NG-350A will be administered using a dose escalation design as described in Section 4.1.5.

Three dose escalation cohorts are planned, with an optional fourth dose escalation cohort. In each cohort, patients will receive three IV infusions of NG-350A on Days 1, 3 and 5. The starting dose in Dose Escalation Cohort 1 will be $1 \times 10^{11}$ vp infused over 5 minutes. It is anticipated the dose in Dose Escalation Cohort 2 will be escalated to $1 \times 10^{12}$ vp infused over 5 minutes. This will be confirmed by the SRC after Dose Escalation Cohort 1. The dose selected for Dose Escalation Cohort 3 and Dose Escalation Cohort 4 (optional) will be determined by the SRC based upon the results from the first two cohorts and guided using the CRM model. This may include investigation of a lower dose of NG-350A on Day 1 to that on Days 3 and 5 (e.g. a "Low-High-High" treatment schedule). The infusion duration will be altered in Dose Escalation Cohorts 3 and 4 to standardise the infusion rate of NG-350A to that in Dose Escalation Cohort 2 ($2 \times 10^{11}$ vp/min).

The results from the dose escalation cohorts will be used to determine the dose and dosing regimen for the safety expansion cohort.

The results from the safety expansion cohort will be used to determine the dose and dosing regimen for Phase Ib.

## 6.3 Labelling, Packaging and Shipping

The vials and secondary packaging will be labelled according to local regulations. Full details are provided in the Pharmacy Manual.

During transport the vials in their secondary package are placed within a box which will be sealed in a bag which protects the box when it is buried under dry ice inside an insulated container. NG-350A will be shipped at less than -70°C±10°C and must immediately be stored upon receipt at the study centre.

## 6.4 Storage

Study treatment must be stored frozen at -70°C±10°C in an alarmed, temperature monitored, secure freezer with restricted access. NG-350A will be stored with appropriate biosafety labelling (indicating the nature of the agent) on the freezer door.

## 6.5 Accountability

The study centre will acknowledge receipt of NG-350A, according to the instructions in the Pharmacy Manual. Any damaged shipments will be replaced.

The Investigator is responsible for study treatment accountability, reconciliation and record maintenance throughout the course of the study. This responsibility may be delegated to designated pharmacy staff who must maintain accurate records of all study treatment receipts from the supplier, dispensed to study patients and the disposal of all unused study treatment. This inventory must be available for review by representatives of the Sponsor (or designee) or regulatory authority on request.

## 6.6 Destruction or Disposal

All NG-350A contaminated materials must be treated as hazardous waste.

All disposable materials and items (e.g. syringes, catheters, needles, tubing, gloves, used or unused vials, containers, etc.) that come in contact with NG-350A must be disposed of in a clearly marked biomedical waste container (e.g. sharps container or biohazard leakproof bag) according to study centre policy.

Non-disposable items that come in contact with NG-350A should be decontaminated either by autoclaving or with an appropriate virucidal agent (2% hypochlorite or 2% Virkon solutions for at least 30 minutes).

At the end of the study, the Sponsor will provide instructions for the return shipment or destruction of any unused study treatment.

## 6.7 Method of Assigning Patients to Treatment Groups

The study is not randomised.

At the screening visit, patients will be sequentially allocated a screening number once written, informed consent has been obtained. They will be identified by this number until entry into study. Patients fulfilling all inclusion and no exclusion criteria will enter the study and will be allocated a unique patient identifier. Once a patient identifier has been assigned, no attempt will be made to use that number again. The patient identifier will be in a coded format with components specifying country, site, cohort and sequential patient number.

In the Phase Ia part of the study, the IT cohort will run in parallel to the dose escalation and safety expansion IV cohorts. Wherever possible, patients with tumours suitable for IT injection will be preferentially allocated to the IT cohort until this cohort is complete. Patients receiving NG-350A by IV infusion will be sequentially allocated to each dose escalation cohort during the dose escalation and then to the safety expansion cohort.

At the end of the safety expansion cohort, an appropriately constituted committee (to include representatives of the Sponsor and Investigators) will review the available data at the end Phase Ia. Following review of any emerging signals and considering also (1) previous clinical experience with enadenotucirev (the platform virus of NG-350A), (2) availability of eligible patients, (3) emerging data with other classes of therapies and (4) unmet need in the particular indication, the committee will make a recommendation as to which tumour types might be studied in the efficacy cohorts on the basis of overall assessment of risk: benefit. Patients will be allocated to the efficacy cohorts on the basis of tumour type.

Replacement of patients will be discussed with the Sponsor on a case by case basis. Replacement patients will be allocated the next available patient identifier.

## 6.8 Selection of Doses, Dosing Schedule and Administration

### *6.8.1 Selection of Doses and Dosing Regimen in the Study*

#### *6.8.1.1 IT Injection*

The dose will be calculated for each patient based on the diameter of the tumour as estimated from routine imaging.

The dose for IT injection has been selected based on the concentration of virus shown to generate a synchronised infection and transgene production with NG-350A (and other

transgene-bearing viruses) in mouse tumour xenograft studies [5], then scaling the volume to aim for similar virus exposure in the larger tumours in humans, whilst allowing the Investigator to use judgement to decide the number of injection sites and injection volumes to give optimal virus delivery to the tumour. The aim is to provide a synchronised virus infection and transgene production (achievable with locally high virus concentration) within as much of the tumour site as possible to (1) optimise the ability to demonstrate the effects of NG-350A on the tumour and (2) help with selecting the best timings for safety and biomarker sample collection for assessing the biological activities of the virus.

The dose selected represents a five fold increase in virus concentration to that investigated previously in the mechanism of action study ColoAd1-1002 in which systemic exposure to virus was shown to be minimal or absent based on aligning with the virus concentrations used since this study to generate pre-clinical virus infection and transgene expression data. The volume per injection site has also been decreased.

Several injections of small volumes of the diluted virus will be made to produce a greater spread of the virus within the tumour. Injecting a large volume into one specific area of a tumour may also result in extensive tumour damage or rupture (known as tumour cracking) with resultant leaks into the vasculature with resultant variability and a loss of effective dose.

#### *6.8.1.2 IV Infusion*

Since the clinical safety and tolerability profile associated with transgene expression are unknown, a starting dose of 1 x $10^{11}$ vp will be administered by IV infusion.

This dosing schedule (three IV infusions of NG-350A on Days 1, 3 and 5) is the same as that tested in two completed and two ongoing studies with enadenotucirev, the platform virus of NG-350A, where up to six repeat cycles of monotherapy were administered. The dosing schedule of three IV infusions over 5 days was designed to deliver a high viral dose with good tolerability.

Data from completed study ColoAd1-1001 suggest an increase in cytokine levels following the first dose of enadenotucirev on Day 1 of Cycle 1 (which returns to baseline levels within 48 hours) compared to lower cytokine levels following dosing on Days 3 or 5. A similar pattern was seen after dosing in Cycle 2, however the initial response on Day 1 was generally smaller in the second cycle. Since the cytokine release is believed to be the most important mediator of the adverse effects of viral therapy, this “tolerising” effect allows a lower risk of adverse events. The initial doses of virus may down-regulate the Kupffer cell clearance, decreasing toxicity and improving circulation for the subsequent doses. This was supported by a recent study analysing interleukin-6 (IL-6) responses in mice following treatment with doses equivalent to between 5.5 x $10^{13}$ vp and 5.5 x $10^{12}$ vp in humans. A low first dose, which itself induced very low or undetectable levels of IL-6 cytokine, was sufficient to attenuate to background levels the innate particle-mediated immune response to subsequent high doses (10 times more viral particles) which induce a significant elevation in systemic IL-6 when given as the first dose [5]. A dosing schedule investigating a lower dose of NG-350A on Day 1 to that on Days 3 and 5 (e.g. a “Low-High-High” schedule) may therefore be included in the dose escalation phase. The highest dose that will be administered on Day 1 will be 3 x $10^{12}$ vp.

This dosing schedule was also designed to minimise potential effects of antibody responses to the virus. In the enadenotucirev clinical programme, anti-virus antibodies have been measured following IV infusion, IT injection and intraperitoneal (IP) administration. Data suggest that following IV infusion or IP administration the anti-virus antibody titre increases over ~21 days in the majority of patients and remains reasonably constant thereafter with or without repeat cycles of dosing. Initial analysis suggests that once the concentration of anti-virus antibodies

plateaus in the serum, the ability of antibodies to neutralise the virus may increase with time. IT injection resulted in a lower anti-virus antibody response than that observed by dosing by IV infusion or IP administration. Infectious virus is retrievable in the majority of patients on Day 1 of Cycle 2 but is less retrievable following subsequent cycles.

The IV infusion rate for an oncolytic virus can potentially influence safety and efficacy. Delivering the total viral dose too rapidly could cause particle mediated toxicity. However, administering the virus too slowly could result in excessive loss of the virus into the viral sinks (binding to blood constituents and uptake by Kupffer cells). Very slow infusion could therefore result in no effective viral build-up in the tumour and thus no efficacy [18, 19, 20]. The infusion rate for IV administration will therefore be standardised at doses of $1 \times 10^{12}$ vp and above. The infusion rate of $2 \times 10^{11}$ vp/minute is based on findings from the enadenotucirev clinical programme. Increases in infusion rate above this level were associated with increased cytokine release and decreases in tolerability. Based upon this infusion rate, the highest dose that will be administered on Days 3 and 5 is $1 \times 10^{13}$ vp over 50 minutes.

### *6.8.2 Selection and Timing of Dose for each Patient*

#### *6.8.2.1 Dosing Schedule*

Each patient will receive a defined dose and dosing regimen of NG-350A:

- Patients in the IT cohort will receive a single dose of NG-350A on Day 1 by IT injection. The dose will be dependent on the size of the tumour
- Other patients will receive NG-350A by IV infusion. Patients will receive three single doses of NG-350A, the dose will be dependent on cohort assignation. The first dose of NG-350A will be given on Day 1. The second and third doses (scheduled days Day 3 and Day 5) must be administered within 7 days of Day 1; doses may not be administered on consecutive days

There are no restrictions on dosing in relation to meals or the time of day of administration.

#### *6.8.2.2 Study Treatment Preparation*

The NG-350A dose preparation will be performed by an appropriately trained and accredited person who has been specifically trained for the study. Each dose will be prepared in a syringe, according to the detailed instructions in the Pharmacy Manual.

The syringe will be labelled with the patient number, the thaw time and the dose and this information will be recorded in the electronic Case Report Form (eCRF).

A spill kit must be available whenever NG-350A is handled or transported (including at the time of administration to the patient). In the event of a spill, people in the immediate area will be alerted and other personnel will be notified as required by study centre policies. The spill area will be contained by limiting non-essential traffic in the area and using barriers to prevent the flow of material beyond the local area. Clean-up must be conducted strictly according to the guidance in the pharmacy manual.

Gloves, gown, surgical/procedure mask and safety glasses with side shields will be worn at all times during handling of NG-350A (including clean-up of spills).

#### *6.8.2.3 Study Treatment Administration*

Study treatment will be administered by the Investigator (or designee). Under no circumstances will the Investigator allow the study treatment to be used other than as directed by this protocol, since the insurance coverage shall otherwise become null and void.

Prior to dosing, IV access points for administration of fluids and blood sampling will be established.

**Note: post-dose assessments will be scheduled in relation to the end of the injection or infusion.**

6.8.2.3.1 IT Injection

NG-350A injection will be performed on Day 1. The dose given to each patient will be dependent on the size of the tumour lesion to be injected.

The stock virus will be diluted to 5 x $10^{11}$ vp/mL (0.7 mL from one 0.7 mL vial diluted one in four with saline to a 2.8 mL total volume) and a syringe (or other suitable injection device) filled with 2 mL. The needle will be inserted to the estimated depth of the lesion and 100 µL to 200 µL virus (wherever possible) injected as slowly as possible to that site while retracting the needle, ideally pausing for 10 seconds (if practical) before final withdrawal. The injection will be repeated approximately 0.5cm to 1 cm away from the first injection and then at further sites across the tumour for maximum coverage up to the total 2 mL volume if the tumour is large enough to do so. The total volume injected and number of injection sites on the tumour will be recorded.

6.8.2.3.2 IV Infusion

Patients will receive an IV infusion of NG-350A starting at time zero administered directly into the venous access point using a syringe pump. The 1 x $10^{11}$ vp dose and 1 x $10^{12}$ vp doses will be administered over 5 minutes (infusion rates of 2 x$10^{10}$ vp/minute and 2 x $10^{11}$ vp/minute, respectively). Other doses tested will be administered at a standard infusion rate of 2 x $10^{11}$ vp/minute.

At the end of the infusion the administration line will be flushed with normal saline to ensure that the full dose has been administered. This flush should only use a sufficient amount of saline to flush the line and should not exceed 30 mL.

It is recommended that patients receive prophylactic IV hydration after the end of each infusion, unless clinically contraindicated. Up to 1 L of normal saline will be administered over 4 hours, adjusted to meet the physiological and clinical requirements of the individual patient (e.g. patient body mass index, concurrent conditions).

*6.8.2.4 Special Precautions*

Patients receiving NG-350A are advised to avoid close contact (e.g. close physical contact or sharing of cutlery) with the following persons until 30 days after their last administration:

- Women who are pregnant or lactating
- Children under 1 year old
- Those who have significant immunodeficiency because of underlying illness (e.g. HIV/AIDS) and/or medication (e.g. systemic corticosteroids)

*6.8.2.5 Antipyretic Prophylaxis*

Patients will receive the following standard antipyretic prophylaxis pre-dose and post-dose on each NG-350A dosing day:

- ~1 hour pre-dose: 650 mg or 1 g oral acetaminophen/paracetamol (depending on local prescribing information). 100 mg IV hydrocortisone will also be given for IV patients only. NSAIDs may also be given to IT patients, if required

- 3 hours post-dose: 650 mg or 1 g oral acetaminophen/paracetamol. 100 mg IV hydrocortisone will also be given for IV patients only. NSAIDs may also be given to IT patients, if required
- Thereafter, paracetamol/acetaminophen (with NSAIDs if required) every 4 to 6 hours as indicated and following the prescribing information for the product(s)

Other medications, including diphenhydramine, may be used in line with the study centre's standard practice providing they are not excluded concomitant medications (see Section 6.10.2).

#### *6.8.2.6 Dose and Schedule Modifications*

Every effort will be made to administer the planned doses of NG-350A.

No intra-patient dose escalations will be performed unless this is part of a planned dosing regimen (e.g. investigation of a "Low-High-High" treatment schedule).

Dose interruptions to the Day 1, 3 and 5 schedule may reduce or nullify the potential benefits of the dosing regimen; however, if a patient is unable to receive a dose on a scheduled day for reasons other than toxicity, then every effort must be made to reschedule the dosing as early as possible up to a maximum of 3 days after the previous dose.

If proteinuria is confirmed on any of the weekly tests, no NG-350A should be administered and a spot ACR and 24 hour urinary protein should be performed (see Section 8.5.2).

If dosing is delayed:

- Tumour assessments for all patients should continue according to the schedule of assessments
- Weekly urinalysis to test for proteinuria must continue

#### *6.8.2.7 Re-treatment*

Re-treatment with NG-350A is not routinely planned.

For IT patients, exposure to a further cycle of NG-350A by IV infusion may be permissible; this will be decided on a case by case and cycle by cycle basis and will be subject to discussion and review by the Medical Monitor and Investigator.

For IV patients, exposure to more than one cycle of NG-350A may be permissible; this will be decided on a case by case and cycle by cycle basis and will be subject to discussion and review by the Medical Monitor and Investigator.

If performed, the same schedule of assessments for the study treatment period will be followed.

## 6.9 Blinding

This is an open label study; therefore, no procedures for blinding are necessary. The study personnel and patient will know the treatment the patient is receiving.

## 6.10 Prior and Concomitant Therapies and Medications

All relevant information (including dose, start and stop dates and indication) should be recorded in the eCRF.

### *6.10.1 Prior and Concomitant Therapy Relating to the Study Indication*

All prior cancer therapies will be documented.

Treatment with any chemotherapy, radiation therapy, biologics for cancer or investigational therapy is not permitted in the 28 days before the first dose of study treatment (patients with prior cytotoxic or investigational products less than 3 weeks prior to study treatment might be eligible after discussion between the Investigator and Medical Monitor, if toxicities from the prior treatment have been resolved to NCI CTCAE Grade 1 and decision is supported by the half-life of previous therapy).

During the study, systemic cancer therapy or local therapy to the primary tumour or its metastases are also not permitted.

Medications for the standard management of symptoms or supportive care for cancer or for the management of the effects of study treatment may be administered at the Investigator's discretion; unless they are excluded concomitant medications.

### *6.10.2 Other Prior and Concomitant Medications*

Other medications (e.g. prescription drugs, over the counter drugs, herbal/homeopathic remedies, nutritional supplements) received by the patient in the 14 days before the first dose of study treatment until the end of the study treatment visit will be also be documented. During the follow-up period, only treatments administered to treat study treatment-related toxicities should be recorded until such toxicities have recovered to baseline or NCI CTCAE Grade 1 (this information does not have to be collected during clinic visits).

Excluded medications include:

- Medications inducing immune suppression e.g. systemic corticosteroids (>10 mg daily prednisolone equivalent) in period from 14 days before the first dose of study treatment until 14 days after the last dose of study treatment. within 14 days of the first dose of study treatment. The exception is if these are required for the following:
  - As part of emergency therapy during the study
  - Required for the treatment of adverse events during the study
  - Used as an inhaled agent for bronchospasm or chronic obstructive pulmonary disease

  If systemic corticosteroid use is required for study treatment-related symptoms, the Medical Monitor should be notified in a timely manner

  Inhaled or topical steroids and adrenal replacement steroid doses are permitted in the absence of autoimmune disease.
- Antiviral agents e.g. ribavirin, adefovir, lamivudine or cidofovir in the period 7 days before the first dose of study treatment; or pegylated interferon in the 14 days before the first dose of study treatment and until 14 days after the last dose of study treatment (and only then if clinically indicated)
- Investigational drug administration for any reason

Patients with active infection requiring antibiotics must be excluded from study entry. Prophylactic antibiotics in preparation for biopsies during the study are permitted. In addition, concomitant use of antibiotics to treat infection is permitted during the study.

### *6.10.3 Treatment Compliance*

Study treatment administration will take place at the study centre and will be administered by the Investigator or designated and trained personnel. The precise date and time of administrations will be recorded in the eCRF. No NG-350A will be taken home by the patients.

## 6.11 Post-study Treatment

The Sponsor does not intend to provide NG-350A after the end of the study or after any early patient discontinuation.

# 7 STUDY PROCEDURES AT EACH VISIT/SCHEDULE OF ASSESSMENTS

The study consists of the following:

- A 30 day screening period before the start of study treatment
- A study treatment period comprising:
  - For IT injection: A single dose of NG-350A on Day 1 and finishing with the end of study treatment visit on Day 57 and interim weekly clinic visits on Days 8, 15, 22 and 29 for safety and pharmacodynamic assessments, and Days 36, 43 and 50 for urinalysis only
  - For IV infusion: A single cycle of NG-350A treatment (with three single doses on Days 1, 3 and 5) and finishing with the end of study treatment visit on Day 57 and interim weekly clinic visits on Days 8, 15, 22 and 29 for safety and pharmacodynamic assessments, and Days 36, 43 and 50 for urinalysis only
- Patients will then be followed up at 8 week intervals until disease progression is confirmed. Patients will then be followed up for overall survival, long-term well-being and further cancer therapy

The schedule of assessments at each visit is shown in Table 1 and Table 2 and listed in Section 7.1 to Section 7.4. The study assessments are described in Section 8.

**Note: any additional visits or assessments performed during the study e.g. to assess adverse events must also be recorded on the unscheduled procedures or unscheduled visits in the eCRF.**

## 7.1 Screening and Baseline Assessments

Written informed consent for participation in the study must be obtained before performing any study specific screening tests or evaluations according to the process in Section 14.4.

Informed consent forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study centre.

The following will be performed at screening:

- Demographics plus height
- Cancer history and therapies
- Medical history including prior medications
- Urine or serum pregnancy test (females of childbearing potential only) – performed in the 24 hours before the first dose of study treatment
- Vital sign measurements
- Physical examination and weight
- 12-lead ECG
- ECOG performance status
- Blood and urine samples for laboratory safety tests (serum chemistry, haematology, coagulation profile, complement and urinalysis)
- Tumour imaging and evaluation
- Adverse events since informed consent

Results of standard of care tests or examinations performed before obtaining informed consent and within 30 days before the start of study treatment may be used; such tests do not need to be repeated for screening.

All screening evaluations must be completed and reviewed to confirm that patients meet all eligibility criteria before the first dose of study treatment. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

## 7.2 Treatment Period Assessments

Procedures are presented by nominal study day.

**Urinalysis must be performed at least once a week during the study treatment period (even if treatment is delayed for any reason). A retained sample will be taken whenever urinalysis results are positive for proteinuria (in case viral shedding or biomarker assessment is required in future).**

If a patient experiences adverse reactions that are of potential inflammatory origin, extra samples may be taken at any time for analysis of cytokines, antibodies and pharmacokinetics. This will be based on clinical judgement.

Post-dose assessments are to be performed immediately after the end of the IT injection procedure or IV infusion, unless otherwise stated.

### *7.2.1 Dosing Day Assessments - Day 1 (All Patients) and Days 3 and 5 (±1 day) (IV Treated Patients only)*

#### *7.2.1.1 Pre-dose*

- Re-check of eligibility criteria (Day 1 only)
- Adverse events since the previous assessment
- New or changes to existing medications
- Physical examination and weight
- Vital sign measurements
- 12-lead ECG
- ECOG performance status
- Blood and urine samples for laboratory safety tests (serum chemistry, haematology, coagulation profile, complement, and urinalysis) – these may be performed up to 24 hours pre-dose to ensure availability of results
- Blood sample for NG-350A pharmacokinetics
- Blood sample for cytokine responses
- Antipyretic prophylaxis administration at 1 hour pre-dose

The following will be performed on Day 1 only:

- Blood sample for thyroid function
- Blood sample for anti-NG-350A and anti-CD40 antibody responses
- Blood sample for immunophenotyping (from patients at selected centres)

- Blood sample for tumour specific serum biomarkers (patients with colorectal, ovarian, pancreatic or prostate cancers only)
- Buccal and rectal swabs and a urine sample for viral shedding
- Tumour biopsies (may be taken any time between screening and Day 1 pre-dose)

*7.2.1.2 NG-350A Administration*

- For IT treated patients the diluted virus will be administered using repeated needle insertions for each patient based upon the available surface area of the tumour.
- For IV treated patients: IV infusion of NG-350A starting at time zero administered directly into the venous access point using a syringe pump

*7.2.1.3 Post-dose*

- Blood sample for NG-350A pharmacokinetics immediately after the end of the injection or infusion (±5 minutes)
- Vital sign measurements immediately after the end of the injection or infusion (±5 minutes) and 30 minutes (±5 minutes), 1 hour (±10 minutes), 4 hours (±30 minutes) and 8 hours (±1 hour) post-dose. The 8 hour sample is required on Day 1 but is optional on Days 3 and 5 for IV treated patients, providing the patient is well (otherwise it is still required)
- Antipyretic prophylaxis at 3 hours post-dose and thereafter every 4 to 6 hours
- Prophylactic IV hydration, unless clinically contraindicated (IV treated patients only)
- Blood sample for cytokine responses 6 to 8 hours post-dose
- Continuous assessment of adverse events

### *7.2.2 Non-dosing Day Assessments (all ±1 day)*

The following will be performed on Days 8, 15, 22 and 29:

- Adverse events since the previous assessment
- New or changes to existing medications
- Physical examination and weight
- Vital sign measurements
- 12-lead ECG
- ECOG performance status
- Blood and urine samples for laboratory safety tests (serum chemistry, haematology, coagulation profile, complement, and urinalysis)
- Blood sample for cytokine responses
- Blood sample for anti-NG-350A and anti-CD40 antibody responses

The following will be performed at the selected visits indicated:

- Blood sample for NG-350A pharmacokinetics (Day 15)
- Blood sample for immunophenotyping (Day 15) (from patients at selected centres)

- Buccal and rectal swabs and a urine sample for viral shedding (Days 8, 15 and 29)
- For patients not undergoing surgical excision/resection: tumour biopsies (Day 15 [required] and Day 29 [optional])
- For patients undergoing surgical excision/resection: surgical excision/resection of the tumour/tumour lesion between Days 8 and 29 (IT injection) or Days 10 and 29 (IV infusion)
- Blood sample for tumour specific serum biomarkers (patients with colorectal, ovarian, pancreatic or prostate cancers only) (Day 29 only)

### *7.2.3 End of Study Treatment Visit Assessments – Day 57 (±3 days)*

The following will be performed:

- Adverse events since the previous assessment
- New or changes to existing medications
- Tumour imaging and evaluation
- Urine or serum pregnancy test (females of childbearing potential only)
- Physical examination and weight
- Vital signs
- 12-lead ECG
- ECOG performance status
- Blood and urine samples for laboratory safety tests (blood chemistry, haematology, coagulation, complement, thyroid function and urinalysis)
- Blood sample for NG-350A pharmacokinetics
- Blood sample for immunophenotyping (from patients at selected centres)
- Blood sample for anti-NG-350A and anti-CD40 antibody responses
- Blood sample for cytokine responses
- Blood sample for tumour specific serum biomarkers (patients with colorectal, ovarian, pancreatic or prostate cancers only)
- Buccal and rectal swabs and a urine sample for viral shedding
- For patients not undergoing surgical excision/resection: tumour biopsies (required) (unless the patient has disease progression before the end of study treatment visit, then these biopsies should be taken at the time of progression)

*Note: Patients discontinuing study treatment and continuing the study should attend the end of study treatment visit on Day 57.*

*Patients discontinuing the study during the study treatment period should, wherever possible, have the end of study treatment visit procedures performed before discontinuation.*

## 7.3 Follow-up Period Assessments

After the end of study treatment visit, patients without confirmed disease progression will attend follow-up visits every 8 weeks (±3 days for the first scan, ±7 days thereafter) to align with the tumour assessment schedule. The following will be performed:

- Tumour imaging and evaluation
- ECOG performance status
- Urinalysis. A retained sample will also be taken (in case viral shedding or biomarker assessment is required in future)
- New study treatment-related adverse events since the end of study treatments visit
- Administration of treatments used to treat study treatment-related toxicities
- Additional, voluntary blood samples for measurement of anti-NG-350A and anti-CD40 antibody responses and tumour specific biomarkers may be taken

Visits will continue to be scheduled until disease progression is confirmed.

Patients will then be followed-up for overall survival, further cancer therapy and its best response and the date of disease progression on further cancer therapy every 8 weeks (±7 days) (unless death or one of the criteria for study discontinuation is met, see Section 5.4.2 or the end of the study is reached, whichever occurs first). Follow-up after disease progression may be performed by telephone calls or at routine visits to the hospital.

Patients with confirmed disease progression at the end of study treatment visit will also continue to be followed-up for overall survival, further cancer therapy and its best response and the date of disease progression on further cancer therapy every 8 weeks (±7 days) as above.

## 7.4 Assessments at Unscheduled Visits

Unscheduled visits and procedures may be required according to by the patient's condition, for example to manage adverse events. All assessments performed will be recorded in the eCRF.

# 8 DETAIL OF STUDY ASSESSMENTS

## 8.1 Demographic and Baseline Assessments

The following will be collected at screening to determine eligibility and baseline status of the patient. Baseline safety assessments will also be performed as detailed in Section 8.5.

### *8.1.1 Demographic Data and Baseline Variables*

Demographic data will include age, sex, height and self-reported race/ethnicity, smoking history, use of alcohol and drugs of abuse.

### *8.1.2 Medical and Cancer History*

Medical history including clinically significant diseases and surgeries will be recorded. **The Investigator must be specifically vigilant to ensure all renal medical history is disclosed and recorded.**

Cancer history (including date of diagnosis and all prior cancer therapies and procedures) will also be recorded, including the microsatellite instability status of the tumour, where available.

### *8.1.3 Prior Medications and Therapies*

All prior cancer therapies and procedures will be recorded.

All other prior medications (e.g. prescription drugs, over the counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient in the 14 days before the start of study treatment will also be recorded.

### *8.1.4 Pregnancy Test*

A urine or serum pregnancy test sensitive to at least 25 IU/L, or equivalent units, of hCG will be performed in female patients of childbearing potential and confirmed to be negative in the 24 hours before the first dose of study treatment. Pregnancy tests will be repeated at the end of study treatment visit.

## 8.2 Efficacy Assessments

### *8.2.1 Tumour Imaging*

#### *8.2.1.1 Imaging Methods and Assessments*

The following is applicable in patients not undergoing surgical excision/resection and patients undergoing surgical excision/resection if the resected lesion was not the target lesion:

Tumour imaging will be performed at baseline (screening or within a maximum of 30 days before the start of study treatment) and then every 8 weeks (±3 days for the first scan, ±7 days of the scheduled visit thereafter) from the first dose of study treatment until disease progression is confirmed, starting at the end of study treatment visit. If there is suspicion of disease progression based on clinical or laboratory findings before the first scheduled assessment, an unscheduled assessment should be performed.

The tumour response will be measured using CT or MRI and (if indicated) isotope bone scan. Bone scan, Positron Emission Tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. For each patient, the same method of assessment and the same technique **must** be used to evaluate each lesion throughout the entire

study. **(Use of spiral CT or MRI is required for baseline lesions <20 mm and must be documented in medical records and used consistently throughout the study.)** The use of oral and IV contrast etc. should, as long as it is clinically possible, be kept consistent. If more than one method is used, the most accurate method should be selected when recording data.

Tumour measurements should be made by the same Investigator/radiologist for each patient during the study to the extent that this is feasible. In case of clinically measurable superficial (such as skin) lesions, repeated photographs should be used to document tumour response. These photographs must include a ruler for documentation purposes.

The images will be assessed using RECIST Version 1.1 [21] (see Appendix 1). All patients will also have their tumor response assessed using iRECIST guidelines [22] (see Appendix 2); because of the possibility of pseudo-progression (tumour oedema and inflammation in response to viral uptake, replication and anti-CD40 antibody expression) it is important that any apparent tumour expansion should not be reported as disease progression until confirmed with a follow-up scan at least 4 weeks (and up to 8 weeks) later according to iRECIST. The principles used to establish objective tumour response with iRECIST are largely unchanged from RECIST Version 1.1, but the major change for iRECIST is the concept of "resetting the bar" if RECIST Version 1.1 disease progression is followed at the next assessment by tumour shrinkage. iRECIST defines unconfirmed disease progression assigned using iRECIST; (iUPD) on the basis of RECIST Version 1.1 principles; however, iUPD requires confirmation, which is done on the basis of observing either a further increase in size (or in the number of new lesions) in the lesion category in which disease progression was first identified in (i.e. target or non-target disease), or progression (defined by RECIST Version 1.1) in lesion categories that had not previously met RECIST Version 1.1 disease progression criteria. However, if disease progression is not confirmed, but instead tumour shrinkage occurs (compared with baseline), which meets the criteria of complete response, partial response or stable disease assigned by iRECIST, then the bar is reset so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment for confirmed progression assigned using iRECIST (iCPD) to be assigned. If no change in tumor size or extent from iUPD occurs, then the time point response would again be iUPD. This approach allows atypical responses, such as delayed responses that occur after pseudo-progression, to be identified, further understood, and better characterised.

#### *8.2.1.2 Local and Independent Imaging Review*

The Investigator will evaluate efficacy outcome measures e.g. radiological disease progression in order to make clinical decisions during the course of the study and to determine the patient's next study visit. The outcome of the patient's response evaluation using RECIST Version 1.1 and iRECIST will be recorded in the patient's source documents and in the eCRF.

Images will be submitted to a central imaging vendor. Each study centre will be trained on how to submit these scans prior to scanning the first patient. Image acquisition guidelines and submission process will be outlined in the Imaging Manual.

Depending on the responses seen, the images may also be reviewed by an Independent Reviewer at the central imaging vendor using RECIST Version 1.1 and iRECIST and assign responses for all patients. The Independent Reviewer will receive anonymised scans/materials and will be blinded to the clinical history, patient outcomes and the responses assigned to them by the treating Investigator.

### *8.2.2 Clinical Progression/Deterioration*

Clinical progression/deterioration of disease will be assessed continuously throughout the study. The determination of clinical progression/deterioration is left to the discretion of the Investigator and the reason(s) for the determination will be recorded in the eCRF.

### *8.2.3 Follow-up beyond Disease Progression*

If the patient dies at any time during the study, the date of death will be recorded in the eCRF. If a patient dies when lost to follow-up, this can be obtained from the public death register.

Once radiological disease progression has been confirmed, patients will be followed-up for overall survival, further cancer therapy and its best response and the date of disease progression on further cancer therapy every 8 weeks (±7 days). This may be performed by telephone calls or at routine visits to the hospital.

## 8.3 Pharmacokinetic Assessments

Blood samples for measurement of NG-350A pharmacokinetics will be taken at the following timepoints:

- IT injection: Day 1 pre-dose and post-dose, Day 15 and the end of study treatment visit
- IV infusion: Days 1, 3 and 5 pre-dose and post-dose, Day 15 and the end of study treatment visit

Post-dose samples will be taken immediately after the end of the injection or infusion (±5 minutes).

Whole blood will be taken into anti-coagulant tubes.

Samples will be taken, handled, stored and shipped for analysis of NG-350A concentration according to the Laboratory Manual.

## 8.4 Pharmacodynamic and Exploratory Assessments

Full details of how all samples will be taken, handled, stored and shipped will be provided in the Laboratory Manual. Any aliquots not used for the analyses described in this section will be retained and may be used for research purposes.

### *8.4.1 Immunogenicity*

Blood samples for anti-NG-350A and anti-CD40 antibody titre analyses will be taken pre-dose on Day 1 and on Days 8, 15, 22 and 29 and the end of study treatment visit

Additional, voluntary blood samples may be taken during the follow-up period.

At each timepoint, blood will be taken into serum tubes, centrifuged, serum aliquoted and stored frozen.

### *8.4.2 Viral Shedding Assessments*

Buccal and rectal swabs and urine samples for viral shedding analysis will be taken pre-dose on Day 1 and on Days 8, 15, 29 and the end of study treatment visit

Buccal and rectal swabs will be taken and frozen. Urine samples will be taken using a clean catch method of collection, aliquoted and stored frozen.

### *8.4.3 Cytokines*

Blood samples for analysis of cytokine responses will be taken at the following timepoints:

- IT injection: Day 1 pre-dose and 6 to 8 hours post-dose; Days 8, 15, 22 and 29 and the end of study treatment visit
- IV infusion: Days 1, 3 and 5 pre-dose and 6 to 8 hours post-dose; Days 8, 15, 22, 29 and the end of study treatment visit

At each timepoint, blood will be taken into a serum tube, centrifuged, serum aliquoted and stored frozen.

### *8.4.4 Tumour Biomarkers*

Tumour samples (tumour biopsies or excised/resected tumour tissue) will be taken to explore pharmacodynamic and potentially predictive markers of study treatment activity and to enhance the understanding around disease biology and mechanism of action of NG-350A. All patients will be required to provide consent to provide fresh tumour tissue. Samples will be taken, handled, stored and shipped to the central laboratory according to the laboratory manual.

Analyses of tumour tissue will be aimed at exploring virus replication, transgene expression and potential immune/inflammatory responses to those activities of NG-350A. A number of different techniques may be applied to these studies (e.g. qPCR, reverse transcription qPCR, Nanostring or other gene expression analysis techniques, immunohistochemistry, protein analyses to detect anti-CD40 antibody).

All patients will have baseline biopsies any time between screening (after eligibility has been confirmed) and Day 1 pre-dose in a manner judged safe by the Investigator. This may include endoscopic biopsy, excisional biopsy, and/or core biopsy. Radiologic or ultrasound guidance may be used as appropriate. Fine needle aspiration will not provide sufficient tissue and should not be performed. Every effort should be made to obtain five cores; at least two cores must be obtained.

Post-dose samples for assessment of tumour biomarkers will then be taken according to Section 8.4.4.1 for patients who are candidates for surgical tumour excision/resection and according to Section 8.4.4.2 for all other patients.

Other tumour samples may also be collected in the event a patient undergoes any surgical procedure whilst taking part in the study.

#### *8.4.4.1 Patients undergoing Surgical Excision/Resection*

For patients undergoing surgical excision/resection, the baseline biopsies must be taken from the tumour to be excised.

These patients will be hospitalised according to study centre standard practice for surgery between Days 8 and 29 for IT injection and between Days 10 and 29 for IV infusion. Appropriate methods will be used for excision/resection of the primary tumour/tumour lesion (e.g. endoscopic, open or robotic surgery, endoscopic resection) according to the judgment of the surgeon and depending on the tumour location. Lymph node resection is optional and may be performed if part of standard procedure for each patient. The excised/resected tissue will be sampled and used for post-dose analysis of tumour biomarkers.

#### *8.4.4.2 Patients not undergoing Surgical Excision/Resection*

For patients not undergoing surgical excision/resection, the baseline sample must be taken using the same core biopsy method as planned for the study biopsies. Post-dose biopsies will then be taken on Day 15 (required), Day 29 (optional) and the end of study treatment visit (required) for all patients (unless the patient has disease progression before the end of study treatment visit, then this biopsy should be taken at the time of progression).

For IT patients, biopsies should be taken from the same regions of tumour that were IT injected where feasible.

All biopsies will only be taken if the clinical risk is deemed acceptable (as judged by the Investigator based upon the patient's health at the time of the visit). Patients will not be discontinued if they do not provide biopsies at all timepoints.

At each timepoint, every effort should be made to obtain five cores; at least two cores must be obtained.

If adequate tissue cannot be obtained during the biopsy procedure, repeat biopsies at that time point are not required. Inadequate tissue collection at baseline does not prohibit the collection of the biopsies during the study treatment period.

### *8.4.5 Tumour Specific Serum Biomarkers*

Blood samples for analysis of tumour specific biomarker responses (prostate specific antigen [PSA], PSA doubling time, carcinoembryonic antigen [CEA], cancer antigen [CA]-125, CA19-9) will be taken from patients with colorectal, ovarian, pancreatic and prostate cancer only pre-dose on Day 1, on Day 29 and at the end of study treatment visit

Additional, voluntary blood samples may be taken during the follow-up period.

At each timepoint, blood will be taken into an anti-coagulant tube, centrifuged, serum aliquoted and stored frozen. The analyses will be performed at the study centre's local laboratory.

### *8.4.6 Immunophenotyping*

Blood samples for immunophenotyping will be taken from patients at selected centres pre-dose on Day 1, on Day 15 and at the end of study treatment visit

Whole blood will be taken into an anti-coagulant tube and shipped immediately to the testing laboratory.

### *8.4.7 Additional Research Assays*

Residual plasma, serum, blood, tissue or tumour samples used for the assessment of primary, secondary and exploratory objectives may be retained for additional research, except where prohibited by local laws or regulations. Additional techniques may be used to explore the mechanism of action of NG-350A (for example to assess virus activities and expression of anti-CD40 antibodies and effects on the tumour cells, immune and inflammatory responses or to identify biomarkers) in order to optimise their applicability for treating patients and/or to explore the development of potential biomarker assays for monitoring patient responses to treatment in future studies. This may also include molecular analysis of viral, cell or tissue DNA or RNA aimed at exploring disease pathways, progression, and response to treatment. The nature of the analyses will be dependent on the information generated in the initial assessments and the most suitable techniques available at the time of analysis. Due to the

exploratory nature of these further assessments and the rapidly evolving nature of research, novel techniques may be utilised.

The results of these additional tests will not affect any of the patients' planned treatment but may help other cancer patients in the future.

After the additional tests have been performed, any leftover samples will be destroyed at the end of the scheduled storage period, no longer than 15 years after the end of the study or the maximum allowed by applicable law. All samples will be coded.

Samples will be taken, handled, stored and shipped according to the laboratory manual.

Pharmacogenetic tests by definition look for genetic variants in a patient's germline DNA that are associated with disease or variable response to specific medications. In this study, there will no such pharmacogenetic testing. DNA or RNA isolated from cells or tissues will only be used in tests exploring possible responses to the treatment.

### *8.4.8 Additional Non-study Samples*

In addition, patients undergoing unplanned surgery, biopsies or collection of body fluids during study treatment or in the follow-up period may be asked to provide samples (both tumour and non-tumour samples) for analysis.

## 8.5 Safety Assessments

### *8.5.1 Adverse Events*

Recording and reporting of adverse events is described in detail in Section 9.1.

### *8.5.2 Laboratory Safety Tests*

Samples for the following laboratory tests will be taken according to the laboratory manual and sent to the study centre's local laboratory for analysis:

| | |
|---|---|
| Serum chemistry | Sodium, potassium, glucose, calcium, blood urea nitrogen or urea, creatinine and eGFR, total and direct bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, lactate dehydrogenase, creatine phosphokinase, uric acid, amylase, lipase, C-reactive protein |
| Haematology: | Haemoglobin, haematocrit, platelet count, red blood cell count, white blood cell count and absolute differential (neutrophils, eosinophils, lymphocytes, monocytes, basophils, other cells) |
| Coagulation profile: | Prothrombin time, activated partial thromboplastin time, fibrinogen and D-dimers |
| Complement: | C3 and C4 proteins |
| Thyroid function: | Thyroid stimulating hormone, with T4 and free T3 reflex testing |

Samples will be taken at screening, pre-dose on Day 1 (all patients), pre-dose on Days 3 and 5 (IV treated patients only) and on Days 8, 15, 22 and 29 and the end of study treatment visit, with the exception of thyroid function tests which will only be performed on Day 1 and the end of study treatment visit.

All samples on each dosing day will be taken pre-dose. A window of -24 hours is permitted on dosing days to allow availability of results before dosing. All results for the Day 1 pre-dose samples must be available before study treatment in the cycle is started. The urinalysis and serum creatinine results must be available before study treatment administration on Days 3 and 5 for IV treated patients.

The Investigator or an authorised physician must interpret the laboratory findings and sign and date the laboratory report to confirm their review. Clinically significant changes during the study should be reported as adverse events.

A urine dipstick for leukocytes, blood and protein will also be performed once a week. The urinalysis on Days 36, 43 and 50 may be performed in the clinic or at home and the results reported to the study centre (a clinic visit will then be required in the event of positive results for proteinuria).

Any urinalysis results that are positive (≥1+) for proteinuria must be confirmed by repeat testing. **Positive results that have not worsened since the previous visit do not need to be confirmed and quantified.**

If proteinuria is confirmed, no NG-350A should be administered and a spot ACR and 24 hour urinary protein should be performed.

If ACR >3 mg/mmol or 24 hour urinary protein ≥0.2 gm/24 hours or there is a decline in eGFR or consumption of complement (C3/C4 proteins) then the Sponsor must be contacted and the following two step process should be performed:

1. Full renal work-up, including examination of urine sediment, then commence high dose corticosteroids and then, if further decline, proceed to step 2.
2. Renal biopsy, followed by plasmapheresis.

Note: the use of anti-viral agents is not recommended.

Cases of treatment-emergent positive proteinuria (≥1+ when negative or trace at baseline) or worsening treatment-emergent proteinuria (when positive at baseline) must be followed until resolution if still present at the end of study treatment visit.

A retained sample will be taken whenever urinalysis results are positive (in case viral shedding or biomarker assessment is required in future).

### *8.5.3 Vital Signs and 12-lead ECGs*

Vital signs will include measurements of supine heart rate, systolic and diastolic blood pressure respiratory rate and temperature.

Vital signs will be measured at screening, on Day 1 (all patients), Days 3 and 5 (IV treated patients only) and on Days 8, 15, 22 and 29 and the end of study treatment visit, On NG-350A dosing days (Day 1 for IT treated patients and Days 1, 3 and 5 for IV treated patients) measurements will be made pre-dose, immediately after the end of the injection or infusion (±5 minutes) and 30 minutes (±5 minutes), 1 hour (±10 minutes), 4 hours (±10 minutes) and 8 hours (±1 hour) post-dose. The 8 hour sample is required on Day 1, it is optional on Days 3 and 5 providing the patient is well (otherwise it is still required). Clinically significant changes during the study should be reported as adverse events.

12-lead ECGs will also be performed at screening, on Day 1 (all patients), Days 3 and 5 (IV treated patients only) and on Days 8, 15, 22 and 29 and the end of study treatment visit. ECG findings (normal, abnormal but not clinically relevant and abnormal and clinically relevant) will be collected.

### *8.5.4 Physical Examination and ECOG Performance Status*

A physical examination will be performed at screening, on Day 1 (all patients), Days 3 and 5 (IV treated patients only) and on Days 8, 15, 22 and 29 and the end of study treatment visit. A complete physical examination, including a complete evaluation of body systems will be

performed at screening. At subsequent visits, examination should be performed and changes from baseline abnormalities recorded. Clinically significant new or worsened abnormalities should be recorded as adverse events.

Weight will be also measured at each timepoint

Performance status, to assess the effect on living ability, will also be assessed at each visit according to the ECOG scale in Table 4 [23].

**Table 4 Eastern Co-operative Oncology Group Performance Status Scale**

| Grade | Scale |
|---|---|
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, i.e. light housework, office work |
| 2 | Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited self-care, confined to bed or chair more than 50% of waking hours |
| 4 | Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair |
| 5 | Dead |

# 9 SAFETY MANAGEMENT

The Sponsor (or designee) has primary responsibility for the ongoing medical review of safety data throughout the study. This includes immediate review of SAEs and timely review of other adverse events reported during the study.

## 9.1 Adverse Events

### *9.1.1 Definitions*

#### *9.1.1.1 Adverse Event*

An adverse event is:

- Any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment
- An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of study treatment, whether or not considered related to the study treatment

An adverse event includes but is not limited to:

- Any clinically significant worsening of a pre-existing condition
- An adverse event occurring from overdose (i.e. a dosage higher than that prescribed by a healthcare professional for clinical reasons, or a dosage higher than that described in the Investigator's Brochure or on the marketed product label) of an investigational or marketed product, whether accidental or intentional
- An adverse event occurring from abuse (e.g. use for non-clinical reasons) of an investigational or marketed product
- An event related to a medical procedure or associated with the discontinuation of the previous use of an investigational or marketed product required by protocol (protocol related adverse event)
- Not all vital sign or laboratory abnormalities will be considered an adverse event. Usually these will be considered as an adverse event:
  - If Grade 3 or Grade 4 in severity
  - If judged to be clinically significant by the Investigator
  - If accompanied by clinical symptoms
  - If meeting the definition of an SAE
  - If resulting in dose modification, interruption or discontinuation of study treatment
  - If requiring specific treatment
- Pyrexia is not considered an adverse event if <100.4ºF (38.0ºC)
- Where possible an abnormal vital sign or laboratory result should be reported using the clinical or diagnostic term rather than the test result e.g. thrombocytopenia rather than decreased or low platelets. Conversely, where a clinical or diagnostic term is used there should be corresponding clinically significant abnormal values on the vital sign or laboratory results eCRF for the timeframe of the event

*9.1.1.2 Adverse Reaction*

An adverse reaction is defined as all untoward and unintended responses to an Investigational Medicinal Product related to any dose administered.

An unexpected adverse reaction is an adverse reaction in which the nature or severity of which is not consistent with the Investigator's Brochure or Prescribing Information.

*9.1.1.3 Serious Adverse Event*

An SAE is any untoward medical occurrence or effect that at any dose that:

- Results in death
- Is life threatening. This term refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- Requires in patient hospitalisation (other than pre-planned hospitalisation including any hospitalisation for chemotherapy and hospitalisation for disease progression) or prolongation of existing hospitalisation
  - In general, hospitalisation signifies that the patient has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in an outpatient setting. Complications that occur during hospitalisation are adverse events. If a complication prolongs hospitalisation or fulfils any other serious criteria, the event is serious
  - The following hospitalisation scenarios are not considered to be SAEs:
    a. Hospitalisation for respite care (hospice facilities, nursing homes)
    b. Planned hospitalisation required by the protocol
    c. Hospitalisation for a pre-existing condition provided that (i) the hospitalisation was planned before the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of the disease and (ii) the patient has not suffered an adverse event
    d. Hospitalisation or prolongation of hospitalisation for scheduled therapy of the target malignancy of the study

    When in doubt as to whether "hospitalisation" occurred or was necessary, the adverse event should be considered serious.
- Results in persistent or significant disability/incapacity

  The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect in offspring of the patient
- Is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above

Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalisations; or development of drug dependency or drug abuse.

#### *9.1.1.4 Suspected Unexpected Serious Adverse Reaction*

A Suspected Unexpected Serious Adverse Reaction (SUSAR) is any suspected adverse reaction related to the study treatment that is both unexpected and serious.

### *9.1.2 Study Reporting Period for Adverse Events*

The reporting period for all adverse events begins on the date the informed consent is signed until the end of study treatment visit or 28 days after the last dose of study treatment, whichever is later and for all serious or study treatment-related adverse events until these are resolved or until patient contact discontinues. The Medical Monitor may specify a longer period of time, if required to assure the safety of the patient.

During the follow-up period the following will be collected:

- Resolution information for ongoing adverse events from the study treatment period
- New treatment-related adverse events (adverse reactions) only

Adverse event information will be collected at study visits and patients will be instructed to call study centre personnel to report any abnormalities during the intervals between study visits and to come to the study centre if medical evaluation is needed and the urgency of the situation permits.

### *9.1.3 Reporting Exemptions*

Disease progression or events clearly determined to be solely due to underlying disease progression will not be captured as an adverse event or SAE unless resulting in death.

Hospitalisation due solely to the progression of underlying malignancy will NOT be considered an SAE.

### *9.1.4 Recording and Assessment of Adverse Events by the Investigator*

All adverse events, both those observed by study centre personnel and those spontaneously reported by the patient, will be recorded in the eCRF. Adverse events will be reported using a recognised medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the Investigator, or appropriately qualified designee, for severity, relationship to study treatment, action taken with study treatment, outcome and whether the event meets criteria as an SAE according to the following guidelines:

#### *9.1.4.1 Assessment of Severity*

Whenever possible, the severity of adverse events will be graded according to the NCI CTCAE Version 5.0 grading system [24]. The scale shown in Table 5 will be used to assess severity of adverse events not listed on the NCI CTCAE grading system.

**Table 5 Severity Grading of Adverse Events not listed on the Common Terminology Criteria for Adverse Events Grading System**

| Grade | Severity | |
|---|---|---|
| 1 | Mild | Asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated; no disruption of normal daily activity. |
| 2 | Moderate | Minimal, local, or non-invasive intervention indicated; discomfort sufficient to reduce or affect daily activity. |
| 3 | Severe | Severe or medically significant, but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; inability to work or perform normal daily activity. |
| 4 | Life-threatening | Represents an immediate threat to life. |
| 5 | Fatal | Death as a result of this adverse event |

Note: It is important to distinguish between serious and severe adverse events. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 9.1.1.1.

#### *9.1.4.2 Assessment of Relationship*

When assessing the relationship of an adverse event to study treatment, the Investigator should consider (but not limited to):

- Temporal relationship of event onset to the initiation of study treatment
- Course of the event in relation to study treatment, discontinuation or reintroduction
- Medical history and presence of risk factors
- Underlying disease and known association of the event with the disease under study
- Concomitant medications and previous medical or surgical treatment
- Social and environmental factors
- Protocol related procedures
- Known association of the event with the study treatment or with similar treatments

The Investigator should also consider their knowledge of the patient, the circumstances surrounding the event and an evaluation of any potential alternative aetiology to determine whether or not an adverse event is considered to be related to study treatment.

The Investigator will assess the relationship of the adverse event as either:

- Related: there is a reasonable causal relationship between the adverse event and study treatment or
- Not related: there is no reasonable causal relationship between the adverse event and study treatment (the patient either did not receive the study treatment or the event is related to aetiology other than the study treatment [the alternative aetiology must be documented in the patient's medical record])

#### *9.1.4.3 Action Taken with Study Treatment*

The action taken with the study treatment will be recorded as:

- None
- Dose interrupted

- Dose reduced
- Dose permanently discontinued
- Not applicable

#### *9.1.4.4 Assessment of Outcome*

The outcome of the adverse event will be assessed as:

- Recovered/resolved
- Recovered/resolved with sequelae
- Not recovered/resolved
- Unknown
- Fatal

#### *9.1.4.5 Investigator Follow-up*

The Investigator should follow-up each adverse event until the event has resolved to baseline or Grade 1, the event is assessed as stable by the Investigator, the patient is lost to follow-up or the patient withdraws consent.

SAEs must be followed up to resolution by the Investigator, even if this extends beyond the study reporting period. Resolution of an SAE is defined as the return to baseline status, NCI CTCAE Grade 1 or stabilisation of the condition with the expectation that it will remain chronic.

### *9.1.5 Reporting Requirements and Procedures for SAEs*

SAEs occurring during the reporting period in Section 9.1.2 require immediate notification to the Sponsor. SAEs occurring any time after the reporting period must be promptly reported to the Sponsor (or designee) if a causal relationship to study treatment is suspected.

#### *9.1.5.1 Immediate Reporting of SAEs to the Sponsor*

The Investigator must report all SAEs immediately to the Sponsor except for those that the protocol or Investigator's Brochure identifies as not requiring immediate reporting.

Immediate reporting allows the Sponsor to take the appropriate measures to address potential new risks in a clinical study. The immediate report should therefore be made by the Investigator within a very short period of time and under no circumstances should this exceed 24 hours following knowledge of the SAE.

The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter.

Should the regulatory authority require that the Sponsor submit additional data on the event, the Investigator will be asked to provide those data to the Sponsor in a timely fashion.

#### *9.1.5.2 Information to be provided by the Investigator for an SAE*

All SAE information available at the time of form completion must be provided.

The Sponsor (or designee) will require all of the following information about the patient and the event:

- Investigator identification

- Patient identification code (e.g. sex, age or year of birth)
- Information on study treatment (e.g. start/stop date, dose and frequency of study treatment administered)
- Description of event

In addition to the above information, the Sponsor will require the Investigator's assessment of the following:

- Severity of the SAE
- Relationship of the SAE to the study treatment
- Outcome of the SAE

Information should be provided on the paper SAE report form signed and dated by the Investigator. The paper SAE report form should be emailed (or faxed) using the information stated on the form.

*9.1.5.3 Follow-up Information on an SAE*

Appropriate diagnostic tests should be performed and therapeutic measures, as medically indicated, should be instituted. Appropriate consultation and follow-up evaluations should be carried out until the event has resolved or is otherwise explained by the Investigator. For all SAEs, the Investigator is obligated to pursue and provide information to the Sponsor. In addition, an Investigator may be requested by the Sponsor to obtain specific information in an expedited manner. This information may be more detailed than that captured on the SAE form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes such as concomitant medication and illnesses must be provided.

After the initial SAE report, the Investigator is required to follow each patient proactively and to report new significant follow-up by submitting an updated SAE report form to the Sponsor (or designee). New significant information includes, but is not limited to, the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

*9.1.5.4 Medical Review and Reporting by the Sponsor*

The Sponsor (or designee) will determine expedited reporting requirements for each reported SAE according to local requirements based upon:

- Investigator's assessment of causality and seriousness, with allowance for upgrading following independent review by the Sponsor (or designee) as needed
- Expectedness

The expectedness of an SAE is assessed by the Sponsor in the overall classification of SAEs for expedited reportability. The current Investigator's Brochure section "Reference Safety

Information" will be used as the reference for determination of expectedness and risk assessment of treatment-related adverse events.

#### *9.1.5.5 Sponsor Responsibility for Expedited Safety Reports*

The Sponsor (or designee) will notify Investigators of all reportable SAEs. This notification will be in the form of an expedited safety report. Upon receiving such notices, the Investigator must review and retain the notice with other study related documentation.

The Investigator should also comply with the IEC/IRB procedures for reporting any other safety information.

The Sponsor will ensure that SAEs are reported to the IEC/IRB and regulatory authority(ies) according to local requirements.

SUSARs and other significant safety issues reported from the development programme shall be reported to the relevant regulatory authorities in all concerned countries according to local regulations (either as expedited safety reports and/or in aggregate reports), by the Sponsor (or designee).

### *9.1.6 Post-Study Adverse Events*

At the final study visit, the Investigator should instruct each patient to report to the Investigator any subsequent adverse events that the patient's personal physician believes could be related to prior study treatment or study procedures.

The Investigator should notify the Sponsor (or designee) of any death, SAE or other adverse event of concern occurring at any time after a patient has discontinued study treatment if the event is believed to be related to prior study treatment or study procedures. The Sponsor (or designee) should also be notified if the Investigator becomes aware of the development of cancer or a congenital anomaly/birth defect in a subsequently conceived offspring of a patient that participated in this study.

The Investigator should record the event in the eCRF; if the eCRF is no longer available, the Investigator should report the event directly to the Sponsor (or designee).

## 9.2 Events of Special Interest

The following renal events of special interest have been prospectively identified for this study:

- Acute kidney injury, blood creatinine increased, glomerulonephritis mebranoproliferative, nephrotic syndrome, proteinuria, renal failure, estimated creatinine clearance decreased, nephrotoxicity

These will be treated as SAEs as detailed in Section 9.1.5.

## 9.3 Overdoses

Study treatment overdose is the accidental or intentional use of the study treatment in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not an adverse event unless it results in untoward medical effects. However, all study treatment administration errors a (not just those associated with adverse events) need careful consideration and monitoring:

- Any study treatment overdose or incorrect administration of study treatment should be recorded in the eCRF as part of the study treatment dose administration information

- Any untoward medical effects associated with an overdose or incorrect administration of study treatment should be recorded in the eCRF as an adverse event. If the associated adverse event fulfils serious criteria, the event should be reported to the Sponsor (or designee) within 24 hours of knowledge of the event

## 9.4 Management of Pregnancy

Contraception requirements for females of childbearing potential and males with sexual partners of childbearing potential are specified in Appendix 3.

### *9.4.1 Notification and Follow-up*

#### *9.4.1.1 Pregnancies in Female Patients*

Female patients of childbearing potential will be instructed to immediately inform the Investigator if they become pregnant during the study or within 6 months after the last dose of study treatment and must be immediately discontinued from study treatment. Any pregnancies during this period must be reported to the Sponsor (or designee) within 24 hours of knowledge of the event. Information should be provided on the paper pregnancy report form signed and dated by the Investigator. The paper pregnancy report form should be emailed (or faxed) using the information stated on the form.

The Investigator should counsel the patient, discussing the risks of the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy.

#### *9.4.1.2 Pregnancies in Female Partners of Male Patients*

Male patients will be instructed to immediately inform the Investigator if their partner becomes pregnant during the study or within 6 months after the last dose of study treatment. Any pregnancies during this period must be reported to the Sponsor (or designee) within 24 hours of knowledge of the event. Information should be provided on the paper pregnancy report form signed and dated by the Investigator. The paper pregnancy report form should be emailed (or faxed) using the information in the contact section of this protocol and as stated on the form.

Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study treatment. The pregnant partner will need to sign an authorisation for use and disclosure of pregnancy health information to allow for follow-up on her pregnancy. The Investigator may provide information on the risks of the pregnancy and the possible effects on the foetus, to support an informed decision in co-operation with the treating physician and/or obstetrician.

### *9.4.2 Outcome*

Additional information on the course and outcome of the pregnancy should be provided to the Sponsor (or designee) when available using the paper pregnancy report form.

The following pregnancy outcomes will be considered to be SAEs and should be reported according to the procedure in Section 9.1.5.1. Pregnancy is not considered an adverse event unless one of these criteria is met:

- Spontaneous abortion (as the Sponsor considers spontaneous abortions to be medically significant events)
- Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient

# 10 DATA QUALITY ASSURANCE AND QUALITY CONTROL

## 10.1 Protocol Violations and Deviations

Major protocol deviations are defined as those that result in harm to the study patients or significantly affect the scientific value of the reported results of the study. Other deviations will be considered minor.

Protocol deviations will be recorded on the source documents and with an explanation for the deviation. All protocol deviations will also be recorded as specified in the monitoring plan and statistical analysis plan.

Major protocol deviations that meet the criteria for a serious breach of ICH GCP should be reported to the Sponsor immediately. No deviation from the inclusion/exclusion criteria will be permitted.

## 10.2 Monitoring

The Sponsor will arrange for the study to be monitored in accordance with the principles of ICH GCP. The frequency of on-site monitoring visits and source document verification will be determined by the rate of patient recruitment.

The following are examples of items that will be reviewed at these visits:

- Compliance with the protocol
- Consent procedure
- Source documents
- Adverse event procedures
- Storage and accountability of study treatment

The monitoring visits also provide the Sponsor with the opportunity to ensure that timely patient accrual and the other Investigator's obligations and all applicable requirements are being fulfilled.

The Investigator must permit the Study Monitor, the IEC/IRB, the Sponsor's auditors and representatives from regulatory authorities direct access to all source documents (see Section 12.1) for confirmation of the accuracy and reliability of data contained within the eCRF (source document verification). Patient confidentiality will be protected at all times. The Study Monitor will carry out source document verification at regular intervals. This is an essential element of quality control, as it allows the rectification of transcription errors and omissions.

In addition to on-site monitoring and source document verification the Contract Research Organisation will perform centralised monitoring with the output reviewed and actions agreed with the Sponsor. All monitoring requirements will be documented in the monitoring plan.

## 10.3 Data Management and Coding

Data for each patient will be recorded on an eCRF. Full data collection must be completed for each patient who signs an informed consent form and receives at least one dose of study treatment. For patients who fail screening and do not receive study treatment, only the date of screening and reason for screen failure and any adverse events relating to screening procedures will be recorded.

eCRF data collection tools will be designed and produced by the Sponsor (or designee) and should be completed by the study centre personnel in accordance with the instructions

provided. The Investigator is responsible for maintaining attributable, legible, contemporaneous, original, accurate medical records from which information will be transcribed directly into the eCRFs using a secure internet connection. The eCRFs should be fully completed by the Investigator (or designee) as stated on the delegation of responsibilities form. The eCRF system will be Food and Drug Administration (FDA) Code of Federal Regulations (CFR) 21 Part 11 compliant.

Data entered into the eCRF will be validated as defined in the data validation specifications. Validation includes, but is not limited to, validity checks (e.g. range checks), consistency checks and customised checks (logical checks between variables to ensure that study data are accurately reported) for eCRF data and external data (e.g. laboratory data and imaging data). A majority of edit checks will be triggered during data entry and will therefore facilitate efficient 'point of entry' data cleaning.

Data management personnel will perform both manual eCRF review and review of electronic edit checks to ensure that the data are complete, consistent and reasonable. The electronic edit checks will run continually throughout the course of the study and the issues will be reviewed manually online to determine what action needs to be taken.

Manual queries may be added to the system by clinical data management, the Medical Monitor or Study Monitor. Clinical Data Managers and Study Monitors are able to remotely and proactively monitor the eCRFs to improve data quality.

External data will be transferred electronically to Data Management. The data will be handled as documented in the Data Management Plan. Discrepancies will be queried to the study centre, laboratory or imaging vendor (as applicable) until the electronic data and the database are reconciled.

All updates to queried data will be made by authorised study centre personnel only and all modifications to the database will be recorded in an audit trail. The audit trail will show the original data, when it was entered (time and date), who entered it, what it was changed to (when and by whom).

Once all the queries have been resolved, the Investigator will review and approve the data entered into the eCRF and the eCRFs will be locked by password protection. Any changes to locked eCRFs will be approved by the Investigator.

Once the full set of eCRFs have been completed and locked, the Sponsor will authorise database lock and all electronic data will be sent to the designated statistician for analysis. Subsequent changes to the database will then only be made only by written agreement of the Sponsor.

Adverse events and medical/cancer history terms will be coded from the verbatim description (Investigator entered term) using the Medical Dictionary for Regulatory Activities (MedDRA dictionary). Prior and concomitant medications and therapies will be coded according to the World Health Organisation drug dictionary. Coding review will be performed by the Sponsor (or designee) prior to database lock.

The clinical data (in statistical analysis software [SAS] format) will be transferred to the Sponsor at the end of the study.

# 11 STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

## 11.1 Sample Size Determination

The number of patients in the IT cohort and dose escalation phase is typical for a Phase I study. However, unlike a standard 3+3 design, up to nine patients evaluable for DLT will be exposed to NG-350A in each dose escalation cohort to provide a better estimate of the MTD. The maximum number of patients evaluable for DLT in the Phase 1a dose escalation phase is 33, with a further 20 patients in the safety expansion cohort. Based on likely scenarios for DLT outcomes, this number of patients would result in the 2-sided upper 95% posterior probability limit for the DLT rate of the recommended dose being within approximately 12% of the most likely estimate.

In Phase 1b of the study, up to three efficacy cohorts of 20 patients will be treated to investigate efficacy in patients with specific epithelial tumour types. For an individual tumour type, if the true response rate is 14% or more it would be highly likely that at least one response would be observed in 20 patients. More specifically, the probability of observing 0 responses in 20 patients is <5% if the true response rate is 14%. Similarly, if responses are observed, 20 patients will allow the response rate to be estimated with sufficient precision prior to performing larger subsequent studies. For example, if a 20% response rate is observed in a cohort of 20 patients its 90% confidence interval would range from 7% to 40%.

In total up to 125 patients are expected to participate in the study (variations are possible if additional cohorts of patients are required if patients not evaluable for DLT are replaced), up to 12 patients receiving NG-350A by IT injection, up to 53 patients receiving NG-350A by IV infusion in Phase 1a and 60 patients receiving NG-350A in Phase 1b.

## 11.2 Statistical and Analytical Plans

This section presents a summary of the planned statistical analyses. Full details of the analysis will be described in the statistical analysis plan that will be approved before database lock. Any analysis that deviates from the statistical analysis plan will be documented and justified in the clinical study report.

### *11.2.1 Study Endpoints*

#### *11.2.1.1 Primary Endpoints*

Incidence of: adverse events, SAEs, adverse events meeting protocol-defined DLT criteria, severe adverse events, adverse events leading to study treatment or study discontinuation, and adverse events resulting in death.

#### *11.2.1.2 Secondary Endpoints*

- Incidence of safety laboratory assessment abnormalities
- Incidence of abnormalities in vital signs or other clinical safety assessments
- ORR, DCR, median DOR, median PFS and PFS rate at 8, 16 and 24 weeks (depending on indication) assessed by RECIST Version 1.1 and iRECIST
- Overall survival
- Blood concentrations of NG-350A
- Anti-NG-350A antibody titres

#### *11.2.1.3 Exploratory Endpoints*

- Anti-CD40 antibody titres
- Measurement of cytokine levels in blood
- Measurement of virus genomes in the tumour
- Measurement of virus genomes in buccal swabs, rectal swabs and urine samples
- Measurement of infectious virus in blood
- Summary measures of: PSA, PSA doubling time, CEA, CA-125, CA19-9 (as appropriate)
- Identification of methods for future use

### *11.2.2 Analysis Sets*

The following analysis sets will be used:

- The safety analysis set will include all patients who receive at least one dose of study treatment
- The full analysis set will include all patients in the safety analysis set who have at least one pre-dose and post-dose efficacy assessment*
- The pharmacokinetic analysis set will include all patients in the safety set with at least one evaluable pre-dose and post-dose pharmacokinetic sample

Additional analysis sets for evaluation of the pharmacodynamic endpoints will be defined in the statistical analysis plan.

Allocation of patients to the analysis sets will be determined at the pre-database lock meeting.

*Patients undergoing surgical excision/resection may not have post-dose efficacy results.

### *11.2.3 Study Analyses*

#### *11.2.3.1 General Principles*

The majority of the analysis will be descriptive in nature. Unless stated otherwise, continuous variables will be summarised using descriptive statistics (number of patients, mean, standard deviation, median, minimum and maximum values) and the number and percentage of patients will be used for categorical variables.

Data will be summarised by administration type, dose level, phase of study and where appropriate, overall.

The procedure for handling missing, unused or spurious data will be described in the statistical analysis plan. In general, missing data will be considered as missing and will not be imputed.

#### *11.2.3.2 Study Patients*

Patient disposition, including reasons for study treatment discontinuation and study discontinuation will be summarised descriptively.

Protocol deviations will be summarised by nature and categorised by major and minor.

The safety analysis set will be used for the analysis of demographic and baseline data. Demographics and baseline characteristics will be listed and summarised descriptively. Medications and therapies will be summarised by anatomic therapeutic chemical classification.

#### *11.2.3.3 Efficacy Analyses*

The full analysis set will be used for the analysis of efficacy. The following will be summarised by dose level and separately for each tumour type in Phase 1b using both RECIST Version 1.1 and iRECIST criteria:

| | |
|---|---|
| ORR: | The number and percentage of patients who achieve either a complete or partial response according to investigator assessments from the date of first dose of study treatment to the end of the study. Complete response or partial response determinations included in the best overall response assessment must be confirmed by a second scan performed at least 4 weeks (and up to 8 weeks) after the criteria for response are first met |
| DCR: | The number and percentage of patients who achieve either complete response, partial response or stable disease |
| DOR: | Duration of response (applicable only to patients whose best overall response is complete response or partial response) is defined as the time interval between the date of the earliest qualifying response (complete response or partial response) and the date of disease progression or death for any cause, whichever occurs earlier. For patients who are alive without disease progression following the qualifying response, duration of response will be censored on the date of last evaluable tumour assessment or last follow-up for disease progression. |
| PFS: | Defined as the interval between the day of the first dose of study treatment to the first documentation of disease progression or death, whichever occurs earlier. |
| PFS Rate: | Number and percentage of patients that are progression free at 8, 16 and 24 weeks (indication dependent). |
| Overall Survival: | Defined as the interval between the day of the first dose of study treatment until the date of death because of any cause. Patients who discontinue the study will be censored at the date of the final study visit. |

Descriptive statistics will also be used to summarise ORR DCR and PFS rate. A Kaplan-Meier method will be used to analyse DOR, PFS and overall survival which takes into account censored data. Response based endpoints (and the derived PFS endpoint) will be based primarily on the investigator assessments. If an Independent Review is performed, analyses will be repeated as a supportive analysis.

#### *11.2.3.4 Pharmacokinetics*

The pharmacokinetic analysis set will be used for the analysis of pharmacokinetic data.

Blood concentrations of NG-350A at each sampling timepoint will be summarised using descriptive statistics. Geometric mean values may be used if deemed appropriate. Individual and mean concentrations will be presented.

*11.2.3.5 Pharmacodynamics and other Exploratory Analyses*

Summaries at baseline and at each post-baseline collection time point as well as the change from baseline to each post-baseline time point, where appropriate, will be presented.

Further details of these and other exploratory analyses will be documented in the statistical analysis plan.

*11.2.3.6 Safety Data*

**Continual Reassessment Method (CRM)**

After enrollment and completion of the DLT assessment period for the first three patients evaluable for DLT in Dose Escalation Cohort 2, the CRM will be implemented to inform subsequent dose levels in the dose escalation stage of Phase 1a. The CRM will be applied to the cumulative DLT data and results made available to the SRC after each subsequent set of three patients evaluable for DLT. The SRC will make the decisions based on the dose recommended by the CRM and the overall tolerability profile. Additionally, the CRM may also be implemented after 10 patients in the safety expansion cohort, followed by SRC review to optimise the dose and dosing regimen in the final 10 patients prior to Phase Ib. The CRM will only be applied to dosing schedules where the dose delivered is constant across administrations.

Instead of basing dose decisions entirely on the DLTs observed at the current dose level, recommendations made by the CRM are informed by outcomes at previous doses and, in this case, prior experience with enadenotucirev. Sixty-one patients were dosed with enadenotucirev in Study ColoAd1-1001 at dose levels ranging from 1 x $10^{10}$ vp to 1 x $10^{13}$ vp. A summary of the DLT data observed with enadenotucirev is displayed in Table 6 along with the prior probabilities incorporated in the CRM model. Based on enadenotucirev data, the prior assumes there is a 2.5% of observing a DLT rate of 42% or more at the 1 x $10^{12}$ vp dose, the first dose at which the CRM will be used. This prior is wider than the confidence interval for the DLT rate observed with the same dose of enadenotucirev, reflecting added uncertainty when applied to NG-350A.

**Table 6 Prior DLT data for Enadenotucirev and CRM Prior Probabilities**

| Dose | Observed DLT Rate | Modelled DLT Rate[a] | 95% CI | Prior for NG-350A[b] | 95% Probability Interval |
|---|---|---|---|---|---|
| 1 x $10^{10}$ vp | 0/3 (0%) | 0% | (0%,44%) | NA | NA |
| 1 x $10^{11}$ vp | 0/3 (0%) | 0% | (0%,33%) | 0.5% | (0%,33%) |
| 1 x $10^{12}$ vp | 0/6 (0%) | 1% | (0%,25%) | 5% | (0%, 42%) |
| 3 x $10^{12}$ vp | 2/20 (10%) | 7% | (2%,24%) | 12% | (0%, 49%) |
| 6 x $10^{12}$ vp | 4/25 (16%) | 20% | (10%,36%) | 21% | (0%, 56%) |
| 1 x $10^{13}$ vp | 2/4 (50%) | 37% | (13%,70%) | 37% | (13%, 71%) |

Abbreviations: CI=confidence interval; DLT=dose limiting toxicity; NA=not applicable, dose level not planned in this study

[a] Estimated from a logistic regression fitted to the observed DLT rates across all dose levels

[b] Median estimates of DLT rates based on a bivariate normal distribution for ln(α) and ln(β) with mean vector (-0.521, 0.01), variance vector (0.5, 2) and covariance=0.3 between parameters

A 2-parameter logistic regression model will be fitted to the DLT data (i.e. absence or presence of DLT) observed during the DLT assessment period defined as Day 1 until 28 days after the first dose of study treatment. This regression model will be combined with the prior to model the dose-toxicity relationship. As more data accumulates on NG-350A, the less influence the

prior will have within the model. To minimise the chance of exposing subjects to toxic doses, dose recommendations will use the EWOC principle, which recommends that the next dose is the one with the highest posterior probability of DLT in the target interval (20%, 33%) among the doses fulfilling the overdose criterion that there is a 25% or lower chance of a ≥33% DLT rate.

The logistic regression model used is:

$$\ln\left(\frac{p(DLT)}{1-p(DLT)}\right) = \ln(\alpha) + \beta\ln(\frac{d}{d^*})$$

where *p(DLT)* denotes the probability of a DLT; *d* denotes the dose; *d** denotes a reference dose, in this case 1 x $10^{13}$ vp; *ln(α)* represents the natural log-odds of a DLT at 1 x $10^{13}$ vp; and *β* governs the rate of increase in toxicity across dose levels. All data observed from the DLT assessment period will be included in the model. If a pattern of late toxicity emerges, the CRM may be re-run with a longer observation period at the request of the SRC. The modelling will be performed in the Bayesian Continual Reassessment Method R package and the model is run each time a decision is made in conjunction with the SRC.

A further description of the model is provided in Appendix 4, which also contains the CRM dose recommendations for possible DLT outcome scenarios.

**Adverse Events**

All adverse events will be listed, including the verbatim description and MedDRA preferred term and system organ class (SOC).

Treatment emergent adverse events (TEAEs) are defined as those occurring after the first dose of study treatment.

TEAEs will be summarised by SOC and by preferred term. The incidence of TEAEs will be based on the numbers and percentages of patients with events and number of events. TEAEs will be further summarised by severity (according to NCI CTCAE Version 5.0) and relationship to study treatment.

An overall summary of adverse event incidence will also be presented by dose level to include the number and percentage of patients with at least one: TEAE, treatment-related TEAE, Grade 3 to Grade 5 TEAE, death, SAE, treatment-related SAE, DLT, TEAE leading to study treatment discontinuation, TEAE leading to dose modifications (e.g. dose reduction) and TEAE leading to study discontinuation.

Narratives will be written for any deaths, other SAEs, DLTs, TEAEs leading to study treatment discontinuation and TEAEs leading to study discontinuation.

**Laboratory Safety Tests**

Severity grading, using NCI CTCAE Version 5, will be assigned to laboratory safety values where applicable. Laboratory results in reported units and standard international units will be listed, including high and low flags, NCI CTCAE grades where applicable, the corresponding normal range and clinical significance.

Laboratory safety tests summaries will be based on results in SI units. Absolute and change from baseline results, including the worst change for each variable for each patient will be summarised using descriptive statistics.

Treatment-emergent out of range results with the corresponding NCI CTCAE grade, normal ranges, baseline results and clinical significance will be separately listed. Shift tables will be

used to show changes from baseline at each timepoint and the worst change in CTCAE grade for each patient.

Specific parameters that are markers of tolerability related to cytokine release, such as albumin concentration, neutrophil and platelet counts, may be subject to more detailed modelling to understand the time profile of changes and their relationship with dose and schedule. Data will be analysed using a repeated measures mixed model for changes from baseline with baseline values included as a covariate. Other patient level covariates such as weight, gender, age, prior therapy etc will also modelled to explore whether other factors can be identified that predict the sensitivity of patients to changes in parameters.

*Vital Signs and 12-lead ECG*

Absolute and change from baseline vital sign and 12-lead ECG results, including the worst change for each variable for each patient will be summarised using descriptive statistics. Treatment-emergent out of range results will be separately listed. Shift tables will be used to show changes from baseline at each timepoint and the worst change in each patient.

*Physical Examination and Eastern Co-operative Oncology Group Performance Status*

Treatment-emergent abnormal physical examination with the corresponding clinical significance will be listed. Shift tables will be used to show changes in physical examination, weight and ECOG performance status from baseline at each timepoint and the worst shift in each patient will be included.

# 12 STUDY DOCUMENTATION, INSPECTIONS AND RECORD KEEPING

## 12.1 Study Documentation

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should contain all essential documents required by ICH GCP and include:

1. Investigator's site file (e.g. protocol and amendments, IEC/IRB and regulatory authority approval with correspondence, sample informed consent, study treatment accountability records, staff curriculum vitae and authorisation forms, correspondence)
2. Patient source documents

   Source documents are defined as the results of original observations and activities of a clinical investigation, including medical notes. All source documents produced in this study will be maintained by the Investigator and made available for inspection. Source data include, but is not limited to, the following and will be identified in a source data location log:

   - Screening/enrolment log
   - Medical notes - which should be updated after each visit to include visit dates, medical history and cancer history, concomitant medication, any clinically relevant findings of clinical examinations or clinically relevant adverse events/medication changes, SAEs and information on patient withdrawal
   - Informed consent form
   - Safety laboratory reports
   - Visit dates
   - Study treatment accountability and inventory forms
3. Patient eCRF data (which includes an audit trail containing a complete record of all changes to data) will be sent to the Investigator at the end of the study

## 12.2 Audits and Study Centre Inspections

Authorised personnel from regulatory authorities and the Sponsor quality assurance function may carry out inspections and audits respectively. The purpose of an audit or inspection is to ensure that ethical, regulatory and quality requirements are fulfilled in Sponsor studies.

If an audit or inspection occurs, the Investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his time and the time of his staff to the auditor or inspector to discuss findings and any relevant issues.

## 12.3 Retention of Records

Records and documents pertaining to the conduct of this study and the distribution of study treatment, including eCRFs, informed consent forms, laboratory safety test results and study treatment inventory and accountability records, must be retained by the Investigator for at least 15 years after completion or discontinuation of the study, or according to local requirements, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

# 13 FINANCE AND INSURANCE

Financial arrangements are detailed in the Investigator Agreement between the Sponsor and Investigator.

Details of the Sponsor's arrangement for clinical study insurance to provide for compensation to patients for any claim for bodily injury or death arising from participation in the clinical study are provided in the informed consent form.

# 14 ETHICAL AND REGULATORY CONSIDERATIONS

## 14.1 Local Regulations/Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformance with the protocol and the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual.

The study must fully adhere to ICH GCP or with local regulations if they afford greater protection to the patient. For studies conducted in the European Union (EU)/European Economic Area countries, the Investigator will ensure compliance with the EU Clinical Trial Directive [25]. For studies conducted in the United States (US) or under US Investigational New Drug (IND), the Investigator will additionally ensure adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 CFR, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects" and part 56, "Institutional Review Boards".

## 14.2 Regulatory Authority Approval

The study will not commence before approval from the regulatory authority been granted according to local requirements. The Sponsor (or designee) will be responsible for the preparation, submission and confirmation of receipt of any regulatory authority approvals required prior to release of study treatment for shipment to the study centre.

During the study, the Sponsor (or designee) is also responsible for submitting subsequent amendments and notifications to the regulatory authority according to local requirements.

## 14.3 Ethics Committee/Institutional Review Board Approval

The Investigator will be responsible for submitting all documents required by the IEC/IRB e.g. this protocol, the informed consent form relevant supporting information and all types of study specific patient recruitment information (including advertisements) and any other written information to be provided to patients, to the IEC/IRB for review. The Investigator or Sponsor should also provide the IEC/IRB with a copy of the Investigator's Brochure or product labelling, information to be provided to patients and any updates. If the IEC/IRB requires modification of the submitted information, the documentation supporting this requirement must be provided to the Sponsor (or designee).

The study must have the initial and at least annual (when required) approval of an IEC/IRB. The signed approval letter must identify the exact protocol title and number, documents approved and the date of approval of the protocol and the informed consent document. The Sponsor will not ship clinical supplies until a signed approval letter has been received and a Clinical Trial Agreement has been signed by the Sponsor and the study centre.

A list of IEC/IRB board members must be provided to the Sponsor (or designee).

The Investigator or Sponsor should provide the IEC/IRB with reports, updates and other information (e.g. expedited safety reports, amendments and administrative letters) according to regulatory requirements or study centre procedures.

The Sponsor (or designee) will ensure the IEC/IRB is notified of any adverse events meeting the criteria for expedited reporting, annual updates and when the study has been completed according to local requirements. The Sponsor (or designee) will provide information to the Investigator who will be responsible for forwarding this to the IEC/IRB.

## 14.4 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent from patients prior to conducting any study related procedures. All consent documentation must be in accordance with applicable regulations and ICH GCP. Each patient is requested to sign and date the informed consent form after (s)he has received and read the patient information sheet and received an explanation of what the study involves, including but not limited to: the objectives, potential benefits and risk, inconveniences and the patient's rights and responsibilities. Patients will be given adequate time to evaluate the information given to them before signing and dating the informed consent form. The informed consent form also be signed and dated by the person obtaining consent. The original signed informed consent form for each patient will be retained on file by the Investigator and the second signed original given to the patient.

Informed consent forms must be retained for enrolled patients and for patients who are not subsequently enrolled and must be available for verification by the Study Monitor at any time.

In the event of changes to the informed consent form during the study, the Investigator must always use the most current IEC/IRB approved form for documenting written informed consent.

## 14.5 Protocol Amendments

The protocol (and other supporting documents that have received approval before the start of the study e.g. informed consent form) may not be modified without written approval from the Sponsor. In the event that an amendment to the protocol (and/or supporting documents) is required, it will be classified into one of the following categories by the Sponsor:

- Substantial amendments are those considered 'substantial' to the conduct of the clinical study and are likely to have a significant impact on e.g. the safety or physical or mental integrity of the patients, the scientific value of the study, the conduct or management of the study or the quality or safety of the study treatment used in the study
- Non-substantial amendments only involve administrative or logistical changes, typographical errors

The Sponsor will determine if regulatory authority and/or IEC/IRB review is required prior to the implementation of the amendment according to local regulations. In general, substantial amendments may not be initiated without approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves. Non-substantial amendments do not require approval.

The Sponsor (or designee) is responsible for obtaining approval for substantial amendments from the regulatory authority. The Investigator is responsible for promptly informing the IEC/IRB of any substantial amendments and providing documentation of favourable opinion to the Sponsor (or designee).

## 14.6 Confidentiality of Study Documents and Patient Records

The Investigator must ensure that patient's anonymity will be maintained and that their identities are protected from unauthorised parties. The Sponsor (or designee) will maintain confidentiality standards by assigning a unique coded identification number to each patient included in the study. Patient names will never be included in data sets that are transmitted to the Sponsor or their representatives or to third parties as permitted by the informed consent form.

Patients should be identified by an identification code rather than by their names on eCRFs or other documents submitted to the Sponsor. The Investigator should keep a patient enrolment log relating codes to the names of patients. The Investigator should maintain documents not for submission to the Sponsor e.g. informed consent forms, in strict confidence. Records will not be destroyed without giving the Sponsor prior written notice and the opportunity to further store such records, at the Sponsor's cost and expense.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the informed consent form signed by the patient, unless permitted or required by law.

# 15 STUDY COMPLETION

All materials or supplies provided by the Sponsor will be returned to the Sponsor upon study completion. The Investigator will notify the IEC/IRB when the study has been completed. The study will be considered complete when the last patient has their last visit. This notification should be made within 3 months of the completion or termination of the study. The final report sent to the IEC/IRB should also be sent to the Sponsor and, along with the completed eCRFs, constitutes the final summary to the Sponsor, thereby fulfilling the Investigator's regulatory responsibility.

# 16 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Section 801 of the US FDA Amendments Act mandates the registration with ClinicalTrials.gov of certain clinical studies of drugs (including biological products) and medical devices subject to FDA regulations for any disease or condition. The International Committee of Medical Journal Editors requires study registration as a condition for publication of research results generated by a clinical study (http://www.icmje.org).

Publication by the study centre of any data from this study must be carried out in accordance with the clinical study agreement and with prior permission from the Sponsor.

The Investigator may prepare data derived from the study for publication. Such data will be submitted to the Sponsor for review and comment prior to publication. In order to ensure that the Sponsor will be able to make comments and suggestions, material for public dissemination will be submitted to the Sponsor for review at least 60 days prior to submission for publication, public dissemination, or review by a publication committee. The Investigator agrees that all reasonable comments made by the Sponsor in relation to a proposed publication will be incorporated into the publication. The Sponsor will be entitled to delay the publication for a period of up to 6 months from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its proprietary information and intellectual property rights and know how.

The Sponsor may present at symposia, national or regional professional meetings and publish in journals, theses or dissertations, or otherwise of their own choosing, methods and results of the study and in particular, post a summary of study results in on-line clinical trials registers before or after publication by any other method. In the event the Sponsor coordinates a multicentre publication, the participation of the Investigator shall be determined in accordance with the Sponsor's policy and generally accepted standards for authorship. If the Investigator is a named author of the multicentre publication, the Investigator will have access to the study data from all study centres as necessary to participate fully in the development of the multicentre publication.

Any publication based on data or other results of the study from individual study centres shall not be made before the first multicentre publication or one year after completion of the study, whichever is the earlier.

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# APPENDICES

## Appendix 1 Tumour Assessments using RECIST Version 1.1

Response and progression in patients will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumours (RECIST) guideline (Version 1.1) [21].

### Response Criteria

#### *Evaluation of Target Lesions*

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

#### *Evaluation of Non-target Lesions*

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumour markers are initially above the upper normal limit, they must normalise for a subject to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

#### *Evaluation of Best Overall Response*

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

## Best Overall Response Assessment Considering Requirement for Confirmation

| Response Category at First Time Point | Response Category at Subsequent Time Point | Best Overall Response |
|---|---|---|
| CR | CR | CR |
| CR | PR | PD unless minimum criteria for SD duration met [a], in which case SD (possible PR [b]) |
| CR | SD | SD if minimum criteria for SD duration met [a], otherwise PD if no further assessment |
| CR | PD | SD if minimum criteria for SD duration met [a], otherwise PD if no further assessment |
| CR | NE | SD if minimum criteria for SD duration met [a], otherwise NE |
| PR | CR | PR |
| PR | PR | PR |
| PR | SD | SD |
| PR | PD | SD if minimum criteria for SD duration met [a], otherwise PD if no further assessment |
| PR | NE | SD if minimum criteria for SD duration met [a], otherwise NE |
| NE | NE | NE |
| SD | CR | SD |
| SD | PR | SD |
| SD | SD | SD |
| SD | PD | SD if minimum criteria for SD duration met [a], otherwise PD if no further assessment |
| PD | NE | SD if minimum criteria for SD duration met [a], otherwise NE |
| PD | CR, PR, SD | SD if minimum criteria for SD duration met [a, c], otherwise PD if no further assessment |
| PD | PD | PD |
| PD | NE | PD if no further assessment |
| NE | CR | SD |
| NE | PR | SD |
| NE | SD | SD |
| NE | PD | PD if no further assessment |
| NE | NE | NE |

Abbreviations: BOR=best overall response; CR=complete response; NE=non-evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

[a] Assignment of SD requires that ≥1 post-baseline scan was obtained ≥8 weeks from start of study treatment and met criteria for SD or better response.

[b] If a true CR occurs at the first timepoint, then any disease seen at a subsequent time point (even disease meeting PR criteria relative to baseline) results in a BOR of PD (because the disease must have reappeared after the CR). The BOR assessment would depend on whether the minimum duration for SD was met. For a patient who retrospectively had only an apparent CR (with small lesions still present, i.e. the subject had PR, not CR, at the first timepoint, the original CR should be converted to a PR and the BOR should be assessed as PR).

[c] Transient worsening of disease early in therapy or during temporary interruption of study treatment (e.g. for drug-related toxicity or intercurrent illness) may not indicate true PD if followed by an SD, PR, or CR.

## Appendix 2 Tumour Assessments using iRECIST

iRECIST is derived from modified RECIST conventions [22].

| Parameter | RECIST Version 1.1 | iRECIST |
|---|---|---|
| Definition of measurable and non-measurable disease; numbers and site of target disease | Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of 5 lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease). | No change from RECIST Version 1.1; however, new lesions are assessed as per RECIST Version 1.1 but are recorded separately on the eCRF (but not included in the sum of lesions for target lesions identified at baseline). |
| CR, PR, or SD | Cannot have met criteria for progression before CR, PR, or SD. | Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD. |
| Confirmation of CR or PR | See table with best overall response assessment Appendix 1 | As per RECIST Version 1.1. |
| Confirmation of SD | Not required. | As per RECIST Version 1.1. |
| New lesions | Result in progression; recorded but not measured. | New lesions should be assessed and categorised as measurable or non-measurable using RECIST Version 1.1. New lesions result in iUPD, but iCPD is only assigned on the basis of this category if at the next assessment, additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for the sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions, when none have previously been recorded, can also confirm iCPD. |
| Confirmation of progression | Not required (unless equivocal). | The next imaging assessment should be performed at ≥4 weeks but ≤8 weeks after iUPD. Disease progression is confirmed if the next imaging assessment confirms a further increase in size of ≥5 mm in the lesion category in which progression was first identified, or progression in a lesion category that had not previously met RECIST Version 1.1 progression criteria, or development of new lesions. However, the criteria for iCPD (after iUPD) are not considered to have been met if iCR, iPR, or iSD criteria (compared with baseline and as defined by RECIST Version 1.1) are met at the next assessment after iUPD. The status is then reset and iCR, iPR, or iSD should be documented. |
| Consideration of clinical status | Not included in assessment. | Clinical stability is considered when deciding whether treatment is continued after iUPD. |

Abbreviations: CR=complete response; iCPD=confirmed progression assigned using iRECIST; iCR=complete response assigned using iRECIST; iPR=partial response assigned using iRECIST; iSD=stable disease assigned using iRECIST; iUPD=unconfirmed progression assigned using iRECIST; PR=partial response; RECIST=Response Evaluation Criteria in Solid Tumours; SD=stable disease.

## Appendix 3 Definition of Women of Childbearing Potential and Contraception Requirements

The recommendations of the Clinical Trial Facilitation Group, September 2014 [26] will be followed.

**Definition of women of childbearing potential and of fertile men**

For the purpose of this study, a woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.

A post-menopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the post-menopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

For the purpose of this study, a man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

**Methods of Contraception for Women of Childbearing Potential**

Women of childbearing potential must use a highly effective method of contraception (one that can achieve a failure rate of less than 1% per year when used consistently and correctly) for the duration of study treatment with NG-350A and 6 months following the last dose of study treatment. Such methods include:

- Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomised partner (provided that partner is the sole sexual partner of the female patient and that the vasectomised partner has received medical assessment of the surgical success)
- Sexual abstinence (only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient)

### Methods of Contraception for Male Patients with Partner(s) of Childbearing Potential

Unless azoospermic, male patients with female partners of childbearing potential must inform all partner(s) of their participation in a clinical study and the need to comply with contraception instructions for the duration of study treatment with NG-350A and 6 months following the last dose of study treatment:

- Male patients must use a condom and refrain from donating sperm
- Male patients with a pregnant or breastfeeding partner must agree to remain abstinent from penile vaginal intercourse or use a male condom during each episode of penile penetration
- Female partners of male patients must consider use of effective methods of contraception (one of the highly effective methods given for female patients above)

## Appendix 4 Continual Reassessment Method Specification and Hypothetical Scenarios

After enrollment and completion of the DLT assessment period for Dose Escalation Cohort 2 in the dose escalation phase, the CRM, guided by the EWOC principle, will be used to inform dose escalation decisions in Phase 1a. Additionally, the CRM may also be implemented after 10 patients in the safety expansion cohort. The CRM will be made available to the SRC who make dose decisions based on the CRM and their assessment of overall tolerability.

The CRM is based on an underlying dose-toxicity model and makes recommendations based on the outcomes from all doses rather than considering each dose separately. In addition, a prior distribution, defined prior to the start of the study, is incorporated into the model reflecting the prior beliefs about the likely DLT rate for each dose level. In this study, the prior distribution is based on enadenotucirev data as it has an identical virus structure to NG-350A.

This appendix provides details of the statistical model, the derivation of the prior distribution for the model parameters, and dosing recommendations for hypothetical data scenarios.

### Statistical Model

A 2-parameter logistic regression model will be fitted to the DLT data (i.e. absence or presence of DLT) observed during the DLT assessment period to model the dose-toxicity relationship combined with a prior to make dose recommendations.

The logistic regression model used is:

$$\ln\left(\frac{p(DLT)}{1-p(DLT)}\right) = \ln(\alpha) + \beta\ln(\frac{d}{d^*})$$

where *p(DLT)* denotes the probability of a DLT; *d* denotes the dose; *d** denotes a reference dose, in this case 1 x $10^{13}$ vp; *ln(α)* denotes the natural log-odds of a DLT at 1 x $10^{13}$ vp; and *β* governs the rate of increase in toxicity across dose levels.

The likelihood for this model will be multiplied by the prior, specified below, for α and β to create a posterior distribution from which the dose recommendations will be made based on the probability of:

- Target toxicity (the probability the DLT rate is in the interval (20%, 33%), and
- Excessive toxicity (the probability the DLT rate is ≥33%).

Following the principle of EWOC, after each cohort of subjects the recommended dose combination is the one with the highest posterior probability of DLT in the target interval (20%, 33%) among the doses fulfilling the overdose criterion that there is a 25% or lower chance of excessive toxicity.

### Prior Derivation

In this study, the prior distribution is based on enadenotucirev data. Sixty-one patients were dosed with enadenotucirev in Study ColoAd1-1001 at dose levels ranging from 1 x $10^{10}$ vp to 1 x $10^{13}$ vp. A summary of the DLT data observed with enadenotucirev is displayed in Table 6 along with the prior probabilities to be incorporated in the CRM model.

The prior for the DLT rate has a bivariate normal distribution for ln(α) and ln(β) with mean vector (-0.521, 0.01), variance vector (0.5, 2) and a covariance of 0.3 between parameters.

The expected DLT rates at each dose for the prior distribution very closely approximates the modelled DLT rate for enadenotucirev. The uncertainty concerning the DLT rate matches or exceeds that observed for enadenotucirev. This appropriately reflects the extra uncertainty about the DLT rate for NG-350A. In particular, the prior probability interval for 1 x $10^{12}$ vp, the dose after which the CRM is first applied, is wider than the corresponding 95% confidence interval for the DLT rate observed with enadenotucirev.

### Hypothetical Scenarios

The dose recommended by the CRM can be determined in advance for any pattern of observed data. This allows an assessment of whether the recommendations appear reasonable clinically. CRM recommendations for a variety of possible data scenarios for this study are shown in Table 7.

**Table 7 Hypothetical Data Scenarios and the Dose Recommended**

| Scenario | Data at Lower Doses | | Current Dose level | | CRM next Recommended Dose[b] |
|---|---|---|---|---|---|
| | Dose | DLTs/Patients[a] | Dose | DLTs/Patients | |
| 1 | 1 x $10^{11}$ vp | 0/3 | 1 x $10^{12}$ vp | 0/3 | 3 x $10^{12}$ vp |
| | | | | 1/3 | 3 x $10^{12}$ vp |
| | | | | 2/3 | 1 x $10^{12}$ vp |
| 2 | 1 x $10^{11}$ vp | 1/6 | 1 x $10^{12}$ vp | 0/3 | 3 x $10^{12}$ vp |
| | | | | 1/3 | 1 x $10^{12}$ vp |
| | | | | 2/3 | 1 x $10^{11}$ vp |
| 3 | 1 x $10^{11}$ vp<br>1 x $10^{12}$ vp | 0/3<br>0/3 | 3 x $10^{12}$ vp | 0/3 | 6 x $10^{12}$ vp |
| | | | | 1/3 | 5 x $10^{12}$ vp |
| | | | | 2/3 | 3 x $10^{12}$ vp |
| 4 | 1 x $10^{11}$ vp<br>1 x $10^{12}$ vp | 0/3<br>1/3 | 3 x $10^{12}$ vp | 0/3 | 5 x $10^{12}$ vp |
| | | | | 1/3 | 3 x $10^{12}$ vp |
| | | | | 2/3 | 1 x $10^{12}$ vp |
| 5 | 1 x $10^{11}$ vp<br>1 x $10^{12}$ vp | 0/3<br>2/3 | 1 x $10^{12}$ vp | 2/6# | 2 x $10^{12}$ vp |
| | | | | 3/6# | 1 x $10^{12}$ vp |
| 6 | 1 x $10^{11}$ vp<br>1 x $10^{12}$ vp | 1/6<br>0/3 | 3 x $10^{12}$ vp | 0/3 | 6 x $10^{12}$ vp |
| | | | | 1/3 | 3 x $10^{12}$ vp |
| | | | | 2/3 | 1 x $10^{12}$ vp |
| 7 | 1 x $10^{11}$ vp<br>1 x $10^{12}$ vp | 1/6<br>1/3 | 1 x $10^{12}$ vp | 1/6# | 3 x $10^{12}$ vp |
| | | | | 2/6# | 1 x $10^{12}$ vp |
| | | | | 3/6# | 1 x $10^{11}$ vp |

Abbreviations: DLT = dose-limiting toxicity.
# Cumulative data at the dose level
[a] 3+3 criteria used for escalation at the first dose level
[b] Highest integer dose that is no greater than a doubling

If one out of six evaluable patients experience a DLT at the first dose level of 1 x $10^{11}$ vp subsequent CRM dose recommendations are identical to 3+3 criteria (Scenarios 2, 6 and 7) with one exception when further expansion at 1 x $10^{12}$ vp would be recommended when a total of two out of six patients have experienced a DLT at 1 x $10^{12}$ vp.

If no patients experience a DLT at the first dose level of 1 x $10^{11}$ vp then subsequent CRM recommendations can exceed those of 3+3 criteria in some circumstances. This occurs when the DLT rate is inconsistent with prior experience with enadenotucirev and when there have been few DLTs previously observed with NG-350A. For example, if one patient experiences a DLT at 1 x $10^{12}$ vp, when previously no patients experience a DLT at the first dose level of 1 x $10^{11}$ vp, the CRM would recommend that the next dose could be escalated to 3 x $10^{12}$ vp. The ultimate decision, however, resides with the SRC who will evaluate the overall pattern of toxicity.