CLINICAL STUDY PROTOCOL

Title:	A Phase 2, Randomised, Double-Blind, Placebo-Controlled, Proof-of-Concept Study to Evaluate the Efficacy, Safety, and Tolerability, and Effects on Tumour Biomarkers of the NOX1/4 Inhibitor Setanaxib, when Administered with the PD-1 Inhibitor Pembrolizumab, in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)
NCT number:	NCT05323656
Unique Protocol ID:	GSN000400
Document Date:	25 April 2023

CLINICAL STUDY PROTOCOL

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Short title:	A Phase 2, Randomised Study of Setanaxib Co-Administered with Pembrolizumab in Patients with Recurrent or Metastatic SCCHN
Protocol number:	GSN000400
Study phase:	Phase 2
Test product:	Setanaxib
Regulatory agency identifier numbers:	Investigational New Drug number: 158611 EudraCT (European Drug Regulating Authorities Clinical Trials) number: 2021-004627-33
Sponsor:	Calliditas Therapeutics Suisse SA, Chemin des Aulx 16, 1228 Plan-les-Ouates, Switzerland Calliditas Therapeutics Suisse SA is a subsidiary of Calliditas Therapeutics AB
Contract research organisation:	ICON Clinical Research Limited, South County Business Park, Leopardstown, Dublin 18, D18 X5R3, Ireland Phone: +353 (1) 291 2000 Fax: +353 (1) 247 6260 ICON is a corporate affiliate of PRA
Protocol version and date:	Version 4.0 (25 April 2023) incorporating Global Amendments 1 and 2

This study will be performed in compliance with the principles of International Council for Harmonisation guidelines on Good Clinical Practice.

This document is a confidential communication of the sponsor. Acceptance of this document constitutes agreement by the recipient that no unpublished information

contained herein shall be published or disclosed without prior written approval, except that this document will be disclosed to the appropriate Institutional Review Board(s)/Independent Ethics Committee(s) under the condition that they keep it confidential.

PROTOCOL SIGNATURE PAGE – SPONSOR

This protocol has been reviewed and approved by the representatives listed below. Any modification of the protocol must be agreed upon by the sponsor and the investigator and must be documented in writing.

Sponsor representatives:

	Chief Medical Officer
Print Name	Title
Signature	Date
	Statistician
Print Name	Title
Signature	Date

PROTOCOL SIGNATURE PAGE – CONTRACT RESEARCH ORGANISATION

This protocol has been reviewed and approved by the representatives listed below. Any modification of the protocol must be agreed upon by the sponsor and the investigator and must be documented in writing.

ICON representative:

	Medical Director
Print Name	Title
Signature	Date

PROTOCOL SIGNATURE PAGE – INVESTIGATOR

I have read this protocol, which has been agreed by the sponsor and given approval/favourable opinion by the Institutional Review Board (IRB)/Independent Ethics Committee(IEC), and I agree that it contains all necessary details for my staff and I to conduct this study as described. I will provide copies of the protocol and any amendments to all study personnel under my supervision and provide access to all information provided by the sponsor or their specified designees. I will discuss the material with the study personnel to ensure that they are fully informed about the study.

I understand that information contained in or pertaining to this protocol is confidential and should not be disclosed, other than to those directly involved in the execution or the ethical review of the study, without written authorisation from the sponsor. It is, however, permissible to provide information to a patient in order to obtain consent.

I agree to conduct this study according to this protocol and to comply with its requirements, subject to ethical and safety considerations and guidelines, and to conduct the study in accordance with the Declaration of Helsinki, International Council for Harmonisation guidelines on Good Clinical Practice (ICH GCP), and applicable regional regulatory requirements.

I agree to comply with the procedures described for data recording and reporting and to permit monitoring and auditing by the sponsor (or designee), and inspection by the appropriate regulatory authorities.

I agree to make my patients' study records available to sponsor's personnel, their representatives and relevant regulatory authorities in order to verify data that I have entered into the electronic case report forms (eCRFs). I will retain the study-related essential documents until the sponsor indicates that they are no longer needed. I am aware of my responsibilities as per ICH GCP, local regulations, the study protocol, and the clinical trial agreement.

I understand that to the sponsor may decide to suspend or prematurely terminate the study at any time for whatever reason; such a decision will be communicated to me in writing. Conversely, should I decide to withdraw from execution of the study, I will communicate my intention immediately in writing to the sponsor (or designee).

PROTOCOL SIGNATURE PAGE – INVESTIGATOR (continued)

Investigator:

Print Name	Title
Institution	
Signature	Date

SERIOUS ADVERSE EVENT, ADVERSE EVENTS OF SPECIAL INTEREST, PREGNANCY, AND OVERDOSE CONTACT INFORMATION

In the event of a serious adverse event (SAE), the investigator will send a safety report form within 24 hours of becoming aware of the SAE to the contact details below.

Any adverse events of special interest (AESIs), pregnancies, or overdoses will also be reported within 24 hours of becoming aware of the event to the contact details below.

Contract Research Organisation

In Europe, Asia-Pacific, and Africa (EAPA):

SPM[2]

Fax +49 (0)621 570 5971

Email patient.safety@calliditas.com

In the Americas:

SPM[2]

Fax +1 978-338-0668

Email patient.safety@calliditas.com

PRODUCT COMPLAINTS

Product complaints will be collected if they occur in the study. A product complaint is any alleged deficiency related to the identity or quality of a study drug, after it is released for distribution to a site or to a patient. This includes all components distributed with the drug, such as packaging, drug containers, labelling, and inserts.

Examples include:

- Packaging that is damaged or broken
- Missing or illegible labelling
- Inability of customer to administer the product
- Product with an unexpected colour, appearance (eg, broken tablets), or taste

Product complaints should be reported by filling out the Product Complaint Report Form and emailing it to CADSCCSX-SCCSXBnetmb@prahs.com.

Any adverse events (AEs) that are associated with a product complaint should be reported per instructions for AE Reporting in Section 7.3.

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Version 4.0, 25 April 2023

Global Amendment 2 (substantial)

Description of change and rationale for change:

To ensure having approximately 50 patients with evaluable Week 9 biomarker and imaging data and mitigate risks from a higher than expected number of patients discontinuing study early or declining to have imaging or biopsies at Week 9, this protocol amendment allows flexibility in increasing the sample size up to 70 patients if needed.

In addition, a number of minor errors have been corrected along with editorial changes to ensure consistency of terminology throughout.

Version 3.0, 13 May 2022

Global Amendment 1 (substantial)

Description of change and rationale for change:

The following revisions and corrections have been incorporated in the protocol and protocol summary where applicable:

1. Genkyotex Suisse SA has been renamed Calliditas Therapeutics Suisse SA effective 01 April 2022.
2. Some of the changes implemented in the local UK, French, and German revised protocols have been incorporated in the global amendment.
3. Background Section 1.1 includes minor revisions to align with the Investigator Brochure, Edition 12.0.
4. Concomitant Medication and Procedures Section 6.8 has been amended to align with the Investigator Brochure, Edition 12.0
5. The Screening Period has been extended for 1 week to facilitate screening activities.
6. Study Follow-up assessments have been clarified.
7. The sample size has been reduced to 50 patients.
8. An exploratory objective/endpoint has been added for assessment of circulating biomarkers, involving collection of additional blood samples.

Version 2.0, 20 October 2021

The protocol has been generated to implement changes mandated by US FDA.

Version 1.0, 31 August 2021
Initial creation

PROTOCOL SUMMARY

Protocol number: GSN000400

Protocol title: A Phase 2, Randomised, Double-Blind, Placebo-Controlled, Proof-of-Concept Study to Evaluate the Efficacy, Safety, and Tolerability, and Effects on Tumour Biomarkers of the NOX1/4 Inhibitor Setanaxib, when Administered with the PD-1 Inhibitor Pembrolizumab, in Patients with Recurrent or Metastatic Squamous Cell Carcinoma of the Head and Neck (SCCHN)

Short title: A Phase 2 Study of Setanaxib Co-Administered with Pembrolizumab in Patients with Recurrent or Metastatic SCCHN

Sponsor: Calliditas Therapeutics Suisse SA

Study phase: Phase 2

Study sites: It is planned to recruit approximately 35 investigational centres in North America and Europe.

Objectives and Endpoints:

Primary Objective	**Primary Endpoint**
• To compare the change in tumour size per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST v1.1) in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• Best percentage change in tumour size, defined as the best percentage change from Baseline in the sum of diameters of target lesions, as assessed by RECIST v1.1
Key Secondary Objectives	**Key Secondary Endpoints**
• To compare the progression-free survival (PFS) per RECIST v1.1 in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• PFS, defined as time from randomisation to the first documented disease progression per RECIST v1.1 or death due to any cause, whichever occurs first. PFS at 3, 6, and 12 months and median PFS will be summarised
• To compare the change from Baseline in cancer-associated fibroblasts (CAFs) level in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• Change from Baseline in CAFs level in tumour tissue
• To compare the change from Baseline in the number of cluster of differentiation 8 ($CD8^+$) tumour-infiltrating lymphocytes (TILs) and regulatory T-cells in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• Change from Baseline in the number of CD8+ TILs and regulatory T-cells in tumour tissue
Other Secondary Objectives	**Other Secondary Endpoints**
• To assess the overall response rate (ORR), the duration of response (DoR) and disease control rate (DCR) per RECIST v1.1 in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab	• ¨Proportion of the patients who have a complete response (CR) or partial response (PR) per RECIST v1.1 will be used to assess ORR

versus patients treated with placebo and pembrolizumab	• The minimum time when CR or PR is first observed to the time of progression of disease (PD) or death will be used to assess DoR • Proportion of the patients in whom the best overall response is determined as CR, PR, or stable disease (SD) per RECIST v1.1 will be used to assess DCR
• To assess the overall survival (OS) in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• OS, defined as the time from Randomisation to death due to any cause. Patients without documented death at the time of the final analysis will be censored at the date of the last follow-up
• To evaluate the safety and tolerability profile of setanaxib and pembrolizumab, versus placebo and pembrolizumab, in recurrent or metastatic SCCHN patients	• Adverse events (AEs): monitoring for AEs at all visits • AEs of special interest (AESIs): o Anaemia o Hypothyroidism • Vital signs: pulse rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) • 12-lead electrocardiogram (ECG): clinically significant abnormalities • Physical examination: abnormal findings • Laboratory tests: o Haematology o Biochemistry o Urinalysis o Thyroid function test
• To compare the change from Baseline in programmed cell death ligand 1 (PD-L1) expression in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• Levels of PD-L1 expression in tumour tissue
• To compare the change from Baseline in patterns of gene expression and differential gene expression in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab, using RNA sequencing	• Gene expression quantification and analysis of patterns of gene activation for CAFs, $CD8^+$ TILs, and regulatory T-cells
• To assess the plasma exposure of setanaxib and its metabolite GKT138184	• Pre-dose and post-dose plasma concentrations of setanaxib and GKT138184: o Area under the concentration-time curve over the last 24-h dosing interval at steady state (AUC[0-24]-ss) o Minimum plasma concentration at steady state (Cmin-ss) o Maximum plasma concentration at steady state (Cmax-ss)
Exploratory Objectives	**Exploratory Endpoints**
• To assess the relationship between setanaxib and GKT138184 plasma exposure and response, if data permits	• Where data permit, the pharmacokinetics (PK) (setanaxib and GKT138184 plasma exposure)/pharmacodynamics (PD) (eg,

	changes in biomarkers, efficacy, and safety parameters) relationship may be explored graphically and/or using appropriate PK/PD modelling techniques
• To compare the change from Baseline in patterns of gene expression and differential gene expression in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab, using RNA sequencing	• Gene expression quantification and analysis of patterns of gene activation for relevant immuno-oncology, inflammatory and other relevant gene signatures
• To compare changes in circulating biomarkers detectable in peripheral blood in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• Evaluations of pre-, on-treatment, and progression peripheral blood samples for circulating biomarkers which may include but will not be limited to panels of cytokines, chemokines and other soluble biomarkers; T-cell receptor repertoire analysis; and analysis of gene expression biomarkers associated with immunomodulatory effects

Study design:

This is a randomised, double-blind, placebo-controlled, proof-of-concept, Phase 2 study assessing setanaxib co-administered with pembrolizumab in patients with recurrent or metastatic SCCHN. The safety and efficacy of setanaxib 800 mg twice daily [BID] will be assessed against matching placebo over up to 105 weeks of treatment.

The study design is outlined in Figure 1 (Study Schematic), and the visit schedule and planned assessments at each visit are detailed in Table 1.

The study will consist of an up to 35-day Screening Period, an up to 24-month Treatment Period (Day 1 to Week 105), and a 28-day Safety Follow-up Period. The total duration of the study for patients remaining in the study until their final follow-up assessment will be up to approximately 114 weeks (approximately 2 years and 2 months).

Patients will be assessed for eligibility during the Screening Period. Patients will attend the Screening Visit within 35 days of Day 1, such that all of the results of the screening tests will be available at the time that patient eligibility is reconfirmed prior to dosing. If serum pregnancy (see Footnote 'd' of Table 1) retest is required, it should be repeated within 7 days prior to randomisation.

Patients who are screen failures may undergo full rescreening once at the discretion of the investigator and medical monitor if there is a reasonable expectation that the patient is potentially eligible for the study.

As part of eligibility criteria, tumour tissue CAFs level must be assessed by a central laboratory and an elevated tumour CAFs level demonstrated. For Baseline biomarker determination and determination of eligibility, a fresh tumour biopsy will be required from all patients before dosing in the study (unless there is tumour material available from a biopsy taken within 30 days prior to the Screening Visit, which can be used for the Baseline biomarker analysis).

In addition, for patients with a suitable archival tumour biopsy sample available, the archival sample may be used to assess CAFs level and determine eligibility (Note: this can only be performed after the patient has provided signed informed consent). This will not dispense from the need for a recent pre-study tumour biopsy, collected during or within 30 days prior to the Screening Period, for patients eligible for the study. To be considered suitable for determination of CAF levels, the archival biopsy must have been collected within 6 months prior to the Screening Visit (Visit 1), and the patient must have received no further anti-cancer therapy since then.

Eligible patients will be randomised to the investigational medicinal product (IMP) setanaxib tablets 800 mg BID, or placebo, according to a 1:1 randomisation ratio, stratified by human papillomavirus (HPV) status. Treatment with pembrolizumab will be initiated on the same day (Day 1) as the first dose of IMP,

and will be administered according to current clinical guidelines and labelling, ie, 200-mg IV infusion every 3 weeks (q3w).
Treatment with pembrolizumab will continue until: RECIST v1.1-defined disease progression as determined by the investigator, unacceptable toxicity, or a maximum of 24 months. If progression is suspected, but not confirmed, study treatment may continue until confirmation of radiological progression.
Treatment with setanaxib or placebo will continue throughout the period of pembrolizumab therapy. When pembrolizumab is discontinued, blinded study treatment will be discontinued at the same time.
Baseline assessments will be performed on Day 1 (Visit 2). Post-Baseline assessments will be performed every 3 weeks up to pembrolizumab discontinuation. Following permanent IMP discontinuation at any time during the study, patients will undergo an End-of-Treatment (EoT) Visit as soon as possible and a Safety Follow-up Visit at 28 days after the last dose. Tumour assessments will be conducted from the date of randomisation and continue until RECIST v1.1-defined disease progression, irrespective of treatment discontinuation. Efficacy Follow-up for PFS and survival will continue until at least 38 progression events have occurred. AEs will be recorded up to 28 days after study treatment discontinuation, while any further anti-cancer medication will be recorded until progression.
Throughout the study, particular attention will be given to the detection and management of potential cases of anaemia and potential cases of hypothyroidism.
Safety and tolerability data will be regularly reviewed by an unblinded Independent Data Monitoring Committee (IDMC), with the first assessment after approximately 12 patients (6 per treatment group) have had the opportunity to complete at least 1 cycle of pembrolizumab +/- setanaxib, followed by periodic assessments at a frequency defined in the IDMC Charter. The IDMC may recommend change(s) to the setanaxib dose regimen or study conduct based on the safety data reviews, as defined in the IDMC Charter.
After approximately 12 patients (6 per treatment group) have completed their Baseline and post-treatment biopsy, initial gene expression and biomarker data in tumour tissue may be reviewed by the sponsor, who will remain masked to randomised treatment assignment. A second review may be performed, if required.

Study duration:

The start of the study will be the date on which the first patient provides informed consent, and the end of the study will be the last patient's last assessment.

The maximum study duration for an individual patient is up to approximately 114 weeks (approximately 2 years and 2 months): An up to 35-day Screening Period, an up to 24-month Treatment Period (Day 1 to Week 105), followed by an EoT Visit as soon as possible and a Safety Follow-up Visit at 28 days after the last IMP dose.

Planned number of patients: It is planned to randomise approximately 50 patients; however, depending on the number of patients providing evaluable Week 9 biopsy and imaging data, an additional up to 20 patients (making a maximum of 70 patients) may be randomised to ensure an adequate amount of data is available for the efficacy and biomarker analyses.

Target population:

Patients aged ≥18 years with recurrent or metastatic SCCHN who are eligible for treatment with pembrolizumab monotherapy.

Inclusion criteria:

1. Male or female patients aged ≥18 years, inclusive, at the time of informed consent.
2. Willing and able to give informed consent and to comply with the requirements of the study.
3. Histologically- or cytologically-confirmed diagnosis of SCCHN (ie, primary tumour arising from the oral cavity [including tongue], nasal cavity, paranasal sinuses, oropharynx, hypopharynx, or larynx) that is recurrent or metastatic (including both HPV^{+ve} and HPV^{-ve} SCCHN), with or without nodal involvement, and with or without metastatic spread, and is not eligible for surgical resection.

4. Candidates for first-line treatment for pembrolizumab for recurrent or metastatic SCCHN, at the discretion of the investigator.
5. A positive CAFs level (defined as CAFs level in tumours ≥5%), performed at a central laboratory, with a fresh tumour biopsy taken during or within 30 days prior to the Screening Period. If available, suitable archival tissue (taken within 6 months prior to the Screening Visit and where the patient has received no further anti-cancer therapy during this 6-month period) can be used to assess tumour CAFs level and determine patient eligibility (Note: patients found to have low CAF levels in archival tissue material should not proceed to have further biopsies or screening activities).
6. Measurable disease, in accordance with RECIST v1.1, and with tumour accessible and of sufficient volume for pre-treatment and on-treatment biopsy.
7. Combined positive score (CPS) ≥1, as determined on the archival or fresh tumour biopsy taken during or within 30 days prior to the Screening Period.
8. HPV status known at randomisation.
9. Life expectancy of at least 6 months in the judgment of the investigator.
10. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
11. Adequate organ and bone marrow function within 35 days of starting study treatment. Criteria "a" to "c" cannot be met in patients with ongoing or recent (within 14 days of screening test) transfusions or who require ongoing growth factor support:
    a. Absolute neutrophil count ≥1,000/mm^3 (≥1.0×10^9/L).
    b. Platelet count ≥100,000/mm^3 (≥100×10^9/L).
    c. Haemoglobin ≥9 g/dL, in the absence of transfusions for at least 2 weeks. Patients requiring ongoing transfusions or growth factor support to maintain haemoglobin ≥ 9g/dL are not eligible.
    d. Total bilirubin ≤1.5×upper limit of normal (ULN) (if associated with liver metastases or Gilbert's disease, ≤3×ULN).
    e. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3×ULN.
    f. Serum creatinine ≤2.0 mg/dL or creatinine clearance ≥40 mL/min (measured or calculated according to the method of Cockcroft and Gault).
12. Female patients of childbearing potential must use a highly effective method of contraception to prevent pregnancy for ≥4 weeks before randomisation and must agree to continue strict contraception up to 120 days after the last dose of IMP or pembrolizumab, whichever is the later.
    a. For the purposes of this study, women of childbearing potential are defined as "fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy."
    b. Postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In female patients who are not using hormonal contraception or hormonal replacement therapy but with suspected menopause and less than 12 months of amenorrhea, a high follicle stimulating hormone (FSH) level in the postmenopausal range will be required at Screening to confirm a postmenopausal state. Confirmation with more than one FSH measurement is required.
    c. Highly effective contraception is defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. These methods are:
        (1) Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)
        (2) Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)
        (3) Intrauterine device
        (4) Intrauterine hormone-releasing system
        (5) Bilateral tubal occlusion

(6) Vasectomised partner
(7) Sexual abstinence (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.
Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception)..

13. Female patients of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline/Randomisation before dosing.
14. Male patients with female partners of childbearing potential must be willing to use a condom and require their partner to use a highly effective contraceptive method (as defined in the list in item 12c). Female condom and male condom should not be used together. This requirement begins at the time of informed consent and ends 120 days after receiving the last dose of IMP or pembrolizumab, whichever is the later.
15. Male patients must refrain from donating sperm, and female patients must refrain from donating eggs, from Baseline until 120 days after the last dose of IMP or pembrolizumab, whichever is the later.

Exclusion criteria:

1. Diagnosis of immunosuppression or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment, with the exception of intranasal and inhaled corticosteroids or systemic corticosteroids at doses not to exceed 10 mg/day of prednisone or equivalent. Steroids as premedication for hypersensitivity reactions due to radiographic contrast agents are allowed.
2. Anti-cancer monoclonal antibody treatment within 4 weeks prior to study Day 1.
3. Chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 (radiation therapy can be allowed for palliative therapy of bone metastasis only).
4. Not recovered from AEs Grade 2 or greater (except for alopecia) due to previously administered agents.
5. Treatment with any investigational agent within 12 weeks of Screening Visit or 5 half-lives of the IMP (if known), whichever is longer, or current enrolment in an interventional clinical study.
6. Prior treatment with setanaxib or participation in a previous setanaxib clinical study.
7. Prior treatment with pembrolizumab.
8. Known additional malignancy that is progressing or requires active treatment excepting basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer that has undergone potentially curative therapy, or malignancy treated with curative intent and with no known active disease ≥2 years before the first dose of IMP and of low potential risk for recurrence.
9. Known active central nervous system metastases and/or carcinomatous meningitis.
10. Active autoimmune disease requiring systemic treatment within the past 3 months or documented history of clinically severe autoimmune disease, or syndrome that requires systemic steroids or immunosuppressive agents. The following are exceptions to this criterion:
    a. Patients with vitiligo or alopecia.
    b. Any chronic skin condition that does not require systemic therapy.
    c. Patients with coeliac disease controlled by diet alone.
11. Any evidence of current interstitial lung disease or pneumonitis, or a prior history of interstitial lung disease or non-infectious pneumonitis requiring high-dose glucocorticoids.
12. Active infection requiring systemic therapy.
13. Known human immunodeficiency virus (HIV) infection or acute or chronic hepatitis B or C infection. Patients with a past or resolved hepatitis B virus infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of hepatitis B surface antigen [HBsAg]) are

eligible provided the hepatitis virus DNA test is negative. Patients positive for hepatitis C antibody are eligible only if polymerase chain reaction (PCR) is negative for hepatitis C virus RNA. Patients with ongoing anti-viral therapy with potent inhibitors of cytochrome P450 (CYP) 3A4 are not eligible. Testing for HIV is only required if clinically indicated and is not mandatory for this study.

14. Serious chronic gastrointestinal conditions associated with diarrhoea.
15. History of significant haematological problems, such as blood dyscrasias requiring treatment, aplastic anaemia, myelodysplastic syndrome, or leukaemia.
16. Surgery (eg, stomach bypass) or medical condition that might significantly affect absorption of medicines (as judged by the investigator).
17. A positive pregnancy test or breastfeeding for female patients.
18. Evidence of any of the following cardiac conduction abnormalities: a QTc Fredericia interval >450 milliseconds for male patients or >470 milliseconds for female patients. Patients with a second- or third-degree atrioventricular block are to be excluded.
19. TSH >ULN at Screening.
20. Unstable cardiovascular disease as defined by any of the following:
    a. Unstable angina within 6 months prior to Screening
    b. Myocardial infarction, coronary artery bypass graft surgery, or coronary angioplasty within 6 months prior to Screening
    c. Cerebrovascular accident within 6 months prior to Screening
    d. New York Heart Association Class III or IV heart failure
21. Presence of any laboratory abnormality or condition that, in the opinion of the investigator, could interfere with or compromise a patient's treatment, assessment, or compliance with the protocol and/or study procedures.
22. Any other condition that, in the opinion of the investigator, constitutes a risk or contraindication for the participation of the patient in the study, or that could interfere with the study objectives, conduct, or evaluation.
23. Use of medications known to be potent CYP3A4 inhibitors or inducers, or potent uridine diphosphate (UDP)-glucuronosyltransferase 1A9 (UGT1A9) inhibitors or inducers, within 21 days prior to IMP administration.
24. Legal incapacity or limited legal capacity.
25. Psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
26. Patients who are unable to provide informed consent, are incarcerated or unable to follow protocol requirements``
27. Previous randomisation in this study.

Test product:

Name: Setanaxib

Setanaxib tablets will contain 400 mg setanaxib powder formulated with excipients and will be provided to each patient in high-density polyethylene (HDPE) bottles.

Dose: 800 mg BID for up to 105 weeks.

Mode of administration: Patients will self-administer 2 tablets of setanaxib 400 mg in the morning and 2 tablets of setanaxib 400 mg in the evening (ie, 800 mg BID). Patients will self-administer setanaxib with food or up to 30 minutes after a meal.

Patients will receive setanaxib in combination with pembrolizumab, administered as 200-mg intravenous (IV) infusion q3w.

Control product:

Name: Placebo

Matching placebo tablets, containing only excipients, will also be provided in HDPE bottles. Placebo tablets are visually identical to setanaxib tablets.

Dose: 2 tablets of matching placebo BID

Mode of administration: Patients will self-administer 2 tablets of matching placebo in the morning and 2 tablets of matching placebo in the evening. Patients will self-administer matching placebo with food or up to 30 minutes after a meal.

Patients will receive placebo in combination with pembrolizumab, administered as 200-mg IV infusion q3w.

Statistical methods:

Sample size

An overall sample size of approximately 50 patients (25 per treatment group) is considered sufficient to assess the primary endpoint of the best percentage change in tumour size following treatment with setanaxib when administered with pembrolizumab, versus placebo when administered with pembrolizumab, in patients with recurrent or metastatic SCCHN. With 25 patients per treatment group, using a 2-sided t-test, there will be 85% power to detect a 20% mean difference between the treatment groups in best percentage change in tumour size, with an estimated standard deviation of 30% and a 2-sided alpha of 20%. To mitigate risks from a higher than expected number of patients discontinuing the study early or declining to have imaging or biopsies at Week 9, an additional up to 20 patients (making a maximum of 70 patients) may be randomised.

The key secondary endpoints of numbers of CAFs, $CD8^+$ TILs, and regulatory T-cells in tumour tissue, and gene expression analysis in tumour tissue will be used to determine proof-of-concept. With 25 patients per treatment group, there will be 90% power to detect a limit fold change (LFC) of more than 1.5 in gene sequencing endpoints measured in tumour tissue, assuming at least 20 patients have an evaluable Baseline and post-Baseline tissue sample.

For the key secondary endpoint of PFS, if the true hazard ratio for PFS is 0.5, at least 38 progression events as defined by RECIST v1.1 will be required to have >80% power to demonstrate a statistically significant difference in PFS with 2-sided $p<0.2$.

For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarised using descriptive statistics, including n, mean, standard deviation (SD), median, minimum, and maximum values. Graphical presentations of the data will be produced to aid interpretation.

An initial data cut-off will occur approximately 9 weeks after completion of enrolment, when all patients are expected to have had at least 3 cycles of pembrolizumab, at least one post-treatment scan, and the opportunity for a post-treatment tumour biopsy. At this point, the primary endpoint of best percentage change in tumour size and some secondary endpoints will be analysed. An updated analysis may be performed after 38 progression events have been reported. During ongoing review of the overall progression event count, if the predicted timing of the initial and updated analyses are expected to be close in proximity, one analysis may be performed. Investigators and patients will continue to be blinded to randomised study treatment after initial unblinding of data for the primary analysis until the final database lock.

For the primary endpoint of best percentage change in tumour size, the absolute values at Baseline and Week 9 and best percentage change in target lesion tumour size will be summarised using descriptive statistics and presented by treatment group in summary tables and waterfall plots. The primary endpoint will be used to assess the effect of the setanaxib + pembrolizumab versus placebo + pembrolizumab. The primary efficacy analysis will be based on the Full Analysis Set (FAS) and will evaluate the effect of setanaxib on best percentage change in tumour size from an analysis of covariance (ANCOVA) model including a term for the best percentage change tumour size, a covariate for Baseline tumour size and a term for treatment. The number of patients, unadjusted mean, and adjusted least-square means (lsmeans) for each treatment group will be presented, together with the difference in adjusted lsmeans, 80% confidence interval, and corresponding p-value from the fitted ANCOVA model.

The key secondary endpoint of PFS will be summarised by Kaplan-Meier plots presented by treatment groups. Median PFS and the proportion of patients who are progression-free at 3, 6, and 12 months will be summarised along with 80% confidence intervals presented for each treatment group. Patients who have not progressed by the time of the data cut-off for the updated analysis will be censored. The comparison between the treatment groups of PFS will be performed by fitting a Cox proportional hazard model with treatment group as the only covariate. The hazard ratio for PFS, based on the profile partial likelihood from the fitted using Cox proportional hazards model, will be calculated as a measure of the treatment effect along with the respective 95% Wald confidence interval and the asymptotic p-value from the Wald test for the difference in the log hazards in the fitted model.

The secondary endpoint of OS will not be formally compared between the groups but will be summarised in a Kaplan-Meier plot together with descriptive statistics, as described for PFS.

The secondary endpoints of ORR, DoR, and DCR will be summarised using descriptive statistics for each treatment group and associated 90% Agresti-Coull confidence interval.

For the key secondary endpoints of numbers of CAFs, $CD8^+$ TILs, and regulatory T-cells, and the secondary endpoint of PD-L1 expression analysis in tumour tissue, it is hypothesised based on the mode of action of setanaxib that there will be a reduction in CAFs level and an increase in the number of $CD8^+$ TILs. Data will be summarised descriptively and will be graphically presented by boxplots displayed for each treatment group and individual patient profiles displaying pre- and post-doses counts. Changes within treatment groups (ie, across paired tissue samples) and between treatment groups will be summarised. An ANCOVA model will be used to assess for significant differences after adjustment for Baseline differences. The treatment effect from the fitted ANCOVA model will estimate the treatment difference based on mean score. A logarithmic transformation will be applied prior to analysis, if appropriate.

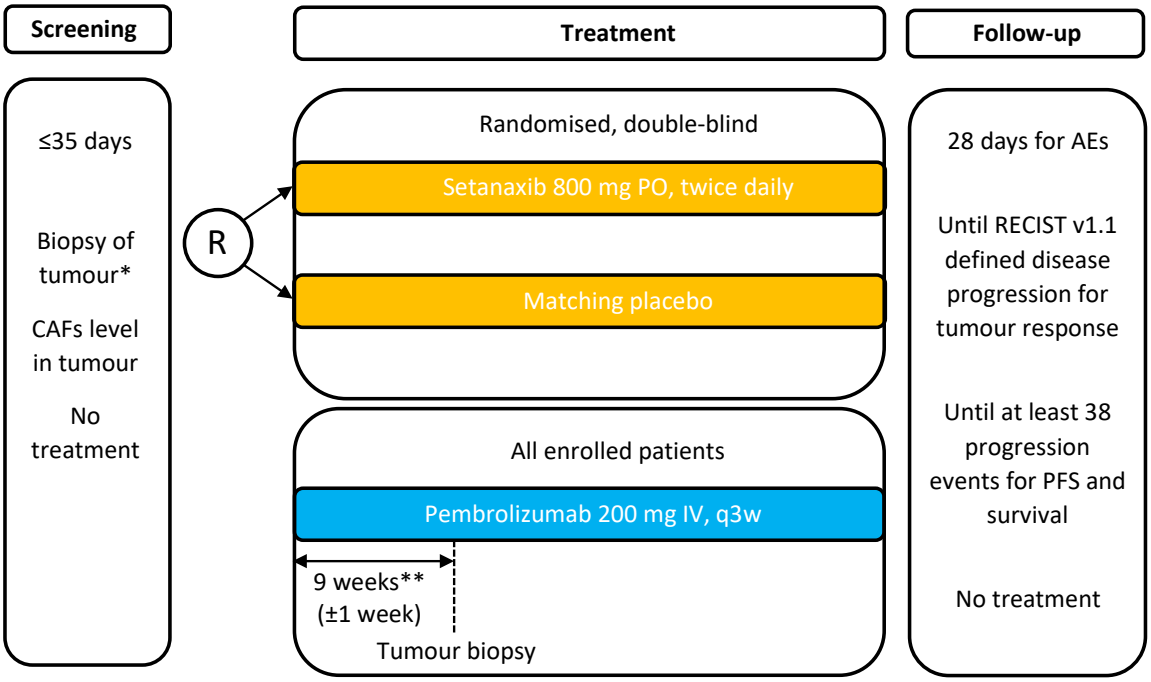
For the secondary endpoint of changes in patterns of gene expression and differential gene expression in tumour tissue, data will be displayed graphically and will be assessed by principal components analysis to identify distinction between clusters of genes.

Changes in tumour biomarkers will be correlated with change in tumour size and other efficacy parameters.

Safety Analysis: The Safety Analysis Set will be used for the analysis of safety data (AEs, including AESIs, clinical laboratory tests, vital signs, 12-lead ECGs, and physical examination). The safety data will be presented descriptively and not formally analysed.
Protocol version and date: Version 4.0 (25 April 2023)

STUDY SCHEMATIC

Figure 1 Study Schematic



AE=adverse event; CAFs=cancer-associated fibroblasts; IV=intravenously; PFS=progression-free survival; PO=per os (orally, or via either a feeding tube or a percutaneous endoscopic gastrostomy device in case patients are unable to swallow tablets); q3w=every 3 weeks; R=randomisation; RECIST v1.1=response evaluation criteria in solid tumours version 1.1
* For patients with a suitable archival tumour biopsy sample available, the archival sample may be used to assess CAFs level and determine eligibility (Note: this can only be performed after the patient has provided signed informed consent). This will not dispense from the need for a recent pre-study tumour biopsy.
** Or earlier if progression occurs before 9 weeks.

SCHEDULE OF ASSESSMENTS

Table 1 Schedule of Assessments

Study Period	Screening	Double-blind Treatment Period			EoT[a]	Follow-up[a]	
Study Weeks:	-5 to -1	BL	3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102	105	EoT Visit	Last IMP Dose+28 (±7 days)	Refer to Footnote 'L'[l]
Study Days (Visit Window):	-35 to -1	1	Every 21 days (±5)	735 (±3)			
Visit:	1	2	3 to 36	37	EoT	Safety Follow-up	Efficacy Follow-up
Informed consent	X						
Determination of eligibility[b]	X	X[b]					
Randomisation		X					
Demographics, ECOG performance status, and relevant medical history	X	X					
Height	X						
Body weight	X		X	X	X	X	
Body temperature	X	X	X	X	X	X	
Physical examination / symptoms-directed physical examination[c]	X	X	X	X	X	X	
Pulse rate, SBP, and DBP	X	X	X	X	X	X	
12-lead ECG[d]	X	X	X	X	X	X	
Blood sampling:							
Pregnancy test (serum)[e]	X[e]						
Haematology and biochemistry[f]	X	X	X	X	X	X	
Thyroid function test[f]		X	X	X	X	X	

Table 1 Schedule of Assessments

Study Period	Screening	Double-blind Treatment Period			EoT[a]	Follow-up[a]	
Study Weeks:	-5 to -1	BL	3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102	105	EoT Visit	Last IMP Dose+28 (±7 days)	Refer to Footnote 'L'[l]
Study Days (Visit Window):	-35 to -1	1	Every 21 days (±5)	735 (±3)			
Visit:	1	2	3 to 36	37	EoT	Safety Follow-up	Efficacy Follow-up
PK[g]		X	X (at Week 3, at time of second tumour biopsy [ie, 9 weeks after the start of study treatment, or earlier if progression occurs before 9 weeks], at Week 24, and at Week 51)	X	X		
Exploratory circulating biomarker blood samples[h]		X	X (9 weeks [±1 week] after the start of study treatment, or earlier if progression occurs before 9 weeks)				
Urine collection:							
Urinalysis[i]	X			X	X	X	
Pregnancy test (urine)[j]		X	X	X	X	X	
Tumour biopsy[k]	X		X (9 weeks [±1 week] after the start of study treatment, or earlier if progression occurs before 9 weeks)				
Tumour assessment	X		X[l]			X[m]	X[m]
Survival assessment[n]			X	X	X	X	X
Treatment dispensation							
Pembrolizumab[o]		X	X				
IMP (setanaxib/placebo)[p]		X	X				
Prior and concomitant medications[q,r]	X	X	X	X	X	X	X
Recording of AEs[r]	X	X	X	X	X	X[s]	X[s]

AE=adverse event; ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BID=twice daily; BL=Baseline; CAFs=cancer-associated fibroblasts; CT=computed tomography; DBP=diastolic blood pressure; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EoT=End-of-Treatment; GGT=gamma glutamyl transpeptidase; IMP=investigational medicinal product; INR=international normalised ratio; MRI=magnetic resonance imaging; PD1-L1=programmed

Table 1 Schedule of Assessments

Study Period	Screening	Double-blind Treatment Period			EoT[a]	Follow-up[a]	
Study Weeks:	-5 to -1	BL	3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102	105	EoT Visit	Last IMP Dose+28 (±7 days)	Refer to Footnote 'L'[l]
Study Days (Visit Window):	-35 to -1	1	Every 21 days (±5)	735 (±3)			
Visit:	1	2	3 to 36	37	EoT	Safety Follow-up	Efficacy Follow-up

cell death-1 ligand 1; PK=pharmacokinetics; RBC=red blood cell; RECIST v1.1=response evaluation criteria in solid tumours version 1.1; SAE=serious adverse event; SBP=systolic blood pressure; T4=thyroxine; TILs=tumour-infiltrating lymphocytes; TSH=thyroid-stimulating hormone; WBC=white blood cell

[a] Patients who permanently discontinue IMP prior to completion of the 105-week Double-blind Treatment Period will have an EoT Visit as soon as possible and a Safety Follow-up Visit at 28 days after the last IMP dose. Efficacy assessments will continue beyond this 28-day follow-up until disease progression.

[b] Eligibility to enter the Double-blind Treatment Period will be determined during Visit 1, with a final check before randomisation on Day 1.

[c] A complete physical examination, including assessments of the standard physical examination items (general appearance, skin, eyes, ears, nose, throat, head and neck, heart, chest and lungs, abdomen, extremities, lymph nodes, musculoskeletal, neurological, and other body systems, if applicable, for describing the status of the patient's health), will be performed during Screening Visit 1 and at the Week 105 Visit (Visit 37). Patients who permanently discontinue IMP prior to or at the Week 105 Visit will have a complete physical examination at the EoT Visit. For Visits 2 to 36, when applicable, a symptoms-directed physical examination will be performed.

[d] At Visit 2 (Study Day 1) and Visit 3, 12-lead ECG will be recorded pre-dose and 2 hours (± 30 minutes) post setanaxib/placebo dosing. From Visit 4 onwards, 12-lead ECG are only required before setanaxib/placebo dosing; additional ECGs may be recorded as clinically indicated.

[e] A blood sample for the serum pregnancy test must be taken within 7 days of Day 1 (female patients of childbearing potential only). Therefore, if Screening Visit is performed more than 7 days prior to Day 1, the serum pregnancy test must be repeated within 7 days of Day 1.

[f] Haematology: haematocrit, haemoglobin, absolute and relative reticulocyte counts, RBC count, WBC count, differential WBC count, platelet count, absolute neutrophil count, mean cell volume, and INR (INR only at Screening).
Biochemistry: ALP, ALT, AST, amylase, total and conjugated bilirubin, GGT, glucose, total protein, albumin, creatinine, urea, total cholesterol, triglycerides, sodium, potassium, and chloride.
Thyroid function test: TSH and free T4

[g] Blood samples for PK assessment will be collected just before the start of pembrolizumab infusion and before the IMP morning dose at Day 1, Week 3, Week 24, Week 51, and Week 105, and PK samples may be collected at any time on the day of the second biopsy and at EoT Visit.

[h] Blood samples (20 mL whole blood) will be collected for analysis of exploratory circulating biomarkers before commencing study treatment, during treatment (at Week 9) and at progression.

[i] Qualitative tests will be performed using urine dipsticks.

[j] Urine pregnancy test, for females of childbearing potential only, will be performed at each visit before dosing.

Table 1 Schedule of Assessments

Study Period	Screening	Double-blind Treatment Period			EoT[a]	Follow-up[a]	
Study Weeks:	-5 to -1	BL	3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 39, 42, 45, 48, 51, 54, 57, 60, 63, 66, 69, 72, 75, 78, 81, 84, 87, 90, 93, 96, 99, 102	105	EoT Visit	Last IMP Dose+28 (±7 days)	Refer to Footnote 'L'[l]
Study Days (Visit Window):	-35 to -1	1	Every 21 days (±5)	735 (±3)			
Visit:	1	2	3 to 36	37	EoT	Safety Follow-up	Efficacy Follow-up

[k] A fresh tumour biopsy will be taken during or within 30 days prior to the Screening Period for assessment of tumour biomarkers (CAFs, $CD8^+$ TILs, regulatory T-cells, and PD1-L1) and gene expression analysis. A second biopsy of tumour for assessment of tumour biomarkers and gene expression analysis will be performed 9 weeks (±1 week) after the start of study treatment, or earlier if progression occurs before 9 weeks. A third optional tumour biopsy can be performed at disease progression (only for patients who had their second biopsy at 9 weeks, and who consented to having a third sample).

[l] Tumour response will be assessed on CT/MRI scan using RECIST v1.1 at Visit 5 (Week 9 ±1 week), and then every 6 weeks (±1 week) through the first year, and every 9 weeks (±1 week) thereafter until RECIST v1.1-defined disease progression.

[m] Tumour assessments will be conducted from the date of randomisation and continue until RECIST v1.1-defined disease progression, irrespective of treatment discontinuation.

[n] Survival will be followed until at least 38 progression events.

[o] Pembrolizumab 200 mg will be administered intravenously every 3 weeks

[p] Setanaxib 800 mg BID or matching placebo will be administered orally (or via either a feeding tube or a percutaneous endoscopic gastrostomy device in case patients are unable to swallow tablets).

[q] Prior medication will be recorded during Screening only.

[r] AEs and changes to concomitant medications will be recorded at each visit. For patients who discontinued study treatment but remain followed for tumour assessment until RECIST v1.1-defined disease progression, AEs will be recorded up to 28 days after study treatment discontinuation, while any further anti-cancer medication will be recorded until progression.

[s] Only SAEs with an onset after the EoT Visit that are considered related to IMP will be reported at the Safety/Efficacy Follow-up Visits.

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LIST OF ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
AUC(0-24)-ss	area under the concentration-time curve over the last 24-h dosing interval at steady state
BID	twice daily
CAF	cancer-associated fibroblast
CCl_4	carbon tetrachloride
CD8	cluster of differentiation 8
Cmax-ss	maximum plasma concentration at steady state
Cmin-ss	minimum plasma concentration at steady state
CPS	combined positive score
CR	complete response
CRO	contract research organisation
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA4	cytotoxic T-lymphocyte antigen 4
CV	coefficient of variation
CYP	cytochrome P450
DBP	diastolic blood pressure
DCR	disease control rate
DoR	duration of response
EAPA	Europe, Asia-Pacific, and Africa
ECG	electrocardiogram

ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EoT	end-of-treatment
EudraCT	European Union Drug Regulating Authorities Clinical Trials
FAS	Full Analysis Set
FoxP3	forkhead box P3
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyltransferase
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HDPE	high-density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HPV	human papillomavirus
HPV^{-ve}	HPV-negative
HPV^{+ve}	HPV-positive
IB	investigator's brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IPF	interstitial pulmonary fibrosis
IEC	Independent Ethics Committee
IgG4	immunoglobulin G4
IMP	investigational medicinal product
IRB	Institutional Review Board
IRT	interactive response technology
IV	Intravenous(ly)

Ki	inhibition constant
LD	longest diameter
LFC	limit fold change
lsmeans	least-square means
mAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MDR2	multidrug resistance protein 2
MRI	magnetic resonance imaging
myCAF	myofibroblastic CAF
NADPH	nicotinamide adenine dinucleotide phosphate oxidase
NASH	nonalcoholic steatohepatitis
NOAEL	no-observed-adverse-effect level
NOX	NADPH oxidase
OAT3	organic anion transporter 3
OD	once daily
ORR	overall response rate
OS	overall survival
PBC	primary biliary cholangitis
PCR	polymerase chain reaction
PD	pharmacodynamics
PD	progressive disease
PD-1	programmed cell death 1
PD-L	PD-ligand
PDGF	platelet-derived growth factor
PEG	percutaneous endoscopic gastrostomy
PET	positron emission tomography
PFS	progression-free survival
P-gp	P-glycoprotein
PK	pharmacokinetics
PO	per os (orally)

PR	partial response
q3w	every 3 weeks
QoL	quality of life
QTL	quality tolerance limit
R/M	recurrent and/or metastatic
RBC	red blood cell
RECIST v1.1	response evaluation criteria in solid tumours version 1.1
ROS	reactive oxygen species
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SD	standard deviation
SEER	Surveillance Epidemiology and End Results
sh	short hairpin
si	small interfering
αSMA	alpha smooth muscle action
SmPC	summary of product characteristics
SOC	system organ class
STAM	stelic animal model
SUSAR	suspected unexpected serious adverse reaction
T4	thyroxine
TEAE	treatment-emergent adverse event
TGF-β	tumour growth factor beta
TIL	tumour-infiltrating lymphocyte
TLR	toll-like receptor
TSH	thyroid-stimulating hormone
UDCA	ursodeoxycholic acid
UDP	uridine diphosphate

UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal
US FDA	United States Food and Drug Administration
WBC	white blood cell

1 INTRODUCTION AND RATIONALE

1.1 Background

1.1.1 Squamous Cell Carcinoma of the Head and Neck

Head and neck cancer describes a range of tumours that arise in the head and neck region, which includes the oral cavity, pharynx, larynx, nasal cavity, paranasal sinuses, thyroid, and salivary glands. Cancer of the head and neck is the sixth most common type of malignancy, representing approximately 6% of all cases; worldwide, approximately 830,000 patients develop head and neck cancer each year, and approximately 430,000 will die from this disease (Bray et al 2018). Although the head and neck region contains a wide diversity of structures and cell types, the vast majority (>90%) of head and neck cancers arise from the mucosa of the upper aerodigestive tract and are squamous cell in origin (squamous cell carcinoma of the head and neck [SCCHN]).

The median age of diagnosis of SCCHN is in the seventh decade, and there is an approximately two-fold higher incidence in men. Alcohol and tobacco use are thought to be important risk factors implicated in approximately 75% of cases of SCCHN; infection with cancer-causing types of human papillomavirus (HPV), especially HPV type 16, is also an important risk factor for oropharyngeal cancers that involve the tonsils or base of the tongue.

Two-thirds of patients with SCCHN present with locally advanced, Stage III or IV disease, commonly involving regional lymph nodes. Distant metastasis at initial presentation is uncommon, arising in approximately 10% of patients. The 5-year survival for all stages combined on the basis of Surveillance Epidemiology and End Results (SEER) data is about 60%.

The treatment of SCCHN at initial presentation usually comprises a combination of chemotherapy, radiotherapy and/or surgery, which is often considered “definitive”. Surgery is a standard treatment for SCCHN but may be limited by the anatomical extent of tumour and desire to achieve organ preservation; radiotherapy is similarly an integral part of primary or adjuvant treatment of SCCHN. Initial chemotherapy regimens are usually reserved for locally advanced disease and typically comprise a combination of platinum plus paclitaxel or fluorouracil.

Treatment is associated with significant morbidity and a relatively static 5-year survival rate of approximately 50% to 60% in patients with HPV-negative (HPV^{-ve}) disease (patients with HPV-positive [HPV^{+ve}] tumours have significantly better survival) (Ward et al 2014, Ferlay et al 2015). At least 50% of patients with locally advanced SCCHN develop locoregional or distant relapses, which are usually detected within the first 2 years of treatment (Argiris et al 2008, Chow 2020). A minority of patients present with locally recurrent, non-metastatic SCCHN that is amenable to salvage surgery and/or re-

irradiation, where long-term survival is possible; however, for the majority of patients, treatment options are limited and historical survival rates have been poor.

In the setting of recurrent and/or metastatic disease (R/M), first-line treatment with platinum combined with fluorouracil or a taxane has typically resulted in a 30% response rate and median progression-free survival (PFS) of 3 to 4 months, and median overall survival (OS) of 6 to 8 months (Gibson et al 2005, Colevas 2006). Addition of the epidermal growth factor receptor (EGFR)-target therapy cetuximab to a platinum-based chemotherapy with fluorouracil (platinum–fluorouracil) has been shown to significantly prolong median OS from 7.4 months (chemotherapy-alone) to 10.1 months (chemotherapy plus cetuximab) with an increase in PFS from 3.3 to 5.6 months (Vermorken et al 2008).

1.1.2 Setanaxib (Investigational Medicinal Product)

Setanaxib is a first-in-class, selective inhibitor of the human protein nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) isoforms 1 and 4. It is a low molecular weight member of the pyrazolopyridine dione chemical class. It selectively inhibits human isolated NOX4 (Ki 0.09 μM) and NOX1 (Ki 0.15 μM) but is less active at inhibiting isolated human NOX2 (Ki 2.13 μM), NOX3 (Ki 0.36 μM), and NOX5 (Ki 0.33 μM). This selectivity against NOX2 means that setanaxib does not compromise phagocyte function. There is no evidence from literature evaluating the effect of gene deletion of NOX isoforms to indicate that chronic inhibition of NOX1 and NOX4 is likely to result in safety concerns.

Setanaxib is being investigated in fibrotic and inflammatory disorders, with clinical studies completed or underway in primary biliary cholangitis (PBC), type 2 diabetes with albuminuria, type 1 diabetes with micro-albuminuria, and interstitial pulmonary fibrosis (IPF).

In vitro studies have shown that setanaxib attenuates the induction of multiple fibrogenic pathways including tumour growth factor beta 1 (TGF-β1), platelet-derived growth factor (PDGF), toll-like receptor 4 (TLR4), Hedgehog, and angiotensin 2. Specifically, setanaxib markedly reduced the induction of markers of myofibroblast activation including alpha smooth muscle action (αSMA), fibronectin, and pro-collagen 1. In addition, setanaxib has shown potent anti-inflammatory effects including reduced expression of adhesion molecules, cytokines, and chemokines. These effects were observed in human podocytes, primary human hepatic stellate cells, macrophages, human aortic endothelial cells, and in rat retinal microglial and Müller cells.

These direct anti-inflammatory and anti-fibrogenic effects translate into anti-inflammatory and anti-fibrotic activity in multiple in vivo models of liver fibrosis. Specifically, setanaxib attenuated the development of liver fibrosis induced by experimental cholestasis (bile duct ligation and multidrug resistance protein 2 [MDR2]-/- mouse models). Setanaxib also prevented liver inflammation and fibrosis in models of

nonalcoholic steatohepatitis (NASH) (stelic animal model [STAM] and fast food diet models) and in toxic hepatitis (carbon tetrachloride [CCl_4]-induced liver injury). Reduced in vivo fibrogenesis was associated with a marked reduction in markers of myofibroblast activation. In addition, setanaxib prevented the induction of adhesion molecules, cytokines, and chemokines. These effects on innate immunity resulted in a profound reduction of macrophage infiltration.

In addition, setanaxib was shown to prevent lung fibrosis in the bleomycin model of IPF. In contrast to the spontaneously reversible fibrosis induced in young mice, bleomycin causes irreversible fibrosis in aged mice. Setanaxib was able to reduce lung fibrosis in both young and aged mice, and also improved survival in aged mice. In these aged mice, setanaxib again prevented the activation and persistence of lung myofibroblasts and facilitated their clearance through apoptosis. These data are consistent with results obtained in mice lacking NOX4, who showed protection in the bleomycin model. NOX4 over-expression in lung tissue of IPF patients has been reported by several groups, suggesting that NOX1/4 inhibition with setanaxib may delay or reverse fibrotic lung remodelling in these patients.

Separately, studies in murine models of diabetic kidney disease have demonstrated that setanaxib reduces podocyte loss, glomerular and interstitial fibrosis, as well as inflammation and macrophage infiltration. Reduced inflammation and fibrosis were associated with reduced albuminuria, a highly validated marker of disease progression in man.

Altogether, the available preclinical evidence in multiple models indicates that setanaxib exerts its direct anti-fibrogenic effects through the down-regulation of multiple fibrogenic and inflammatory pathways.

A total of 120 healthy adult male subjects have been exposed to single oral doses of setanaxib ranging from 10 mg up to 1800 mg in the 5 completed Phase 1 studies. In the multiple dose study, setanaxib was administered at doses up to 900 mg daily over 10 successive days. A sixth Phase 1 study has recently also been performed, to evaluate higher multiple oral doses of setanaxib than previously assessed. A total of 46 healthy male and female subjects were enrolled and received single oral doses of setanaxib of up to 1600 mg (N=30) or multiple oral doses of setanaxib of up to 800 mg twice daily (BID) (total daily dose 1600 mg) for 10 days (N=32). In the Phase 1 program, setanaxib was well tolerated with low incidence of AEs. There were no deaths, no serious AEs (SAEs), and no AE of severe intensity. Most were treatment-emergent adverse events (TEAEs) and were mild and self-limiting and were considered by the investigator to be not related to treatment.

A total of 4 Phase 2 clinical studies have been initiated with setanaxib in PBC (one study), diabetic kidney disease (2 studies), and IPF (one study).

In PBC, setanaxib has been evaluated in a total of 111 patients with inadequate response to ursodeoxycholic acid (UDCA); patients were randomised to receive setanaxib 400 mg once daily (OD), 400 mg BID or matching placebo for 24 weeks in addition to continued treatment with a stable dose of UDCA. The primary efficacy endpoint was the percent gamma-glutamyltransferase (GGT) reduction from Baseline to Week 24; secondary efficacy endpoints included alkaline phosphatase (ALP) changes, liver stiffness measured by transient elastography (Fibroscan®), and quality of life (QoL). Overall, setanaxib was safe and well tolerated at all doses; treatment with setanaxib attenuated markers of cholestatic injury (GGT, ALP), markedly reduced liver stiffness in patients with elevated liver stiffness, and improved QoL by reducing fatigue and the emotional and social QoL domains. In addition, setanaxib did not worsen pruritus.

For further details, refer to the investigator's brochure (IB).

1.1.3 Pembrolizumab

Pembrolizumab is a potent and highly selective humanised monoclonal antibody (mAb) of the immunoglobulin G4 (IgG4)/kappa isotype designed to directly block the interaction between programmed cell death 1 (PD-1) and its ligands, PD-L1 and PD-L2. The PD-1 receptor-ligand interaction is a major pathway hijacked by tumours to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumours.

The safety and clinical activity of pembrolizumab was first evaluated in patients with recurrent or metastatic SCCHN in an open-label, multicentre, Phase 1b study (KEYNOTE-012) (Seiwert et al 2016). In this study, 60 patients with PD-L1-positive SCCHN were enrolled and treated. The proportion of patients with an overall response by central imaging review was 18% (8/45 patients); the proportion was higher in HPV^{+ve} (5/20 [25%]) than HPV^{-ve} patients (7/36 [19%]). Pembrolizumab was well tolerated, with 10 (17%) of 60 patients having Grade 3 to 4 drug-related AEs, the most common of which were increases in alanine aminotransferase (ALT) and in aspartate aminotransferase (AST), and hyponatraemia, each occurring in two of 60 patients; one patient developed a Grade 3 drug-related rash. A total of 27 (45%) of 60 patients experienced an SAE. There were no drug-related deaths.

In a second study (KEYNOTE-055) in 171 patients with recurrent or metastatic SCCHN who had experienced disease progression within 6 months of platinum and cetuximab treatment, an overall response rate (ORR) of 16% and a median duration of response (DoR) of 8 months was observed following treatment with pembrolizumab 200 mg every 3 weeks (q3w) (Bauml et al 2017). Response rates were similar in all HPV and PD-L1 subgroups; median PFS was 2.1 months, and median OS was 8 months. At the time of the analysis, 109 patients (64%) experienced a treatment-related AE, with 26 patients (15%)

experiencing a Grade ≥3 event. Seven patients (4%) discontinued treatment, and one died of treatment-related pneumonitis.

Two Phase 3 studies have further evaluated the efficacy and safety of pembrolizumab in patients with recurrent or metastatic SCCHN. In KEYNOTE-040 (Cohen et al 2019), 495 patients with SCCHN who had progressed during or after platinum-containing treatment for recurrent or metastatic disease (or both), or whose disease recurred or progressed within 3 to 6 months of previous multimodal therapy containing platinum for locally advanced disease, were randomly assigned to treatment with pembrolizumab 200 mg q3w or investigator's choice of standard doses of methotrexate, docetaxel or cetuximab ("standard-of-care"). In this study, the median OS was 8.4 months with pembrolizumab and 6.9 months with standard-of-care (p=0.0161). Fewer patients treated with pembrolizumab than with standard-of-care had Grade 3 or worse treatment-related AEs (33 [13%] of 246 pembrolizumab-treated patients versus 85 [36%] of 234 standard-of-care-treated patients). The most common treatment-related AE was hypothyroidism in 33 (13%) patients with pembrolizumab and fatigue in 43 (18%) patients treated with standard-of-care. Treatment-related death occurred in 4 patients treated with pembrolizumab (unspecified cause, large intestine perforation, malignant neoplasm progression, and Stevens-Johnson syndrome) and 2 patients treated with standard-of-care (malignant neoplasm progression and pneumonia).

KEYNOTE-048 was a Phase 3, randomised, open-label study conducted in patients with recurrent or metastatic SCCHN that was not curable by local therapy (Burtness et al 2019). Patients were randomly allocated (1:1:1) to pembrolizumab alone, pembrolizumab plus a platinum and 5-fluorouracil (pembrolizumab with chemotherapy), or cetuximab plus a platinum and 5-fluorouracil (cetuximab with chemotherapy); randomisation was stratified by PD-L1 expression, p16 status, and performance status. A total of 882 patients were allocated to receive pembrolizumab alone (n=301), pembrolizumab with chemotherapy (n=281), or cetuximab with chemotherapy (n=300); of these, 754 (85%) patients had a PD-L1 combined positive score (CPS) of 1 or more and 381 (43%) had CPS of 20 or more.

At the second interim analysis, pembrolizumab alone improved OS versus cetuximab with chemotherapy in the CPS of 20 or more population (median 14.9 versus 10.7 months, p=0.0007) and CPS of 1 or more population (median 12.3 versus 10.3 months, p=0.0086) and was non-inferior in the total population. Pembrolizumab with chemotherapy improved OS versus cetuximab with chemotherapy in the total population (13.0 versus 10.7 months, p=0.0034) at the second interim analysis and in the CPS of 20 or more population (14.7 versus 11.0 months, p=0.0004), and CPS of 1 or more population (13.6 versus 10.4 months, p<0.0001) at final analysis.

At final analysis, Grade 3 or worse all-cause AEs occurred in 164 (55%) of 300 treated patients in the pembrolizumab-alone group, 235 (85%) of 276 in the pembrolizumab with chemotherapy group, and 239 (83%) of 287 in the cetuximab with chemotherapy group.

Adverse events led to death in 25 (8%) patients in the pembrolizumab-alone group, 32 (12%) patients in the pembrolizumab with chemotherapy group, and 28 (10%) patients in the cetuximab with chemotherapy group.

Based on the efficacy and safety outcomes of KEYNOTE-048, it was concluded that pembrolizumab plus platinum and 5-fluorouracil is an appropriate first-line treatment for recurrent or metastatic SCCHN and pembrolizumab monotherapy is an appropriate first-line treatment for PD-L1-positive recurrent or metastatic SCCHN.

1.2 Study Rationale

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades (Disis 2010). Accumulating evidence shows a correlation between tumour-infiltrating lymphocytes (TILs) in cancer tissue and favourable prognosis in various malignancies (Dong et al 2002, Sharpe & Freeman 2002, Brown et al 2003, Thompson et al 2007, Francisco et al 2010). In particular, the presence of cluster of differentiation 8 ($CD8^+$) T-cells and the ratio of $CD8^+$ effector T-cells/forkhead box $P3^+$ ($FoxP3^+$) regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumours.

Studies treating recurrent or metastatic SCCHN patients with anti-PD-1/PD-L1 checkpoint inhibitors have produced ORR of approximately 15% (Ferris et al 2016, Cohen et al 2019), and these drugs are now approved for subsets of patients with advanced disease. Anti-PD-1/PD-L1 efficacy is predicated upon boosting a pre-existing anti-tumour immune response; the morphological correlate of this in cancer tissues is the presence of TILs; in numerous cancer types, including SCCHN, high TIL levels correlate significantly with longer survival (Ward et al 2014, Chakravarthy et al 2016, Ottensmeier et al 2016, Wood et al 2016, Chakravarthy et al 2018), and many patients who respond to checkpoint inhibitors fall into this category. This perhaps explains the better survival in HPV^{+ve} SCCHN patients, where the majority of tumours (~85%) contain significant TIL levels (Ward et al 2014). TIL_{low} tumours are commonly categorised as 'immune desert' (absent T-cells) or 'immune excluded' (excluded T-cells). For the latter group, strategies for promoting T-cell infiltration into tumours could significantly improve response to anti-PD-1 therapy.

Although now recognised as a heterogenous cell population (Sahai et al 2020), the term cancer-associated fibroblast (CAF) has been used mostly to refer to cells with an 'activated' myofibroblastic phenotype (myCAF). These contractile, αSMA-positive cells are generated principally through TGF-β signalling/mechanotransduction (Calvo et al 2013), and secrete extracellular matrix analogous to myofibroblasts found in healing wounds and fibrotic disorders. MyCAFs are a prominent component of most solid tumours and are generally associated with poor prognosis (Hanley et al 2018); multiple studies have shown their positive influence on tumour progression, promoting metastasis, immune evasion, and therapy resistance (Gaggioli et al 2007, Kraman et al 2010, Arwert et al 2020, Orimo et al 2005). Recent analyses of clinical studies and murine tumour

models indicate that myCAFs promote resistance to anti-PD-1 checkpoint immunotherapy (Mariathasan et al 2018, Dominguez et al 2020, Ford et al 2020, Kieffer et al 2020), and specifically exclude $CD8^+$ T-cells from tumours, thereby promoting resistance to therapeutic vaccination and anti-PD-1 (Ford et al 2020). Notably, some 50% of HPV^{-ve} SCCHN are dominated by the presence of myCAFs, which are invariably present in metastasis (Marsh et al 2011). Notably, 'immune hot tumours' frequently harbour sub-clonal immune-resistance mutations (Chakravarthy et al 2018); the relative paucity of immune-resistance mutations in 'immune cold' myCAF-rich tumours (presumably due to the lack of immune selection pressure for them) suggests that immunotherapy could be particularly effective in these tumours if lymphocyte exclusion could be overcome.

Previous attempts to target myCAFs clinically have been unsuccessful (Hofheinz et al 2003, Narra et al 2007, Catenacci et al 2015); therapeutic possibilities include myCAFs depletion or inhibiting myCAFs differentiation and/or function. Recent studies have shown that CAFs are a plastic population of cells that are not fixed in a state of terminal differentiation (Öhlund et al 2017, Hanley et al 2018); a further possibility, therefore, is to skew myCAFs to a normal or immune permissive fibroblast phenotype (Grauel at al 2020), which may suppress tumour progression (Chen & Song 2019).

Recently it has been shown that the reactive oxygen species (ROS)-producing enzyme NOX4, is a critical regulator of fibroblast-to-myofibroblast transdifferentiation (acting downstream of TGF-β1), regulates myCAFs accumulation in multiple tumour types, and is relatively specific to myCAFs (Hanley et al 2018, Ford et al 2020). Genetic (small interfering [si] RNA/short hairpin [sh] RNA) or pharmacological (setanaxib) inhibition of NOX4 suppresses myCAFs differentiation and slows growth of myCAF-rich tumours (Hanley et al 2018). Notably, inhibiting NOX4 in myCAFs, cultured ex vivo, reverts cells to a quiescent, fibroblastic phenotype, abrogating their tumour-promoting functions (Hanley et al 2018, Ford et al 2020), and suggesting that NOX4 is required not only during myCAFs differentiation, but is also needed to maintain the differentiated phenotype. Studies have shown that myCAFs can be targeted in vivo using setanaxib. Setanaxib suppressed intratumoral myCAFs accumulation and tumour growth (Chen & Song 2019), overcoming $CD8^+$ T-cells exclusion and promoting an influx of intratumoral $CD8^+$ T-cells into the tumour (Ford et al 2020). Treatment of mice with setanaxib overcame myCAF-mediated resistance to both anti-cancer vaccination (TC-1; E7 DNA vaccine) and anti-PD-1 (MC38) immunotherapies (Ford et al 2020).

In summary, CAF-rich tumours respond poorly to anti-PD-1/PD-L1 immunotherapy, and currently there are no pharmacological means of targeting this cell type specifically. Studies suggest that CAF-mediated immunotherapy resistance results from the exclusion of $CD8^+$ T-cells from the tumour mass. In preclinical studies, this phenomenon can be successfully overcome by reversing the CAF phenotype through NOX4 inhibition using setanaxib, a drug with considerable data in both healthy volunteers and patients, and which has an acceptable safety profile. A significant proportion of solid cancers are CAF-

rich, and preclinical data suggest that the combination of NOX4 inhibition and immunotherapy would improve clinical outcome in these tumours.

This study is being conducted to determine the tumour response in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab.

The results of this study may be used to aid further development of setanaxib and potentially be used for submission to regulatory authorities.

1.3 Benefit/Risk Assessment

Setanaxib is a selective inhibitor of NOX1 and NOX4 isoforms of the NADPH oxidase family of enzymes and is the first drug in this class of NOX inhibitors to enter the clinic. The NOX1 and NOX4 isoforms have been shown to play a key role in a broad range of inflammatory and fibrotic disorders (Krause & Bedard, 2008; Paik et al 2014; Liang et al 2016; Teixeira et al 2017). Inhibition of NOX1 and NOX4 with setanaxib has resulted in marked anti-inflammatory and anti-fibrotic effects in multiple in vitro and in vivo models of inflammatory and fibrotic disorders. Therefore, setanaxib is being investigated in inflammatory and fibrotic disorders, with several clinical studies completed or underway.

CAFs are important cells in the tumour stroma of many cancers, and their presence is often associated with a poor prognosis. CAFs are involved in the adaptive anti-tumour immune response and contribute to the exclusion of $CD8^+$ T lymphocytes from the tumour microenvironment, and therefore, represent a brake on the action of immunotherapies that target these lymphocytes. CAFs also affect the biology of dendritic cells by inhibiting their migration, maturation, and their ability to present the antigen.

CAFs can also participate in the development of a fibrous capsule around tumours and within tumours around the vessels. This barrier affects the recruitment and activity of cells of the immune system. The NOX enzymes participate in establishing conditions that are favourable to the growth and to the local or remote extension of malignant tumours. It has been shown that NOX4 is strongly induced in many human cancers and plays a role in activation of CAFs. Pre-clinically, setanaxib has been shown to inhibit the activation of CAFs and thereby allows $CD8^+$ T lymphocytes to reach and infiltrate the tumour.

Immune checkpoint inhibitors are now a widely used therapy in many cancer settings, including SCCHN. However, of the proportion of cancer patients who can be treated with these agents, only a minority generally respond positively to the treatment. Identifying and overcoming the mechanisms that prevent immune checkpoint inhibitors being effective is a key goal within the oncology arena. The ability of tumours to exclude immune system elements is known to be a main cause of resistance to immunotherapies, such as immune checkpoints inhibitors that target inhibitory receptors such as cytotoxic T-lymphocyte antigen 4 (CTLA4) or PD1 and its ligand PD-L1.

Potential Benefits

Patients with recurrent or metastatic SCCHN have a poor prognosis with a median survival of approximately 1 year. Immune checkpoint inhibitors have shown that they can enhance clinical outcomes in this disease setting and are well tolerated, but only a minority of patients (~20%) show a response to treatment. Increasing response to immune checkpoint inhibitors represents a major challenge, and there is a high unmet medical need for safe and efficacious treatment options in this disease setting. The addition of setanaxib therapy to pembrolizumab may enhance the ability of $CD8^+$ T lymphocytes to reach and infiltrate the tumour and thereby increase the degree of response to pembrolizumab, thus increasing the proportion of patients who respond to pembrolizumab therapy, and thereby delaying the onset of disease progression and increasing OS.

Participation in this study provides the patient with a standard-of-care treatment option in the form of the approved agent pembrolizumab, and a potential opportunity to take setanaxib, which is being evaluated for efficacy in this clinical study. While NOX1/4 inhibition represents an attractive therapeutic strategy, therapeutic benefits in patients with SCCHN have yet to be demonstrated. During this study patients will undergo the regular medical evaluations and assessments for their cancer, as part of the study procedures.

Potential Risks

As summarised in Section 1.1.2, setanaxib has been extensively investigated in nonclinical and clinical studies.

In the completed Phase 1 and Phase 2 studies, the safety profile of setanaxib has been shown to be acceptable, with no clinical safety signal and no dose limiting toxicity identified. The safety signals identified in the toxicology studies (thyroid function, electrocardiogram [ECG] abnormalities, haematological changes) have been carefully monitored in all clinical studies completed to date. No treatment-related clinical or pathological findings have been observed, irrespective of dose, treatment duration or type of clinical study.

The dose of setanaxib under investigation in this study has been evaluated in healthy subjects but is higher than that used in clinical study of PBC patients in the GSN000300 study; the duration of dosing in this study will be longer than in the healthy volunteer studies, with an anticipated median duration of dosing of 3 to 6 months dependent on clinical response of patients. Due to the higher setanaxib dose being evaluated in the current study and the longer duration of treatment, there is a potential risk of new safety signals that have not been observed to date in the previous clinical studies.

Safety and tolerability data will be regularly reviewed by an unblinded Independent Data Monitoring Committee (IDMC), with the first assessment after approximately 12 patients

(6 per treatment group) have had the opportunity to complete at least 1 cycle of pembrolizumab +/- setanaxib, followed by periodic assessments at a frequency defined in the IDMC Charter (see Section 9.4).

More detailed information about the known and expected benefits, risks, and reasonably expected AEs of setanaxib can be found in the IB.

The safety profiles, potential overlapping toxicities with the combinations, toxicity management and risk mitigation for the individual agents and combinations are discussed in detail in Table 2.

Table 2 Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study intervention: setanaxib		
Important Identified Risk None identified	Across the setanaxib clinical program, the occurrence rates of adverse events have been low and similar between setanaxib and placebo. No treatment or dose-related adverse reactions have been observed to date. There have been no serious adverse drug reactions reported in the setanaxib development program to date.	Not applicable.
Important Potential Risk None identified		Not applicable.

Potential Risk: Drug-drug interaction	Cytochrome P450 (CYP) 3A4 and uridine diphosphate (UDP)-glucuronosyltransferase 1A9 (UGT1A9) are the major metabolic pathways for setanaxib. Potent CYP3A4 and UGT1A9 inhibitors and inducers should be avoided. When administered at a dose of 300 mg BID for 10 days or 800 mg BID for 6 days, setanaxib increased the plasma area under the concentration-time curve (AUC) of the sensitive CYP3A4 substrate midazolam by 34% and 24%, respectively, and thus setanaxib is not considered to be an inhibitor of CYP3A4 in vivo at the 800 mg BID dose level. When administered at a dose of 800 mg BID setanaxib increased the plasma AUC of the sensitive substrates of CYP2C9 (losartan) and CYP2C19 (omeprazole) by 45% and 60%, respectively. Setanaxib is considered a weak inhibitor of these enzymes at the 800 mg BID dose level. Setanaxib also has potential induction effects on CYP2B6. Thus, sensitive substrates of CYP2C9, CYP2C19 and CYP2B6 should be used with caution. Since setanaxib has been shown to inhibit organic anion transporter (OAT) 1 and OAT3 in vitro, the effect of setanaxib 800 mg BID has been assessed on substrates of OAT1 (adefovir) and OAT3 (sitagliptin) in healthy subjects. The AUC of adefovir and sitagliptin was increased by 18% and 33%, respectively, and thus setanaxib is considered a weak inhibitor of OAT3 and not to be an inhibitor of OAT1. It is recommended that medications that are primarily eliminated through OAT3 should be used with caution..	1. Setanaxib should not be administered concomitantly with potent CYP3A4 inhibitors and inducers, nor with potent UGT1A9 inhibitors and inducers. The medications being taken by a patient will be carefully evaluated by the investigator before the patient is enrolled into the study, and concomitant medications will be recorded throughout the study. 2. Setanaxib should be used with caution when co-administered with drugs that are sensitive substrates of CYP2C9, CYP2C19, CYP2B6, OAT3, BCRP or P-gp. 3. Appendix III and Section 6.8 contain a list of common medications that should be avoided or used with caution.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	In addition, setanaxib inhibited BCRP and MDR1 (P-glycoprotein [P-gp]) in vitro. This may result in increased exposures of applicable concomitant medications, hence caution should be exercised with use of sensitive BCRP and P-gp substrates.	
Potential Risks based on preclinical studies: Abnormal thyroid function	In canine toxicology studies, chronic administration of high-dose setanaxib was occasionally associated with increases in plasma thyroid-stimulating hormone (TSH) levels, reduced plasma free thyroxine (T4) levels, and with thyroid cell follicular hypertrophy. Hypothyroidism is an identified risk for the concomitant study drug, pembrolizumab. The combined regimen could theoretically lead to an increased risk of hypothyroidism due to setanaxib use.	1. Patients with TSH levels > upper limit of normal (ULN) at Screening will be excluded. 2. Patients included in the study will have regular laboratory blood tests that include thyroid function tests. 3. In the case of TSH ≥10 mIU/L, IMP administration will be interrupted while the patient undergoes evaluation for hypothyroidism.
Electrocardiogram (ECG) abnormalities	In canine studies, chronic administration of high doses of setanaxib was associated with reversible QT prolongation and atrioventricular block events. Significant, but limited, increases in QT interval were observed at 3-4 hours post-dose in dogs receiving doses of 100 mg/kg or above. Setanaxib and its main active metabolite have no effect on the human ether-a-go-go related gene (hERG) channel, with a half maximal inhibitory concentration (IC_{50}) > 300 µM. In clinical studies, there has been no evidence of clinically relevant changes in ECGs associated with setanaxib, including QT prolongations.	1. Setanaxib will not be administered to patients taking concomitant drugs that prolong the QT interval. 2. Patients included in the study will undergo regular monitoring for evidence of cardiac disorders by 12-lead ECGs. 3. Appendix III contains a list of common medications that should be avoided.

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Haematological changes	In canine toxicology studies, administration of high-dose setanaxib was associated with a reduction in bone marrow erythroid precursors, reduced reticulocyte and red blood cell counts in peripheral blood, leading to severe aplastic anaemia in a dog. In clinical studies, there has been no evidence of bone marrow toxicity related to setanaxib exposure.	1. Setanaxib should not be administered concomitantly with drugs that have known bone marrow toxicities. 2. Patients included in the study will have regular laboratory blood tests that include haematology (including haemoglobin and reticulocytes count). 3. Patients with a history of bone marrow disorder, including aplastic anaemia, or any current marked anaemia defined as haemoglobin <9.0 g/dL will be excluded from the study. 4. In the case of significant anaemia (Grade ≥3) not attributable to other causes, setanaxib administration will be interrupted while the patient undergoes further evaluation.
Study intervention: setanaxib in combination with pembrolizumab		
Pembrolizumab is an approved established standard-of-care for the indication under study, and a key risk of treatment is immune-related adverse reactions (including immune-related pneumonitis, colitis, hepatitis, nephritis and endocrinopathies); severe and fatal cases have occurred in patients receiving pembrolizumab. Severe infusion-related reactions, including hypersensitivity and anaphylaxis have occurred. Potential overlapping toxicities for the combination are: Thyroid disorders.	Risks identified based on clinical data from the pembrolizumab summary of product characteristics (SmPC). Thyroid disorders, including hypothyroidism, hyperthyroidism and thyroiditis, have been reported in patients receiving pembrolizumab and can occur at any time during treatment. Hypothyroidism is more frequently reported in patients with SCCHN with prior radiation therapy.	Risk minimisation activities are reflected in the study protocol specific inclusion and exclusion criteria, alongside the safety monitoring strategy and toxicity management guidelines (Section 5.3.2.2). 1. Patients with TSH levels >ULN at Screening will be excluded. 2. Patients included in the study will have regular laboratory blood tests that include thyroid function tests. 3. In the case of TSH ≥10 mIU/L, IMP administration will be interrupted while the patient undergoes evaluation for hypothyroidism Pembrolizumab-induced adverse drug reactions will be managed in line with the respective product labelling. Further details can be found in the setanaxib investigator's

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
		brochure and the pembrolizumab SmPC.
Study intervention: study procedures - tumour biopsy		
Injury from requirement for up to 2 tumour biopsies to be performed during the study.	An inclusion criterion is that patients have high or moderately elevated tumour CAFs level and secondary objectives of the study include analysis of tumour-related biomarkers before and after treatment. These require patients to have up to 2 biopsies of the tumour during the study. The risks of biopsy are primarily: • Bleeding • Infection • Accidental injury to adjacent structures	Biopsies are routinely performed in patients with SCCHN for diagnostic purposes and will be performed by clinicians skilled in performing biopsies. Patients with tumour location or other factors that make it challenging to safely perform a biopsy will not enter the study. Archival tumour material can be used where available to check that patients are eligible for the study and thus minimise the number of patients who have a biopsy but are found to be ineligible.

It is the sponsor's position that setanaxib does not have immunosuppressive properties. In addition, the available literature and expert assessment concludes that patients taking pembrolizumab and other immune checkpoint inhibitors should be considered for Covid-19 vaccination. Many cancer patients are extremely vulnerable and, therefore, the overall consensus is that the benefits of the Covid-19 vaccine will potentially outweigh the risks. All approved Covid-19 vaccines are allowed in setanaxib studies. It is important that the cancer treatments and Covid-19 vaccinations are not delayed.

There is no foreseeable risk in the use of a placebo group in the study design because all of the patients will be treated with pembrolizumab.

There are currently no important identified or potential risks for setanaxib. The identified and potential risks for pembrolizumab and tumour biopsy are established. Important risk mitigation is included in pembrolizumab product labelling. Risks due to tumour biopsies are minimised by limiting these procedures to experienced, qualified physicians. Risk minimisation activities are reflected in the study protocol specific inclusion and exclusion criteria, restrictions on concomitant medications alongside the safety monitoring strategy and toxicity management guidelines (Section 5.3.2.1 and Section 5.3.2.2). These risks are monitored via routine pharmacovigilance and managed via routine risk minimisation activities and standard treatment practices.

Overall Benefit/Risk Conclusion

Despite advances in treatments, outcomes for patients with SCCHN have remained mostly unchanged for the past few decades, especially for HPV^{-ve} SCCHN, and short-term and long-term treatment-associated morbidities are still substantial. Most patients

still present with advanced-stage disease and are treated with platinum-based chemotherapy regimens. In the randomised Phase 3 KEYNOTE-048 study of patients with untreated locally incurable recurrent or metastatic SCCHN, pembrolizumab monotherapy improved OS in patients with a PD-L1 CPS of 1 or more and had non-inferior OS in the total study population compared with standard-of-care therapy with cetuximab, a platinum, and 5-flurouracil. Compared with standard therapy, the incidence of AEs of any grade and of Grade 3 or worse was lower with pembrolizumab monotherapy. In the CPS of 1 or more population, median OS with pembrolizumab alone was 12.3 months versus 10.3 months for cetuximab with chemotherapy (hazard ratio 0.78; 95% confidence interval 0.64 to 0.96, p=0.0086). Nevertheless, there remains a considerable unmet medical need for new therapies and/or combinations to further improve treatment outcome in this poor prognosis group of patients with recurrent or metastatic SCCHN.

Considering the measures taken to minimise risk to the patients participating in this study, the potential risks identified in association with setanaxib are justified by the anticipated benefits that may be afforded to patients with SCCHN. All patients will receive a standard-of-care agent in the form of the approved treatment, pembrolizumab.

The nonclinical profile and emerging clinical safety profile from the early clinical studies with setanaxib have not identified risks that would preclude investigation in this setting.

Moreover, the study design aims to minimise potential risks in several ways. Adverse drug reactions to setanaxib will be managed as per the toxicity management guidelines. Adverse drug reactions to pembrolizumab will be managed as per the local product labels or clinical practice guidelines at the discretion of the investigator. Furthermore, a dose modification strategy for the management of setanaxib and pembrolizumab related toxicities is in place for those risks deemed to be most likely or serious (Section 5.3.2.1, and Section 5.3.2.2). Appropriate inclusion and exclusion criteria in the study protocol ensure patient safety. For example, to be enrolled, patients must be eligible for pembrolizumab treatment (as per local investigator assessment), which is administered in both groups of the study. Second, the protocol includes safety monitoring in excess of standard-of-care monitoring, with the intent of protecting patients involved in the study.

Taking into account the measures to minimise risk to the patients participating in this study, the potential risks identified in association with setanaxib and pembrolizumab are justified by the anticipated benefits that may be afforded to patients with SCCHN.

2 STUDY OBJECTIVES AND ENPOINTS

2.1 Primary Objective and Endpoint

Primary Objective	Primary Endpoint
• To compare the change in tumour size per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST v1.1) in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• Best percentage change in tumour size, defined as the best percentage change from Baseline in the sum of diameters of target lesions, as assessed by RECIST v1.1

2.2 Secondary Objectives and Endpoints

Key Secondary Objectives	Key Secondary Endpoints
• To compare the PFS per RECIST v1.1 in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• PFS, defined as time from randomisation to the first documented disease progression per RECIST v1.1 or death due to any cause, whichever occurs first. PFS at 3, 6, and 12 months and median PFS will be summarised
• To compare the change from Baseline in CAFs level in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab • To compare the change from Baseline in the number of $CD8^+$ TILs and regulatory T-cells in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• Change from Baseline in CAFs level in tumour tissue • Change from Baseline in the number of $CD8^+$ TILs and regulatory T-cells in tumour tissue
Other Secondary Objectives	**Other Secondary Endpoints**
• To assess the ORR, the DoR and disease control rate (DCR) per RECIST v1.1 in recurrent or metastatic SCCHN patients treated	• Proportion of the patients who have a complete response (CR) or partial response (PR) per RECIST v1.1 will be used to assess ORR

with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• The minimum time when CR or PR is first observered to the time of progression of disease (PD) or death will be used to assess DoR • Proportion of the patients in whom the best overall response is determined as CR, PR, or stable disease (SD) per RECIST v1.1 will be used to assess DCR
• To assess the OS in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• OS, defined as the time from Randomisation to death due to any cause. Patients without documented death at the time of the final analysis will be censored at the date of the last follow-up
• To evaluate the safety and tolerability profile of setanaxib and pembrolizumab, versus placebo and pembrolizumab, in recurrent or metastatic SCCHN patients	• AEs: monitoring for AEs at all visits • AESIs: o Anaemia o Hypothyroidism • Vital signs: pulse rate, systolic blood pressure (SBP), and diastolic blood pressure (DBP) • 12-lead electrocardiogram (ECG): clinically significant abnormalities • Physical examination: abnormal findings • Laboratory tests: o Haematology o Biochemistry o Urinalysis o Thyroid function test
• To compare the change from Baseline in PD-L1 expression in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab	• Levels of PD-L1 expression in tumour tissue
• To compare the change from Baseline in patterns of gene expression and differential gene expression in tumour tissue from recurrent or metastatic SCCHN	• Gene expression quantification and analysis of patterns of gene activation for CAFs, $CD8^+$ TILs, and regulatory T-cells

patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab, using RNA sequencing	
• To assess the plasma exposure of setanaxib and its metabolite GKT138184	• Pre-dose and post-dose plasma concentrations of setanaxib and GKT138184: o Area under the concentration-time curve over the last 24-h dosing interval at steady state (AUC[0-24]-ss) o Minimum plasma concentration at steady state (Cmin-ss) o Maximum plasma concentration at steady state (Cmax-ss)

2.3 Exploratory Objectives and Endpoints

Exploratory Objectives	Exploratory Endpoints
• To assess the relationship between setanaxib and GKT138184 plasma exposure and response, if data permits	• Where data permit, the pharmacokinetics (PK) (setanaxib and GKT138184 plasma exposure)/pharmacodynamics (PD) (eg, changes in biomarkers, efficacy, and safety parameters) relationship may be explored graphically and/or using appropriate PK/PD modelling techniques
• To compare the change from Baseline in patterns of gene expression and differential gene expression in tumour tissue from recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab, using RNA sequencing	• Gene expression quantification and analysis of patterns of gene activation for relevant immuno-oncology, inflammatory, and other relevant gene signatures
• To compare changes in circulating biomarkers detectable in peripheral blood in recurrent or metastatic SCCHN patients treated with setanaxib and pembrolizumab versus	• Evaluations of pre-, on-treatment, and progression peripheral blood samples for circulating biomarkers which may include but will not be limited to panels of cytokines, chemokines and

patients treated with placebo and pembrolizumab	other soluble biomarkers; T-cell receptor repertoire analysis; and analysis of gene expression biomarkers associated with immunomodulatory effects

3 STUDY PLAN

3.1 Overall Study Design and Plan

This is a randomised, double-blind, placebo-controlled, proof-of-concept, Phase 2 study assessing setanaxib co-administered with pembrolizumab in patients with recurrent or metastatic SCCHN. The safety and efficacy of setanaxib 800 mg BID will be assessed against matching placebo over up to 105 weeks of treatment. It is planned to randomise approximately 50 patients at up to approximately 35 investigational centres in North America and Europe. However, depending on the number of patients providing evaluable Week 9 biopsy and imaging data, an additional up to 20 patients (making a maximum of 70 patients) may be randomised to ensure an adequate amount of data is available for the efficacy and biomarker analyses.

The study design is outlined in Figure 1 (Study Schematic), and the visit schedule and planned assessments at each visit are detailed in Table 1.

The study will consist of an up to 35-day Screening Period, an up to 24-month Treatment Period (Day 1 to Week 105), and a 28-day Safety Follow-up Period. The total duration of the study for patients remaining in the study until their final follow-up assessment will be up to approximately 114 weeks (approximately 2 years and 2 months).

The investigator will obtain signed informed consent from the patient before any study procedures are performed. For further details regarding the informed consent process, see Section 9.3. Patients will be assessed for eligibility during the Screening Period. Patients will attend the Screening Visit within 35 days of Day 1, such that all of the results of the screening tests will be available at the time that patient eligibility is reconfirmed prior to dosing. If serum pregnancy (see Footnote ‘d’ of Table 1) retest is required, it should be repeated within 7 days prior to randomisation.

As part of eligibility criteria, tumour tissue CAFs level must be assessed by a central laboratory and an elevated tumour CAFs level demonstrated. For Baseline biomarker determination and determination of eligibility, a fresh tumour biopsy will be required from all patients before dosing in the study (unless there is a tumour material available from a biopsy taken within 30 days prior to the Screening Visit, which can be used for the Baseline biomarker analysis).

In addition, for patients with a suitable archival tumour biopsy sample available, the archival sample may be used to assess CAFs level and determine eligibility (Note: this can only be performed after the patient has provided signed informed consent). This will not dispense from the need for a recent pre-study tumour biopsy, collected during or within 30 days prior to the Screening Period, for patients eligible for the study.

To be considered suitable for determination of CAF levels, archival biopsy must have been collected within 6 months prior to the Screening Visit (Visit 1), and the patient must

have received no further anti-cancer therapy since then (see Section 5.2.2 for more details on suitability). Elevated CAF levels in suitable archival tumour tissue will meet the eligibility requirement based on CAF levels, but an additional pre-study biopsy (during or within 30 days of the Screening Period) is needed for reliable Baseline biomarker analysis.

Eligible patients will be randomised to the investigational medicinal product (IMP) setanaxib 800 mg BID, or placebo, according to a 1:1 randomisation ratio, stratified by HPV status. See Section 6.3 for further details on the method of assigning patients to the treatment groups, and see Section 6.4 for further details on the dose and administration of setanaxib and placebo. Treatment with pembrolizumab will be initiated on the same day (Day 1) as the first dose of IMP, and will be administered according to current clinical guidelines and labelling, ie, 200-mg intravenous (IV) infusion q3w. See Section 6.7 for further details on the dose and administration of pembrolizumab.

Treatment with pembrolizumab will continue until: RECIST v1.1-defined disease progression as determined by the investigator (Eisenhauer et al 2009), unacceptable toxicity, or a maximum of 24 months. If progression is suspected, but not confirmed, study treatment may continue until confirmation of radiological progression.

Treatment with setanaxib or placebo will continue throughout the period of pembrolizumab therapy. When pembrolizumab is discontinued, blinded study treatment will be discontinued at the same time.

Baseline assessments will be performed on Day 1 (Visit 2). Post-Baseline assessments will be performed every 3 weeks up to pembrolizumab discontinuation. Following permanent IMP discontinuation at any time during the study, patients will undergo an End-of-Treatment (EoT) Visit as soon as possible and a Safety Follow-up Visit at 28 days after the last dose. Tumour assessments will be conducted from the date of randomisation and continue until RECIST v1.1-defined disease progression, irrespective of treatment discontinuation. Efficacy Follow-up for PFS and survival will continue until at least 38 progression events have occurred. AEs will be recorded up to 28 days after study treatment discontinuation, while any further anti-cancer medication will be recorded until disease progression.

Throughout the study, particular attention will be given to the detection and management of potential cases of anaemia (see Section 5.3.2.1), and potential cases of hypothyroidism (see Section 5.3.2.2).

Safety and tolerability data will be regularly reviewed by an unblinded IDMC, with the first assessment after approximately 12 patients (6 per treatment group) have had the opportunity to complete at least 1 cycle of pembrolizumab +/- setanaxib, followed by periodic assessments at a frequency defined in the IDMC Charter (see Section 9.4). The IDMC may recommend change(s) to the setanaxib dose regimen or study conduct based

on the safety data reviews, as defined in the IDMC Charter. The role and responsibilities of the IDMC will be outlined in the IDMC Charter.

After approximately 12 patients (6 per treatment group) have completed their Baseline and post-treatment biopsy, initial gene expression and biomarker data in tumour tissue may be reviewed by the sponsor, who will remain masked to randomised treatment assignment. A second review may be performed, if required.

The investigator, site personnel, the sponsor and their representatives involved in monitoring and conducting the study, and the patients will be blinded to the IMP administered. See Section 6.2 for details on access to the treatment codes in the event of emergency unblinding.

3.2 Discussion of Study Design

This study will be randomised, double-blind, and placebo-controlled. Study randomisation will prevent bias in treatment allocation. In addition, stratification by HPV status will help to ensure that the treatment groups are balanced in terms of population characteristics, thereby minimising factors that could confound the interpretation of study results. The double-blinding of the study with regard to setanaxib and placebo treatment assignments will minimise bias in the assessment of treatment effect.

The patients included in this study will have recurrent or metastatic SCCHN. All patients included in this study will receive pembrolizumab. Therefore, setanaxib or placebo will be given as add-on therapy to a recognised and approved standard-of-care agent.

The primary endpoint is best percentage change in tumour size. A population with measurable disease will be selected to generate the maximum tumour response data. The use of best percentage change in tumour size has been proposed as an endpoint to compare treatments and make decisions in early drug development (Claret et al 2009) as it has been shown to be a predictor of overall survival (Claret et al 2009; Wang et al 2019) and offers greater statistical power that the traditional categorical response of ORR for comparison of treatment groups. Waterfall plots of best percentage change in tumour size clearly display both the magnitude and the variability of the response. Traditional efficacy endpoints of PFS, ORR, DoR, and DCR are retained as secondary endpoints.

The secondary endpoints related to numbers of CAFs, $CD8^+$ TILs, and regulatory T-cells in tumour tissue, and gene expression analysis in tumour tissue will be used to demonstrate the underlying mechanisms of action of setanaxib and support the primary objective.

Setanaxib Dose Rationale and Justification of Safety Margins

The tolerability, safety, and pharmacokinetics (PK) of setanaxib have been evaluated in 5 completed Phase 1 studies. A total of 120 healthy adult males have been exposed to

single oral doses of setanaxib of up to 1800 mg and multiple oral doses of setanaxib of up to 900 mg daily for 10 days. A sixth Phase 1 study has recently also been performed, to evaluate higher multiple oral doses of setanaxib than previously assessed. A total of 46 healthy male and female subjects were enrolled and received single oral doses of setanaxib of up to 1600 mg (N=30) or multiple oral doses of setanaxib of up to 800 mg BID (total daily dose 1600 mg) for 10 days (N=32).

In the Phase 1 program, setanaxib has been generally well tolerated, with a low incidence of AEs. There have been no deaths, no SAEs, and no AE of severe intensity. Most were TEAEs and were mild and self-limiting and were considered not related to treatment by the investigator.

In a clinical study in patients with PBC (GSN000300), a total of 111 patients with PBC and inadequate response to UDCA were randomised in equal proportions to receive placebo, setanaxib 400 mg OD, or setanaxib 400 mg BID for 24 weeks. This dosing regimen was considered safe and well tolerated, and the treatment was pharmacologically active (based on observed dose-related improvements in liver enzymes); however, the observed clinical efficacy in the target patient population was considered insufficient, and a Phase 2b/3 clinical study in patients with PBC is planned in which doses of up to 800 mg BID for 52 weeks will be evaluated (GSN000350).

In this study in SCCHN, setanaxib 800 mg BID will be evaluated. This is the same as the proposed highest dose in the planned Phase 2b/3 study in PBC (GSN000350) and represents a two-fold increase compared to the highest dose evaluated in the previous study in patients with PBC (GSN000300), where there were no safety signals of concern. At this dose, the expected exposures will be around the defined no-observed-adverse-effect level (NOAEL) for both the parent (setanaxib) and metabolite (GKT138184); however, the NOAEL defining toxicology signals can be monitored in the clinical setting, and were not observed in either healthy volunteers at 800 mg BID for 10 days or patients at 400 mg BID for 24 weeks.

In this study in SCCHN, setanaxib (or placebo) will be co-administered with pembrolizumab until pembrolizumab is discontinued. It is anticipated that approximately 20 patients (80% of the 25 patients randomised to setanaxib) will receive treatment with setanaxib for ≥3 months, 12 patients (approximately 50%) for ≥6 months, and 8 patients (approximately 30%) for ≥12 months. The maximum duration of pembrolizumab treatment (and, hence, corresponding setanaxib/placebo treatment) is 24 months.

For the proposed dose (setanaxib 800 mg BID [total daily dose 1600 mg]), toxicology studies in the dog, the most sensitive species, provide a safety margin of ≥1, when the combined concentration of setanaxib and its main active metabolite (GKT138184) is considered. The safety margin of setanaxib alone is also ≥1. However, for the main active metabolite GKT138184, the safety margin is calculated to be 0.7. Please see Table 3 for the calculation of safety margins based on the 39-week repeat dose study in the dog.

Table 3 Calculation of Safety Margins Based on 39-Week Repeat Dose Study in Dogs

Timepoint	PK Parameter		Exposure at NOAEL[a] in 39-Week Dog	Human Exposure at 800 mg BID[b]	Exposure Margins
Week 1	Setanaxib	C_{max} (µg/mL)	77.3	27.3	2.8
		AUC (µg•h/mL)	453.6	193	2.4
	GKT138184	C_{max} (µg/mL)	8.2	3.9	2.1
		AUC (µg•h/mL)	69.6	38.2	1.8
	Combined	C_{max} (µg/mL)	85.5	31.2	2.7
		AUC (µg•h/mL)	523.2	231.2	2.3
Week 13	Setanaxib	C_{max} (µg/mL)	57.4	27.3	2.1
		AUC (µg•h/mL)	286.8	193	1.5
	GKT138184	C_{max} (µg/mL)	6.2	3.9	1.6
		AUC (µg•h/mL)	47.9	38.2	1.3
	Combined	C_{max} (µg/mL)	63.6	31.2	2.0
		AUC (µg•h/mL)	334.7	231.2	1.4
Week 39	Setanaxib	C_{max} (µg/mL)	50.6	27.3	1.9
		AUC (µg•h/mL)	195.5	193	1.0
	GKT138184	C_{max} (µg/mL)	4.6	3.9	1.2
		AUC (µg•h/mL)	27.0	38.2	0.7
	Combined	C_{max} (µg/mL)	55.2	31.2	1.8
		AUC (µg•h/mL)	222.5	231.2	1.0

AUC=area under the concentration-time curve; BID=twice daily; C_{max}=maximum concentration; NOAEL=no-observed-adverse-effect level; PK=pharmacokinetics

[a] 300 mg/kg/day.

[b] Data derived from Day 8 data from GSN000310.

3.3 End of Study

A patient is considered to have completed the study if he/she has discontinued study treatment, completed all tumour assessments until RECIST v1.1-defined disease progression, and performed the EoT and Safety/Efficacy Follow-up Visits. The end of the study is defined as the date of the last visit or last procedure of the last patient in the study.

3.4 Stopping Rules

At any time point during the study, recruitment will pause if at least one of the following events occurs:

- Fatal event deemed related to study therapy by the Sponsor and, in discussion with the IDMC, probable or certain causality after full etiological work up. This will also result in a comprehensive review of safety.

- Unexpected and life-threatening events deemed related to study therapy by the Sponsor and in discussion with the IDMC.

Recruitment may restart following detailed review of the available data only upon the recommendation of the IDMC and a substantial protocol amendment.

4 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1 Inclusion Criteria

The following inclusion criteria must be met for a patient to be eligible for inclusion in the study:

1. Male or female patients aged ≥18 years, inclusive, at the time of informed consent.

2. Willing and able to give informed consent and to comply with the requirements of the study.

3. Histologically- or cytologically-confirmed diagnosis of SCCHN (ie, primary tumour arising from the oral cavity [including tongue], nasal cavity, paranasal sinuses, oropharynx, hypopharynx, or larynx) that is recurrent or metastatic (including both HPV^{+ve} and HPV^{-ve} SCCHN), with or without nodal involvement, and with or without metastatic spread, and is not eligible for surgical resection.

4. Candidates for first-line treatment for pembrolizumab for recurrent or metastatic SCCHN, at the discretion of the investigator.

5. A positive CAFs level (defined as CAFs level in tumours ≥5%), performed at a central laboratory, with fresh tumour biopsy taken during or within 30 days prior to the Screening Period. If available, suitable archival tissue (taken within 6 months prior to the Screening Visit and where the patient has received no further anti-cancer therapy during this 6-month period)can be used to assess tumour CAFs level and determine patient eligibility (Note: patients found to have low CAF levels in archival tissue material should not proceed to have further biopsies or screening activities).

6. Measurable disease, in accordance with RECIST v1.1, and with tumour accessible and of sufficient volume for pre-treatment and on-treatment biopsy.

7. CPS ≥1, as determined on the archival or fresh tumour biopsy taken during or within 30 days prior to the Screening Period.

8. HPV status known at randomisation.

9. Life expectancy of at least 6 months in the judgment of the investigator.

10. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

11. Adequate organ and bone marrow function within 35 days of starting study treatment. Criteria “a” to “c” cannot be met in patients with ongoing or recent (within 14 days of screening test) transfusions or who require ongoing growth factor support:

    a. Absolute neutrophil count ≥1,000/mm^3 (≥ 1.0×10^9/L).

    b. Platelet count ≥100,000/mm^3 (≥ 100×10^9/L).

    c. Haemoglobin ≥9 g/dL, in the absence of transfusions for at least 2 weeks. Patients requiring ongoing transfusions or growth factor support to maintain haemoglobin ≥ 9g/dL are not eligible.

    d. Total bilirubin ≤1.5×upper limit of normal (ULN) (if associated with liver metastases or Gilbert's disease, ≤3×ULN).

    e. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3×ULN.

    f. Serum creatinine ≤2.0 mg/dL or creatinine clearance ≥40 mL/min (measured or calculated according to the method of Cockcroft and Gault).

12. Female patients of childbearing potential must use a highly effective method of contraception to prevent pregnancy for ≥4 weeks before randomisation and must agree to continue strict contraception up to 120 days after the last dose of IMP or pembrolizumab, whichever is the later.

    a. For the purposes of this study, women of childbearing potential are defined as “fertile, following menarche and until becoming postmenopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.”

    b. Postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In female patients who are not using hormonal contraception or hormonal replacement therapy but with suspected menopause and less than 12 months of amenorrhea, a high follicle stimulating hormone (FSH) level in the postmenopausal range will be required at Screening to confirm a postmenopausal state. Confirmation with more than one FSH measurement is required.

    c. Highly effective contraception is defined as methods that can achieve a failure rate of less than 1% per year when used consistently and correctly. These methods are:

        (1) Combined (oestrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, or transdermal)

(2) Progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, or implantable)

(3) Intrauterine device

(4) Intrauterine hormone-releasing system

(5) Bilateral tubal occlusion

(6) Vasectomised partner

(7) Sexual abstinence (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. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method are not acceptable methods of contraception).

13. Female patients of childbearing potential must have a negative serum pregnancy test at Screening and a negative urine pregnancy test at Baseline/Randomisation before dosing.

14. Male patients with female partners of childbearing potential must be willing to use a condom and require their partner to use a highly effective contraceptive method (as defined in the list in item 12c). Female condom and male condom should not be used together. This requirement begins at the time of informed consent and ends 120 days after receiving the last dose of IMP or pembrolizumab, whichever is the later.

15. Male patients must refrain from donating sperm, and female patients must refrain from donating eggs, from Baseline until 120 days after the last dose of IMP or pembrolizumab, whichever is the later.

4.2 Exclusion Criteria

A patient who meets any of the following exclusion criteria will not be eligible for inclusion in the study:

1. Diagnosis of immunosuppression or receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment, with the exception of intranasal and inhaled corticosteroids or systemic corticosteroids at doses not to exceed 10 mg/day of prednisone or equivalent. Steroids as premedication for hypersensitivity reactions due to radiographic contrast agents are allowed.

2. Anti-cancer mAb treatment within 4 weeks prior to study Day 1.

3. Chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 (radiation therapy can be allowed for palliative therapy of bone metastasis only).

4. Not recovered from AEs Grade 2 or greater (except for alopecia) due to previously administered agents.

5. Treatment with any investigational agent within 12 weeks of Screening Visit or 5 half-lives of the IMP (if known), whichever is longer, or current enrolment in an interventional clinical study.

6. Prior treatment with setanaxib or participation in a previous setanaxib clinical study.

7. Prior treatment with pembrolizumab.

8. Known additional malignancy that is progressing or requires active treatment excepting basal cell carcinoma of the skin, squamous cell carcinoma of the skin, in situ cervical cancer that has undergone potentially curative therapy, or malignancy treated with curative intent and with no known active disease ≥2 years before the first dose of IMP and of low potential risk for recurrence.

9. Known active central nervous system metastases and/or carcinomatous meningitis.

10. Active autoimmune disease requiring systemic treatment within the past 3 months or documented history of clinically severe autoimmune disease, or syndrome that requires systemic steroids or immunosuppressive agents. The following are exceptions to this criterion:

    a. Patients with vitiligo or alopecia.

    b. Any chronic skin condition that does not require systemic therapy.

    c. Patients with coeliac disease controlled by diet alone.

11. Any evidence of current interstitial lung disease or pneumonitis, or a prior history of interstitial lung disease or non-infectious pneumonitis requiring high-dose glucocorticoids.

12. Active infection requiring systemic therapy.

13. Known human immunodeficiency virus (HIV) infection or acute or chronic hepatitis B or C infection. Patients with a past or resolved hepatitis B virus infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of hepatitis B surface antigen [HBsAg]) are eligible provided the hepatitis virus DNA test is negative.

Patients positive for hepatitis C antibody are eligible only if polymerase chain reaction (PCR) is negative for hepatitis C virus RNA. Patients with ongoing anti-viral therapy with potent inhibitors of CYP3A4 are not eligible. Testing for HIV is only required if clinically indicated and is not mandatory for this study.

14. Serious chronic gastrointestinal conditions associated with diarrhoea.

15. History of significant haematological problems, such as blood dyscrasias requiring treatment, aplastic anaemia, myelodysplastic syndrome, or leukaemia.

16. Surgery (eg, stomach bypass) or medical condition that might significantly affect absorption of medicines (as judged by the investigator).

17. A positive pregnancy test or breastfeeding for female patients.

18. Evidence of any of the following cardiac conduction abnormalities: a QTc Fredericia interval >450 milliseconds for male patients or >470 milliseconds for female patients. Patients with a second- or third-degree atrioventricular block are to be excluded.

19. TSH >ULN at Screening.

20. Unstable cardiovascular disease as defined by any of the following:

    a. Unstable angina within 6 months prior to Screening

    b. Myocardial infarction, coronary artery bypass graft surgery, or coronary angioplasty within 6 months prior to Screening

    c. Cerebrovascular accident within 6 months prior to Screening

    d. New York Heart Association Class III or IV heart failure

21. Presence of any laboratory abnormality or condition that, in the opinion of the investigator, could interfere with or compromise a patient's treatment, assessment, or compliance with the protocol and/or study procedures.

22. Any other condition that, in the opinion of the investigator, constitutes a risk or contraindication for the participation of the patient in the study, or that could interfere with the study objectives, conduct, or evaluation.

23. Use of medications known to be potent CYP3A4 inhibitors or inducers, or potent uridine diphosphate (UDP)-glucuronosyltransferase 1A9 (UGT1A9) inhibitors or inducers, within 21 days prior to IMP administration.

24. Legal incapacity or limited legal capacity.

25. Psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

26. Patients who are unable to provide informed consent, are incarcerated or unable to follow protocol requirements``

27. Previous randomisation in this study.

4.3 Screen Failures

Screen failures are defined as patients who consent to participate in the clinical study but who do not meet one or more criterion required for participation and are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients, to meet the Consolidated Standards of Reporting Trials publishing requirements, and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Patients who are screen failures may undergo **full** rescreening once at the discretion of the investigator and medical monitor if there is a reasonable expectation that the patient is potentially eligible for the study. In these cases, the rescreened patient should be assigned a new unique screening number.

Of note, during the Screening Period, some assessments (eg, laboratory tests, ECGs, vital signs) can be repeated if abnormal without being considered as screen failure. In these cases, a whole new rescreening is not required.

4.3.1 Premature Discontinuation of Investigational Medicinal Product

Patients should discontinue the IMP if any of the following occurs:

1. The patient withdraws his/her consent to participate in the study.

2. The patient develops an illness that would interfere with his/her continued participation in the study, at the investigator's discretion.

3. The patient is noncompliant with study procedures or medication, that in the opinion of the investigator, impacts patient safety and/or the integrity of the study results.

4. The patient takes a prohibited medication that warrants the IMP discontinuation at the discretion of the investigator (see Section 6.7).

5. The patient is confirmed to be pregnant.

6. The sponsor or regulatory agency requests withdrawal of the patient.

7. The patient is withdrawn for safety reason per the investigator's judgment.

8. IMP rechallenge results in anaemia or hypothyroidism IMP interruption criteria being met again (see Section 6.4.2).

At the time of premature IMP discontinuation, the patient should complete the assessments indicated at the EoT Visit (see Table 1). The patient will also be required to attend a Safety Follow-up Visit at 28 days after the last IMP dose. In addition, patients who discontinue study treatment prior to radiological progression will continue to be followed for tumour assessments until RECIST v1.1-defined disease progression, and for survival.

Patients who withdraw consent should be asked whether they would still allow contact for determination of survival follow-up. If patients consent to survival follow-up, they will be withdrawn from study treatment and other study procedures but are not considered to have withdrawn from the study.

Patients who discontinue IMP prematurely will not be replaced.

For details of permitted IMP dechallenge and rechallenge, see Section 6.4.2.

Patients who fail to meet the eligibility criteria should not under any circumstances be enrolled or receive study medication. There can be no exceptions to this rule. Where a patient does not meet all the eligibility criteria but is incorrectly started on-treatment, the investigator should inform the medical monitor and the Calliditas Study Physician immediately, and a discussion should occur between the medical monitor, the Calliditas Study Physician, and the investigator regarding whether to continue or discontinue the patient from treatment. The Calliditas Study Physician must ensure all decisions are appropriately documented.

4.3.2 Premature Discontinuation from the Study

Participation in the study is strictly voluntary. A patient has the right to withdraw from the study at any time for any reason, without any reprisal.

The investigator has the right to terminate participation of a patient for any of the following reasons:

- Violation of the protocol jeopardising patient safety and/or integrity of study results
- Any other reason relating to the patient's safety
- Any other reason relating to the integrity of the study data

Investigators should make every effort to discuss with the study monitor/sponsor before discontinuing a patient from the study.

If a patient is withdrawn from the study, the study monitor/sponsor will be informed immediately. If there is a medical reason for withdrawal, the patient will remain under the supervision of the investigator until satisfactory health has returned.

If the patient withdraws consent for disclosure of further information, the sponsor may retain and continue to use any collected data before such a withdrawal of consent. If a patient withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Although a patient is not obliged to give his/her reason(s) for withdrawing prematurely from a study, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the patient's rights.

At the time of premature study discontinuation, the investigator should make every effort to ensure the patient completes the assessments indicated at the EoT Visit (see Table 1).

Patients who prematurely discontinue from the study cannot subsequently re-join the study.

For details on the discontinuation of study sites or the study as a whole, see Section 14.

4.3.3 Lost to Follow-up

A patient will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a patient fails to return to the clinic for a required study visit:

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule, and ascertain whether or not the patient wishes to and/or should continue in the study.

- Before a patient is deemed lost to follow-up, the investigator (or designee) must make every effort to regain contact with the patient (where possible, 2 telephone calls and, if necessary, a certified letter to the patient’s last known mailing address or local equivalent methods). These contact attempts should be documented in the patient’s medical notes.

- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study.

5 DESCRIPTION OF STUDY ASSESSMENTS

Refer to Table 1 for the schedule of assessments.

Patients will be reminded to bring the IMP with them to each study visit. On visit days, patients will take their morning doses of IMP with food (or up to 30 minutes after a meal) after the study procedures have been completed. In general, study assessments may be performed on any days within the allowed visit windows around nominal visit dates, in particular tumour assessment (biopsy and imaging) may be carried out on a different day to the main study visit, refer to Section 5.2 for details of efficacy assessments.

In general, the assessments will be conducted in the following order:

- AEs/concomitant medications recording
- Physical examinations/vital signs/ECGs
- Laboratory assessments/Tumour assessment (tumour assessment must be performed before tumour biopsy when applicable)
- Dispense IMP
- Patient takes morning dose of IMP with food (or up to 30 minutes after a meal) (see Section 6.4)

5.1 Demographics and Other Screening Assessments

Patients will attend the Screening Visit within 35 days of Day 1. If serum pregnancy (see Footnote ‘d’ of Table 1) retest is required, it should be repeated within 7 days prior to randomisation. Screening Period extensions of up to 7 days may be considered on a case-by-case basis, if agreed by the investigator and medical monitor.

Demographics, ECOG performance status, and relevant medical history will be collected as described in Sections 5.1.1 and 5.1.1, respectively.

Safety assessments, including laboratory assessments, that are also part of the screening assessments are described in Section 5.3.

The screening assessment of tumour response will be assessed as described in Section 5.2.1.1.

A fresh tumour biopsy will be taken during the Screening Period for assessment of tumour biomarkers (CAFs, $CD8^+$ TILs, regulatory T-cells, and PD1-L1) and gene expression analysis, as described in Section 5.2.2.

Prior medications will be assessed at Screening, as described in Section 6.6.

5.1.1 Demographics

Demographic data, including year of birth/age, sex, and race, will be recorded in the electronic case report form (eCRF).

5.1.2 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed as described in Appendix II and recorded in the eCRF.

5.1.3 Medical History

Medical history, including any ongoing illnesses up to the time the patient has provided informed consent, will be recorded in the eCRF, with the start date and stop date (if applicable) of the illness/condition.

Any pre-study procedures will be recorded in the eCRF as part of the medical history assessment.

5.2 Efficacy Assessments

5.2.1 Tumour Imaging and Assessment of Disease

Tumour assessments will include all known or suspected disease sites. For all patients, study imaging assessments will include computed tomography (CT) or magnetic resonance imaging (MRI) scans. Other imaging assessments, eg, positron emission tomography (PET) CT and bone scans, may be performed if needed to further investigate or delineate abnormalities seen on CT/MRI.

The same imaging technique regarding modality, ideally the same scanner, and the use of contrast should be used in a patient throughout the study to optimise the reproducibility of the assessment of existing and new tumour burden and improve the accuracy of the assessment of response or progression based on imaging. During follow-up, lesions should be recorded on the eCRF page in the same order as they were recorded at screening. Note: for the purposes of assessing tumour imaging, the term “investigator” refers to the local investigator at the site and/or the radiological reviewer located at the site or at an offsite facility. Expedited confirmation of measurable disease based on RECIST v1.1 will be used to determine patient eligibility.

The RECIST guidelines v1.1 for measurable (target) and non-measurable (non-target) lesions, and the objective tumour response criteria (CR, PR, SD, or PD) are presented in Appendix IV. The RECIST criteria will be used to programmatically determine ORR, DoR, and DCR.

5.2.1.1 Initial Tumour Imaging

Initial tumour imaging at Screening must be performed within 35 days prior to the date of treatment. The site study team must review screening images to confirm the patient has measurable disease per RECIST v1.1. This scan will also be used as the Baseline scan for the tumour assessments in this study.

All measurable lesions confirmed and assessed by radiological methods (CT or MRI scans) up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions, recorded and measured at Baseline, and at the time points specified in the protocol.

5.2.1.2 Tumour Imaging During the Study

The first on study imaging assessment should be performed at Visit 5 (Week 9 ±1 week), and then every 6 weeks (±1 week) through the first year, and every 9 weeks (±1 week) thereafter for up to 24 months. Tumour assessments will be conducted from the date of randomisation and continue until RECIST v1.1-defined disease progression, irrespective of treatment discontinuation. Any further anti-cancer medication will be recorded until progression.

Imaging timing should follow the planned schedule relative to randomisation and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until radiological progressive disease is confirmed by the investigator, withdrawal of consent, death, or notification by the sponsor, whichever occurs first.

A patient will be determined to have progressed if they have progression of target lesions, unequivocal progression of existing non-target lesions, or the appearance of one or more new lesions during follow-up. Death will be regarded as a progression event in those patients who die before disease progression. Unequivocal malignant disease not identified prior to starting study treatment on additional anatomical imaging (eg, CT, MRI or bone scan confirmed by X-ray) prompted by symptoms, is considered disease progression and should be recorded as new lesions. If progression is uncertain, patients may continue on-treatment until the next scheduled assessment. If an unscheduled assessment is performed, it is important to return to the correct scanning schedule for subsequent scans relative to randomisation, so that the 2 treatment groups are comparable. If the investigator is in doubt as to whether progression has occurred, it is advisable to continue treatment and reassess at the next scheduled assessment, or sooner, if clinically indicated.

To achieve ‘unequivocal progression’ on the basis of non-measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of treatment. A modest increase in the size of one or

more non-target lesions is usually not sufficient to qualify for unequivocal disease progression status.

Response will be calculated in comparison to the baseline tumour measurements obtained before starting treatment. Progression will be calculated in comparison to when the tumour burden was at a minimum (nadir). Overall visit response will be recorded on the eCRF. A copy of the CT/MRI scans and radiologist report performed for tumour assessment may be collected by a Calliditas appointed representative and analysed centrally for further scientific determination of changes in tumour size by volumetric assessment.

Refer to Appendix IV for further details on RECIST v1.1 methodology.

5.2.2 Tumour Biopsy

Up to 2 mandatory fresh tumour biopsies will be collected for assessment of tumour biomarkers (CAFs, $CD8^+$ TILs, regulatory T-cells, and PD1-L1) and gene expression analysis.

Tumour biopsies can be taken from primary tumour site, involved lymph node or metastasis site. Any decision to perform the on-treatment biopsy must consider the patient's condition at that time point, and not be done if the risk to the patient appears unacceptable. Investigators must ensure appropriate clinical judgment is applied when considering whether to perform tumour biopsies as this is a surgical procedure that may not intrinsically benefit individual patients but may benefit medical research.

The first biopsy will be collected during or within 30 days prior to the Screening Period and will be used to determine the CPS score and CAFs level in tumour tissue as part of eligibility criteria, in case no archival tissue was available. Other assessments will include:

- Levels of PD-L1 expression in tumour tissue using the PD-L1 IHC 22C3 pharmDx assay (Agilent), a qualitative immunohistochemical assay using monoclonal mouse anti-PD-L1 clone 22C3 intended for use in the detection of PD-L1 protein in formalin-fixed, paraffin-embedded non-small cell lung cancer, gastric or gastroesophageal junction adenocarcinoma, oesophageal squamous cell carcinoma, cervical cancer, urothelial carcinoma, SCCHN, and triple-negative breast cancer tissues, using EnVision FLEX visualisation system on Autostainer Link 48
- Number of $CD8^+$ TILs and regulatory T-cells in tumour tissue
- RNA sequence analysis

To be considered suitable for initial determination of CAF levels, archival tissue biopsy material must have been collected within 6 months prior to the Screening Visit, and the

patient must have received no further anti-cancer therapy since then. To be considered suitable for full Baseline (pre-treatment) biomarker assessment, tumour biopsy specimens must have been collected within 30 days prior to Screening. Samples may be from the primary SCCHN site, regional lymph node, or metastatic site.

Tumour sample may be from either a surgical resection or core needle biopsy or collected as an excisional or incisional tumour biopsy from either the primary or metastatic site during surgery or interventional procedure. Fine needle aspirates are not acceptable. Formalin-fixed paraffin-embedded needle core biopsies may have been obtained via direct visualisation of tumour, or with CT, fluoroscopy, or ultrasound image guided needle biopsy procedures. The tissue cores should have been obtained by the use of an 18 gauge (or larger core diameter) biopsy needle. If smaller needle is used, then additional biopsy cores are to be provided in the block. 10% Neutral buffered formalin is recommended as the tissue fixative.

Samples meeting any of the criteria below are not acceptable:

- Archived tissue with limited tumour content: preferably at least 30% of viable tumour cells
- Cytology samples and fine needle aspirates
- Tissues fixed with other unacceptable fixatives, including 95% alcohol, alcohol formalin acetic acid, and PREFER™
- Specimens from bone lesions are generally not acceptable unless there is significant soft tissue component or there is no bone tissue in the biopsy

The second biopsy (mandatory for all patients) will be performed 9 weeks (±1 week) after the start of study treatment or earlier if progression occurs before 9 weeks.

A third optional tumour biopsy can be performed at disease progression (only for patients who had their second biopsy at 9 weeks, who consented to having a third sample).

CAFs will identified in formalin-fixed, paraffin-embedded tissue sections using immunohistochemistry for αSMA. CAFs are positive for α-SMA, and tumour stroma will be assessed for CAFs as previously described (Marsh et al 2011). SMA staining and evaluation of CAF scores will be performed by a single pathologist (or a suitably qualified and trained deputising pathologist) at a central laboratory. The semi-quantitative scoring system separates tumours into 3 groups: low (<5% stroma positive), moderate (5 to 50% stroma positive) and high (>50% stroma positive). Patients with tumours containing moderate or high levels of CAFs will be eligible for the study.

The tumour samples will be used for analyses of biomarkers related to SCCHN. The biomarker analyses results will be used to explore the potential relationship with setanaxib response and/or disease progression data obtained in this study.

The samples may be analysed as part of a multistudy assessment of genetic factors involved in the response to setanaxib or IMPs of this class to understand study disease or related conditions.

The tumour sample will be collected, processed, stored, sent for central review, and analysed as defined in the central laboratory manual. Refer to the central laboratory manual for further details.

5.2.3 Peripheral Blood for Circulating Biomarkers Analysis

Blood samples (20 mL whole blood) will be collected for analysis of exploratory circulating biomarkers, before commencing study treatment, during treatment and at progression, as outlined in Table 1. The blood samples will be used for analyses of circulating biomarkers related to SCCHN. The results of biomarker analyses will be used to explore the potential relationship with setanaxib response and/or disease progression data obtained in this study. Samples collected before treatment will be analysed for predictive biomarkers of response to treatment and may be used to develop future in vitro diagnostic tests. Samples collected during treatment and at progression will be used for additional exploratory research which may include but is not limited to interrogation of changes in genetic expression and potential mechanisms of resistance to treatment. A range of oncology and immunological biomarkers that may corelate with drug response will be examined; these may include but are not limited to panels of cytokines, chemokines and other soluble biomarkers; T-cell receptor repertoire analysis; and analysis of gene expression biomarkers associated with immunomodulatory effects.

The samples may be analysed as part of a multistudy assessment of genetic factors involved in the response to setanaxib or IMPs of this class to understand study disease or related conditions.

The blood samples will be collected, processed, stored, sent for central review, and analysed as defined in the central laboratory manual. Refer to the central laboratory manual for further details.

5.3 Safety Assessments

5.3.1 Adverse Events

AEs will be followed, recorded, and reported in line with the procedures described in Section 7. AESIs are defined in Section 7.1.5.

Particular attention will be given to the detection and management of potential cases of anaemia (Section 5.3.2.1), or potential cases of hypothyroidism (see Section 5.3.2.2).

5.3.2 Clinical Laboratory Evaluations

Laboratory assessments will be performed by a central laboratory, unless otherwise specified. The central laboratory will analyse the samples or send them to reference laboratory(ies) for analysis, as indicated in the central laboratory manual. Laboratory assessments of PK are described in Section 5.4.

Blood and urine samples will be collected pre-dose at the times indicated in Table 1. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples. The blood volumes to be collected per patient during the study will be provided in the informed consent form (ICF) and/or in the central laboratory manual. For further details, refer to the central laboratory manual.

Sampling for the analysis of clinical laboratory parameters will be performed before the administration of IMP.

The following parameters will be assessed:

Haematology: haematocrit, haemoglobin, absolute and relative reticulocyte counts, red blood cell (RBC) count, white blood cell (WBC) count, differential WBC count, platelet count, absolute neutrophil count, mean cell volume, and international normalised ratio (INR only at Screening)

Biochemistry: ALP, ALT, AST, amylase, total and conjugated bilirubin, GGT, glucose, total protein, albumin, creatinine, urea, total cholesterol, triglycerides, sodium, potassium, and chloride

Thyroid function test: TSH and free T4

Pregnancy test (serum): See Section 5.3.3.

Urinalysis: qualitative tests will be performed using urine dipsticks (refer to the central laboratory manual for more details)

Pregnancy test (urine): See Section 5.3.3.

In case the HPV status is not known or not documented in the medical records, HPV status will need to be determined before randomisation as per site standard operating procedures (eg, p16 immunohistochemistry or HPV DNA detection [PCR or in situ hybridisation]). The methodology used for HPV testing will be recorded in the eCRF.

Refer to the central laboratory manual for details regarding the collection, processing, and shipping of the blood and urine samples.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

All laboratory tests with values considered clinically significantly abnormal during the patient's participation in the study or within 28 days after the last dose of IMP, whichever is later, should be repeated until the values return to normal, to Baseline levels, or have stabilised and are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/Baseline within a period of time judged reasonable by the investigator, then the aetiology should be identified, and the sponsor (or designee) notified.

If required due to Covid-19-related restrictions, laboratory samples to follow up an AE, including the retests for haemoglobin (see Section 5.3.2.1), or TSH and free T4 (see Section 5.3.2.2), may be collected by a qualified healthcare professional at a location other than the study site. For other circumstances pertaining to patient safety during Covid-19-related restrictions, follow-up with the sponsor (or designee).

Laboratory samples taken to follow up an AE, including the retests for absolute haemoglobin, or TSH and free T4 noted above, may be tested locally so that the results are communicated to the investigator's site promptly. If required due to Covid-19-related restrictions, the results of local safety laboratory tests may be provided to the investigator by telephone. Local laboratory results will not be entered into the eCRF. However, where unscheduled central laboratory confirmation is not possible for protocol-specified retests for evaluation of potential anaemia or hypothyroidism, the retest results may be requested.

5.3.2.1 Detection and Management of Anaemia

Particular attention will be given to the detection and management of potential cases of anaemia. In case of Grade ≥3 severity anaemia, the investigator will instruct the patient to interrupt IMP administration and to return to the study centre within 7 days so that haemoglobin can be retested. If the severity of anaemia is still Grade ≥3, and if an alternative cause for the anaemia cannot be documented (alternative cause may include the underlying cancer), IMP will not be resumed and will be permanently discontinued. IMP administration will be resumed only if the retest value for haemoglobin is ≥9 g/dL and an alternative cause for the anaemia can be documented. The patient will continue to be closely monitored (at least weekly) until normalisation of haemoglobin, ie, return to Baseline values.

Anaemia will be reported to the sponsor (or designee) as an AESI, as defined in Section 7.1.5, following the same procedure as for SAEs (Section 7.4).

5.3.2.2 Detection and Management of Hypothyroidism

Particular attention will be given to the detection and management of potential cases of hypothyroidism. In case of TSH ≥10 mIU/L, the investigator will instruct the patient to interrupt IMP administration and to return to the study centre within 5 days so that TSH and free T4 values can be retested. If the retest value is ≥10 mIU/L and the patient presents with signs and symptoms consistent with hypothyroidism or if overt biological hypothyroidism is confirmed (ie, TSH ≥10 mIU/L and reduced free T4), IMP will not be resumed. If drug-induced hypothyroidism is not confirmed, IMP administration will be resumed as per protocol. The patient will continue to be closely monitored by at least their clinical status and TSH/free T4 levels (at least weekly) until normalisation of the TSH and free T4 values, ie, return to Baseline values.

Hypothyroidism will be reported to the sponsor (or designee) as an AESI, as defined in Section 7.1.5, following the same procedure as for SAEs (Section 7.4).

5.3.3 Pregnancy

All patients are required to meet the requirements relating to pregnancy and use of contraception described in the inclusion and exclusion criteria (see Section 4.1 and Section 4.2, respectively). Male and female patients of childbearing potential must receive pregnancy prevention counselling and be advised of the risk to the foetus if they become pregnant or father a child during treatment and for 6 months after the last dose of IMP or pembrolizumab, whichever is the later. Additional medications given during the study may alter the contraceptive requirements. These additional medications may require female patients to use highly effective methods of contraception and/or for an increased length of time. In addition, male patients are also required to use contraception. The investigator must discuss these contraceptive changes with the patient.

For female patients who are considered postmenopausal but have less than 12 months of amenorrhea and who are not on concomitant oestrogen replacement therapy, a high FSH level in the postmenopausal range will be required at Screening. Confirmation with more than one FSH measurement is required.

Serum (beta human chorionic gonadotrophin) or urine pregnancy tests will be performed for female patients of childbearing potential at the time points indicated in Table 1.

Female patients of childbearing potential must have a serum pregnancy test at the Screening Visit. The blood sample for the serum pregnancy test must be taken within 7 days of Day 1. Therefore, if Screening Visit is performed more than 7 days prior to Day 1, the serum pregnancy test must be repeated within 7 days of Day 1. The result must be negative for the patient to be eligible for the study. If the test result is positive,

the patient must be excluded from the study. The serum pregnancy tests will be analysed by the central laboratory. A negative urine pregnancy test result is required at Baseline/Randomisation and at each visit before dosing. Urine pregnancy tests will be analysed locally.

Any pregnancies in female patients and the partners of male patients will be recorded from the patient's inclusion in the study until 6 months after the last dose of IMP or pembrolizumab, whichever is the later. Male patients will be required to inform the investigator if their partner becomes pregnant during the study and for 6 months after the last dose of IMP or pembrolizumab, whichever is the later. The investigator should inform the sponsor (or designee) within 24 hours of learning of the pregnancy or partner pregnancy by completing and submitting a Pregnancy Report Form to the sponsor (or designee) using the contact details provided. (Note: Sites are not required to provide any information on the pregnancy notification form that violates the country or regions local privacy laws).

If a patient becomes pregnant, she will permanently discontinue IMP and attend an EoT Visit as soon as possible and a Safety Follow-up Visit at 28 days after the last dose of IMP, after which the patient will be encouraged to continue study assessments until disease progression.

After obtaining the female patient's signed authorisation for release of pregnancy and infant health information, the investigator will collect pregnancy and infant health information and complete the pregnancy questionnaire for any female patient who becomes pregnant while taking IMP or pembrolizumab through 6 months following the last dose of IMP or pembrolizumab, whichever is the later. This information will be forwarded to sponsor (or designee). Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable).

Any termination of pregnancy will be reported to sponsor (or designee), regardless of foetal status (presence or absence of anomalies) or indication for procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE. Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital abnormalities, ectopic pregnancy) will be considered SAEs.

Any SAE occurring as a result of a post-study pregnancy which is considered reasonably related to the study treatment by the investigator, will be reported to sponsor (or designee). While the investigator is not obligated to actively seek this information in former study patients, he or she may learn of a SAE through spontaneous reporting.

For any male study patient's partner who becomes pregnant, the investigator will attempt to collect pregnancy information on the male patient's partner while the male patient is in this study until 6 months after the last dose of IMP or pembrolizumab, whichever is the

later. The investigator will record pregnancy information on the appropriate form and submit it to the sponsor (or designee) within 24 hours of learning of the partner's pregnancy. The investigator will obtain informed consent from the female partner to collect information about the pregnancy and its outcome. Information on the status of the mother and child will be forwarded to the sponsor (or designee). Generally, infant follow-up will be conducted up to 12 months after the birth of the child (if applicable). Any termination of the pregnancy will be reported regardless of foetal status (presence or absence of anomalies) or indication for the procedure. Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital abnormalities, ectopic pregnancy) will be considered SAEs.

5.3.4 Breastfeeding

Breastfeeding women will be excluded from the study.

5.3.5 12-lead Electrocardiogram

12-lead ECG will be obtained as outlined in Table 1.

At Visit 2 (Study Day 1) and Visit 3, 12-lead ECG will be recorded pre-dose and 2 hours (± 30 minutes) post setanaxib/placebo dosing. From Visit 4 onwards, 12-lead ECG are only required before setanaxib/placebo dosing; additional ECGs may be recorded as clinically indicated.

The ECGs will be conducted in the supine position after 5 minutes' rest.

The ECG tracing printout should be signed and dated by the person who made the interpretation locally (for purposes of patient safety management); the tracing printout will be archived at the study site. The machines will provide heart rate, PR, QRS, QT, and QTc intervals. If the ECG tracing printouts are in a non-archivable quality, including fading ink, a certified copy should be printed, signed and dated by the person who made the copy and labelled "certified copy". Electronically archived ECG tracings are acceptable as source data provided the electronic archival system is validated.

If there is any evidence of the cardiac conditions or abnormalities noted in Section 4.3.1, IMP is to be permanently discontinued.

Further details regarding the ECG assessments are provided in the site operations manual or manual provided by the vendor.

5.3.6 Vital Signs

Vital signs will be measured as outlined in Table 1 with the patient in a sitting position after 5 minutes' rest and will include pulse rate, SBP, and DBP. Body temperature will be measured at Screening Visit 1 according to local standard-of-care.

5.3.7 Physical Examination, Including Height and Body Weight

Patients will undergo complete physical examination or symptoms-directed physical examinations as outlined in Table 1.

The complete physical examination will include assessments of the standard physical examination items, including general appearance, skin, eyes, ears, nose, throat, head and neck, heart, chest and lungs, abdomen, extremities, lymph nodes, musculoskeletal, neurological, and other body systems, if applicable, for describing the status of the patient's health.

Body weight and height (height at Screening Visit only) will also be measured and recorded. The patient should be dressed in light clothing, without shoes.

Investigators should pay special attention to clinical signs related to previous serious illnesses. Any new abnormalities or worsening of existing abnormalities that are associated with signs and/or symptoms (except for SCCHN related -pre-existing- conditions, including disease progression) should be reported as AEs or SAEs, as appropriate (see Section 7).

5.4 Pharmacokinetics

Blood samples will be collected for measurement of plasma concentrations of setanaxib and its metabolite GKT138184 for all patients during the study at the visits specified in Table 1. The PK blood volumes to be collected during the study will be provided in the ICF and/or in the central laboratory manual.

PK samples will be collected just before the start of pembrolizumab infusion and before the IMP morning dose at Day 1, Week 3, Week 24, Week 51, and Week 105, and anytime for the PK samples taken on the day of the second biopsy and at EoT Visit.

Instructions for the collection and handling of biological samples will be provided by the sponsor (or designee) and will be included in the central laboratory manual. The actual date and time that each sample is collected will be recorded.

The measurement of plasma setanaxib and GKT138184 concentrations will be performed by a central laboratory.

6 TREATMENTS

6.1 Investigational Medicinal Product

6.1.1 Description of Investigational Medicinal Product

Test Product	
IMP/non-IMP:	IMP
Name:	Setanaxib
Dose:	800 mg BID (2 tablets in the morning and 2 tablets in the evening) Setanaxib tablets will contain 400 mg setanaxib powder formulated with excipients.
Mode of administration:	Orally (or via either a feeding tube or a percutaneous endoscopic gastrostomy device in case patients are unable to swallow tablets)
Manufacturer:	Aptuit Via Alessandro Fleming, 4 37135 Verona VR Italy

Placebo	
Substance:	Matching placebo tablets, containing only excipients, will be provided. The placebo tablets will be visually identical to setanaxib tablets to maintain the blind.
Dose:	Not applicable
Mode of administration:	Orally (or via either a feeding tube or a percutaneous endoscopic gastrostomy device in case patients are unable to swallow tablets)
Manufacturer:	Aptuit Via Alessandro Fleming, 4 37135 Verona VR Italy

6.1.2 Preparation, Handling, and Storage

Refer to the pharmacy manual for full details regarding the preparation of setanaxib and placebo tablets.

The investigator (or designee) is responsible for the safe and proper storage of IMP at the site. The bottles containing setanaxib and placebo tablets will be stored under controlled conditions according to the storage requirements described on the label. The IMP is to be

stored at room temperature (15-25°C). The tablets must not be frozen or stored above 25ºC or 77ºF. The investigator (or designee) will instruct the patients to store the IMP in accordance to the instructions on the label.

6.1.3 Labelling and Shipment

Setanaxib and placebo bottles will be labelled in accordance with all applicable regulatory requirements and Good Manufacturing Practice guidelines.

Setanaxib and placebo will be provided in high-density polyethylene (HDPE) bottles containing:

- Setanaxib 400 mg tablets
- Matching placebo tablets

Each bottle will contain 70 tablets.

The labelling of the placebo will be the same as the test product to maintain the blind.

Setanaxib and placebo will be shipped and stored under controlled conditions according to the storage requirements. The IMP is to be stored and shipped at room temperature (15-25ºC).

Refer to the pharmacy manual for full details for labelling and shipment of the IMP.

An authorised service provider will label the IMP bottles and will supply the IMP to local depots/study sites on behalf of the sponsor (or designee).

6.2 Blinding

The study is double-blinded. The investigator, the site personnel, the sponsor and their representatives involved in monitoring and conducting the study, and the patients will be blinded to treatment assignments.

Randomisation data will be kept strictly confidential, accessible only to authorised staff and the IDMC until the time of unblinding. Authorised staff may include the randomisation statistician, who will store the master randomisation list in a secure system, an unblinded statistician, and unblinded programmers, who will provide the IDMC with unblinded safety data for review, and as and when required, in accordance with the procedures described in the IDMC Charter. All authorised unblinded staff must be documented.

The setanaxib and placebo tablets are visually identical to maintain the blind. Setanaxib and placebo bottles will be coded and labelled in a manner that protects blinding. The

coding system will permit rapid identification of the product (in case of medical emergencies), that does not permit undetectable breaking of the blind.

Breaking of the blind is only allowed in the case of an emergency, when knowledge of the IMP is essential for the clinical management of the patient. In such emergency situations, the responsibility to break the treatment code resides solely with the investigator. The investigator will have immediate access to break the blind through the interactive response technology (IRT). The investigator must contact the sponsor within 1 working day after the event, without revealing to the sponsor (or contract research organisation [CRO]) the results of the code break, except to the designated global patient safety representative. The investigator must document the date of unblinding and the reason.

Emergency unblinding will be organised through IRT. The investigator must record the date of unblinding and the reason. All breaks of the blind must be adequately documented.

If an SAE is reported, the designated global patient safety representative may unblind the treatment assignment for the individual patient through IRT to meet regulatory reporting requirements.

6.3 Method of Assigning Treatment

Each patient will have a unique patient screening number obtained from the IRT. This will be assigned at the Screening Visit. If a patient is rescreened (see Section 4.3), the rescreened patient should be assigned a new unique screening number. The investigator will keep a record (the patient screening log) of patients who entered Screening.

Once the patient has been successfully screened and the investigator has determined that the patient is eligible, the patient will be confirmed as enrolled within the IRT.

Randomisation will be performed via a centralised IRT. On Day 1, eligible patients will be assigned to setanaxib or placebo in a 1:1 ratio, stratified by HPV status. Each patient will receive a unique randomisation number when he/she is assigned treatment. Patients will be allocated to treatment according to the randomisation code.

The randomisation codes will be prepared by the randomisation statistician. The randomisation statistician will store the master randomisation list in a secure system.

If a patient withdraws from study participation, his/her unique identification number(s) cannot be re-used for another patient.

6.4 Dose and Administration

At each dispensing visit, patients will receive setanaxib or placebo bottles. Each bottle contains 70 tablets. Patients will be dispensed 1 to 3 IMP bottles at each dispensing visit, as described in the site operations manual, to ensure that the patient has sufficient IMP to last until the next scheduled visit.

Patients will take 4 tablets per day. Two tablets will be taken in the morning and 2 tablets will be taken in the evening.

- Patients allocated to setanaxib 800 mg BID will self-administer 2 tablets of setanaxib 400 mg in the morning and 2 tablets of setanaxib 400 mg in the evening.

- Patients allocated to placebo will self-administer 2 placebo tablets in the morning and 2 placebo tablets in the evening.

Patients will be instructed not to take their morning IMP dose on PK visit days until after the study assessments have been completed, except the PK visit days where tumour biopsy is collected and the EoT Visit.

Patients should take the first dose at the clinic under supervision of site staff to ensure the first dose is taken and that patients can swallow the tablets. The first dose taken should be documented in medical records.

For patients that can swallow setanaxib/placebo tablets, the tablets should be taken orally with food or up to 30 minutes after a meal. Each tablet should be taken separately and swallowed with water. The patients will be instructed to distribute their morning and evening doses as evenly as possible.

Patients who cannot swallow tablets and have either a feeding tube or a percutaneous endoscopic gastrostomy (PEG) device inserted are allowed to disperse setanaxib tablets in water using a compatible syringe and administer the dispersed tablets through the feeding device. See further details in the pharmacy manual. A separate patient information leaflet should be provided to the patient and verbal instructions given by the investigator or other appropriately trained staff at the clinic on how to disperse and administer the IMP.

Patients will be provided with a patient IMP dosing card. Patients will be instructed to record the date and time of each dose that they take, as well as the route of administration (oral, feeding tube, or PEG device), on the dosing card straight after they have taken the tablet.

Patients will be reminded to bring the IMP (including any empty bottles) and the patient IMP dosing card with them to each study visit.

The IMP dosing card will be considered as a source document. Site personnel will record the date and time of the IMP dose as well as the route of administration (oral, feeding tube, or PEG device) prior to PK Visits (ie, prior to the PK sample) in the eCRF.

6.4.1 Dose Modification

Dose interruptions are required in case of anaemia and hypothyroidism, when the events meet the criteria as defined in Section 5.3.2.1, and Section 5.3.2.2, respectively. Events that require permanent discontinuation of IMP are listed in Section 4.3.1.

Dose reduction of setanaxib to 400 mg BID to manage anaemia, hypothyroidism, or any Grade 3 or otherwise intolerable toxicity, which is considered related to setanaxib may be instituted at the investigator's discretion after discussion with the medical monitor.

6.4.2 Dechallenge and Rechallenge

Investigational medicinal product should be interrupted in cases of anaemia (as described in Section 5.3.2.1) or hypothyroidism (as described in Section 5.3.2.2). If the criteria specified in those sections are met, IMP may be resumed. If the rechallenge results in the IMP interruption criteria being met again, the IMP must be permanently discontinued (see Section 4.3.1).

6.4.3 Intervention After the End of the Study

Continued access to IMP is not planned beyond the completion of the study.

6.5 Precautions and/or Lifestyle Considerations

There are no other lifestyle considerations (such as dietary or physical activity restrictions) for this study further to those listed in the inclusion/exclusion criteria (Section 4).

6.6 Prior Medication

See Section 4 for details of the prior medication that is permitted or prohibited according to the inclusion and exclusion criteria.

The following medications are prohibited:

- Anti-cancer mAb treatment within 4 weeks prior to study Day 1
- Chemotherapy, targeted small molecule therapy or radiation therapy within 2 weeks prior to study Day 1 (radiation therapy can be allowed for palliative therapy of bone metastasis only)

- Treatment with any investigational agent within 12 weeks of Screening Visit 1 or 5 half-lives of the IMP (if known), whichever is longer

- Current enrolment in another interventional clinical study

- Medications known to be potent CYP3A4 inhibitors or inducers, as well as potent UGT1A9 inhibitors or inducers, within 21 days prior to IMP administration

Live-attenuated vaccines should be avoided where possible within 30 days before study treatment but may be used where other alternatives are not available, considered inferior, or otherwise unsuitable.

6.7 Background Treatment

Setanaxib or matching placebo will be administered in combination with pembrolizumab.

Pembrolizumab (KEYTRUDA, Merck) is a PD-1-blocking antibody indicated for the first-line treatment of patients with metastatic or unresectable recurrent SCCHN. Pembrolizumab is administered as 200-mg IV infusion q3w. Treatment will be initiated on Day 1, ie, at the same time as the first dose of IMP.

Pembrolizumab is considered as a non-investigational product and will be administered according to current clinical guidelines and labelling.

Refer to the pharmacy manual for full details for labelling and shipment of pembrolizumab.

6.8 Concomitant Medication

See Section 4 for details of the prior medication that is permitted or prohibited according to the inclusion and exclusion criteria. The prohibited (prior) medications and devices listed in Section 6.6 are also prohibited during the study. The following medications are prohibited during the study:

- Drugs that have known bone marrow toxicities

- Potent CYP3A4 inhibitors (boceprevir, clarithromycin, conivaptan, elvitegravir/ritonavir, fluconazole, indinavir, itraconazole, ketoconazole, lopinavir/RIT, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, tipranavir/ritonavir, troleandomycin, voriconazole)

- Potent CYP3A4 inducers (avasimibe, carbamazepine, enzalutamide, mitotane, nevirapine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, St John's wort)

- Potent UGT1A9 inhibitors/inducers (UGT1A9 inhibitors/inducers include belumosudil, cannabidiol, cannabinol, deferasirox, diflunisal, eltrombopag, fosphenytoin/phenytoin, isavuconazole, medical cannabis, mefenamic acid, methylene blue, morniflumate, niflumic acid, perampanel, regorafenib, rifampicin, sorafenib, umifenovir)

Setanaxib is considered to be a weak inhibitor of CYP2C9, CYP2C19, and OAT3. Sensitive CYP2C9, CYP2C19 and OAT3 substrates, such as warfarin and phenytoin (CYP2C9), S-mephenytoin (CYP2C19), and acyclovir, cefaclor, ceftizoxime, famotidine, furosemide, methotrexate, oseltamivir carboxylate, and penicillin G (OAT3), should be used with caution when co-administered with setanaxib due to risk of increased drug concentrations. Setanaxib has potential induction effects on CYP2B6. Sensitive substrates of CYP2B6, such as tamoxifen, valproic acid, and cyclophosphamide should be used with caution due to risk of decreased drug concentration and reduced efficacy.

In addition, setanaxib inhibited BCRP and MDR1 (P-gp) in vitro. This may result in increased exposures of applicable concomitant medications, and hence caution should be exercised with use of sensitive BCRP and P-gp substrates, such as digoxin.

Appendix III contains a list of common medications that should be avoided or used with caution.

Regarding Covid-19 vaccination, as setanaxib does not have immunosuppressive properties based on nonclinical and clinical safety data, and as the available literature and expert assessment concludes that patients taking pembrolizumab and other immune checkpoint inhibitors should be considered for Covid-19 vaccination, the sponsor considers that study patients may undergo Covid-19 vaccination during the study. All approved Covid-19 vaccines are allowed in setanaxib studies and are to be recorded as a concomitant medication. It is important that the Covid-19 vaccinations are not delayed.

If patients receive a prohibited medication, investigators should consider whether IMP administration should be temporarily interrupted or permanently discontinued. Additionally, if a patient has taken a prohibited medication (eg, short-term antifungal therapy) and the investigator learns about it later, this might not lead to the permanent discontinuation of IMP.

All medication (including vaccines, over-the-counter or prescription medicines, vitamins, and/or herbal supplements) taken from 3 months (90 days) before Screening Visit until the end of the Safety/Efficacy Follow-up Period will be recorded in the appropriate section of the eCRF.

The following details must be recorded in the eCRF:

- Medication name, ideally the generic and/or brand names
- Reason for use
- Start and end date of administration
- The dose, route and frequency of administration

The medical monitor should be contacted if there are any questions regarding prior or concomitant medication or procedures.

For patients who discontinued study treatment but remain followed for tumour assessment until RECIST v1.1-defined disease progression, any further anti-cancer medication will be recorded until progression.

6.9 Overdose

For this study, a single intake of 5 or more setanaxib tablets and/or a total daily dose of 7 or more tablets will be considered an overdose.

The sponsor does not recommend specific treatment for an overdose with setanaxib.

Decisions regarding dose interruptions will be made by the investigator based on the clinical evaluation of the patient.

In the event of an overdose, patients should be closely observed/hospitalised for close observation and appropriate symptomatic/supportive medical care and be followed until resolution/stabilisation of any clinical issues.

Any instance of overdose (suspected or confirmed and irrespective of whether or not it involved setanaxib) must be communicated to the sponsor (or a specified designee) using the overdose report form within 24 hours of becoming aware of its occurrence, using the contact details provided.

Any overdose associated with clinical symptoms will be recorded as an AE or SAE, as appropriate. Note that an overdose without clinical symptoms will not be recorded as an AE or SAE, even if the patient was hospitalised for observation. Details of any signs or symptoms and their management should be recorded, including details of any treatments

administered for the overdose. All overdoses with clinical symptoms meeting the SAE criteria must be reported as described in Section 7.4.

6.10 Compliance

The investigator (or designee) will explain the correct use of the IMP to each patient and will check that each patient is following the instructions properly. Patients will document the IMP doses that they take on a patient IMP dosing card.

Compliance will be assessed by counting the returned tablets and will be documented in the source documents and eCRF. Any deviation from the correct use of the IMP will be recorded in the eCRF.

A record of the number of IMP tablets dispensed to and taken by each patient will be maintained and reconciled with IMP and compliance records. The IMP start and stop dates, including dates for IMP interruptions, will also be recorded in the eCRF.

6.11 Accountability

The IMP must not be used for any purpose other than that defined in this protocol. All supplies of IMP will be accounted for in accordance with Good Clinical Practice (GCP).

The pharmacist or (designee) should maintain accurate records of all IMP supplies received during the study. These records should include the dates and amounts of IMP that were received at the site, dispensed, and destroyed or returned to the sponsor (or designee). The records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the IMP and study patients. If errors or damage in the IMP shipments occur, the investigator should contact the sponsor (or its designee) immediately. Copies of the IMP accountability records will be provided by each investigator for inclusion in the trial master file. The study monitor will periodically check the supplies of IMP held by the investigator or pharmacist to verify accountability of the IMP used.

The investigator (or designee) will dispense the IMP only to the identified and randomised patients in this study, according to the procedures described in this study protocol. Details of IMP dispensed to patients will be recorded in the eCRF. Investigators should maintain records that document adequately that the patients were provided the doses specified by the protocol and reconcile all IMP received from the sponsor (or designee). Patients will be reminded to bring the IMP with them to each study visit. Details of returned IMP will be recorded in the eCRF and accountability records.

After the end of the study, all unused IMP and all medication containers should be destroyed at the study centre or returned to the drug depot for destruction, as instructed in the pharmacy manual. In either instance, complete documentation will be returned to the sponsor (or designee). The IMP resupply will be managed by the IRT.

7 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical study patient administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

AEs that occur, having been absent before the date and time of the first dose of the IMP, or having worsened in severity or seriousness after initiating the IMP until 28 days after the date and time of last dose of IMP, will be classified as TEAEs.

An event solely attributed to tumour progression should not be reported as an AE, unless the signs and symptoms of the event are more severe than expected for the patient`s condition. If the criteria for an AE is not met, disease progression will be recorded as efficacy data. Any event that meets one or more of the seriousness criteria will be reported as an SAE per the procedures outlined in Section 7.4.

7.1.2 Serious Adverse Events

An SAE is any event that meets any of the following criteria:

- Results in death (investigators should identify 1 SAE that is the leading cause of death).
- Is life-threatening.
- Requires inpatient hospitalisation or prolongation of existing hospitalisation.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is an important medical event that may not result in death, be life-threatening, or require hospitalisation. The event will be considered an SAE when, based upon appropriate medical and scientific judgment, the event may jeopardise the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include: intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not

result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

Definition of Terms

Life-threatening: an AE is life-threatening if the patient was at immediate risk of death from the event as it occurred; ie, it does not include a reaction that, if it had occurred in a more severe form, might have caused death. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening even though drug-induced hepatitis can be fatal. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Hospitalisation: AEs requiring hospitalisation should be considered SAEs. Hospitalisation for elective surgery, or for procedures planned prior to the patient providing informed consent, or routine clinical procedures that are not the result of an AE (eg, elective surgery for a pre-existing condition that has not worsened) need not be considered AEs or SAEs. If anything untoward is reported during the procedure, that occurrence must be reported as an AE, either 'serious' or 'nonserious' according to the usual criteria.

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 the physician's office or outpatient setting. When in doubt as to whether hospitalisation occurred or was necessary, the AE should be considered serious.

Disability/incapacity: an AE is incapacitating or disabling if the experience results in a substantial and/or permanent disruption of the patient’s ability to carry out normal life functions.

7.1.3 Suspected Unexpected Serious Adverse Reactions

A suspected unexpected serious adverse reaction (SUSAR) is defined as an untoward and unintended response to a study drug, which is not listed is the applicable product information (eg, IB for an unapproved IMP or the SmPC for an authorised medicinal product), and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalisation or prolongation of an existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect, or is an important medical event that may not result in death, be life-threatening, or require hospitalisation; and is assessed as causally related to the IMP. For SUSARs, the blind will be broken for safety reporting purposes.

7.1.4 Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities without clinical significance should not be recorded as AEs or SAEs. However, laboratory abnormalities as per the investigator's assessment (eg, clinical chemistry, haematology, and urinalysis abnormalities) that require medical or surgical intervention or lead to IMP interruption, modification, or discontinuation must be recorded as an AE or SAE, as applicable. In addition, laboratory or other abnormal assessments (eg, in ECGs, X-rays, or vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in Sections 7.1 and 7.1.2. Any worsening of existing abnormalities that are associated with signs and/or symptoms (except for SCCHN-related pre-existing conditions, including disease progression [see Section 7.3]) should be reported as AEs or SAEs, as appropriate. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (eg, anaemia), not the laboratory result (ie, decreased haemoglobin).

For specific information on handling of clinical laboratory abnormalities, see Section 5.3.2.

7.1.5 Adverse Events of Special Interest

The AESIs for this study are anaemia and hypothyroidism.

AESIs of anaemia will be defined as CTCAE Grade ≥3 anaemia. Please refer to Section 5.3.2.1 for details regarding the detection and management of potential cases of anaemia.

AESIs of hypothyroidism will be defined as TSH levels of ≥10 mIU/L. AESI will be unconfirmed with only one test. Please refer to Section 5.3.2.2 for details regarding the detection and management of hypothyroidism.

The AESI should be reported by the investigative site to the ICON Drug Safety Centre within 24 hours of learning about the event by completing the paper safety report form and sending it via email or fax. The documentation and processing of AESIs is further detailed in the investigator site file.

Investigators will indicate on the relevant Adverse Event eCRF page if the event meets the criteria for an AESI.

7.2 Assessment of Adverse Events

7.2.1 Severity

The terms serious and severe are not synonymous. The general term "severe" is often used to describe the intensity (severity) of a specific event; the event itself, however, may

be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as serious, which is usually associated with events that pose a threat to a patient's life or ability to function (see Section 7.1.2). A severe AE (classified as Grade 3) does not necessarily need to be considered serious. For example, a WBC count of 1000/mm^3 to less than 2000/mm^3 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

Investigators will grade all AEs by severity using CTCAE (Version 5.0).

If an AE is not listed in the CTCAE criteria, a corresponding grading is to be performed by the investigator based on his/her best medical judgment as follows:

- Mild (Grade 1): asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
- Moderate (Grade 2): minimal, local, or noninvasive intervention indicated; limited age-appropriate instrumental activities of daily living (ADL)
- Severe (Grade 3): medically significant but not immediately life-threatening; hospitalisation or prolongation of hospitalisation indicated; disabling; or limiting self-care ADL
- Life-threatening (Grade 4): life-threatening consequences; urgent intervention indicated
- Death (Grade 5): death related to an AE

7.2.2 Causality

Investigators are required to systematically assess the causal relationship between the AEs and SAEs and the exposure to the IMP using the following definitions:

Related:

- The AE has a reasonable possibility of an association with the IMP because:
    - The AE follows a reasonable temporal sequence to IMP administration, and cannot be reasonably explained by the patient's clinical state or other risk factors (eg, disease under study, concurrent diseases, or concomitant medications).
    - The AE follows a reasonable temporal sequence to IMP administration, and it is a known reaction to the drug under study or a related chemical group or is predicted by known pharmacology or nonclinical safety.

Not Related:

- The AE does not follow a reasonable sequence from IMP administration, or it can be reasonably explained by the patient's clinical state or other risk factors (eg, disease under study, concurrent diseases, and concomitant medications).

7.3 Documenting and Reporting Adverse Events

Reporting of AEs will begin when the patient has provided informed consent and will continue up to the 28 days after the last IMP administration.

Occurrence of AEs may be volunteered spontaneously by the patient; discovered as a result of general, nonleading verbal questioning by the study staff; or determined by physical examination or other safety assessments. All AEs will be monitored and recorded in the eCRF throughout the entire study. Note that worsening of SCCHN-related pre-existing conditions, including disease progression, will not be reported as AEs. An event solely attributed to tumour progression should not be reported as an AE, unless the signs and symptoms of the event are more severe than expected for the patient`s condition. If the criteria for an AE is not met, disease progression will be recorded as efficacy data. Worsening of other existing abnormalities that are associated with signs and/or symptoms should be reported as AEs (or SAEs), as appropriate. Any event that meets one or more of the seriousness criteria will be reported as an SAE per the procedures outlined in Section 7.4.

For all AEs, the investigator must pursue and obtain adequate information (a description of the event, severity, time of occurrence, including whether the AE onset was before, during, or after the IMP administration if the AE started on a dosing day, duration, and any action, eg, treatment/follow-up tests). The outcome of the event should be provided along with the investigator's assessment of the relationship to the IMP. The investigator must also assess whether the event meets the criteria for classification as an SAE.

It is the investigator's responsibility to review all documentation (eg, hospital notes, laboratory reports, and diagnostic reports) related to an AE. Wherever possible, the investigator's diagnosis, not the individual signs and symptoms, will be documented as the AE.

Investigators are not obligated to actively seek AEs or unrelated SAEs after the patient's conclusion of study participation. However, if the investigator learns of any SAE, including death, at any time after a patient has been discharged from the study, and he/she considers the event to be reasonably related to the IMP or study participation, the investigator must promptly notify the sponsor. The investigator is expected to follow a potentially related SAE until it has resolved, it has resolved with sequelae, or the patient is lost to follow-up.

7.4 Reporting of Serious Adverse Events

For SAEs with an onset inside the reporting period (ie, onset after provision of informed consent and up to the EoT Visit) and SAEs considered related to IMP that occur after this reporting period (ie, after the EoT until the Safety/Efficacy Follow-up Visits), the investigator must immediately (no later than 24 hours after becoming aware of the event) inform the sponsor (or designee) of the SAE utilising the safety report form (refer to the SAE contact information at the beginning of this protocol).

The investigator is obliged to respond to any request for follow-up information (eg, additional information, event outcome, final evaluation, or other records where needed) or to any question the sponsor (or designee) may have concerning the SAE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the sponsor (or designee) and, as applicable, to allow the sponsor to meet strict regulatory timelines associated with expedited reporting obligations for events of this nature.

7.5 Adverse Event and Serious Adverse Event Follow-up

During the study (and after the patient's participation in the study has ended), all AEs and SAEs should be followed proactively by the investigator until the event resolves or the condition stabilises to a level acceptable to the investigator, until the event is otherwise explained, or until the patient is lost to follow-up. At the time the patient's study participation ends, all ongoing AEs and SAEs should be evaluated for resolution. New or updated information will be recorded in the originally completed eCRF, and the investigator will submit any updated SAE information to the sponsor (or designee) within 24 hours of receipt of the information.

7.6 Safety Reporting Oversight

In accordance with ICH guidelines GCP, the sponsor (or designee) will inform investigators of "findings that could affect adversely the safety of patients, impact the conduct of the study, or alter the Institutional Review Board (IRB)/Independent Ethics Committee (IEC)'s approval/favourable opinion to continue the study."

The sponsor (or designee) has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of an IMP under clinical investigation. The sponsor (or designee) will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators. To support compliance with these requirements, the investigator must provide requested information in a timely manner.

An investigator who receives an investigator safety report describing SAEs or other specific safety information (eg, summary or listing of SAEs) from the sponsor (or

designee) will file it along with the IB and will notify the IRB/IEC, if appropriate, according to local requirements.

8 STATISTICS

8.1 General Procedures

The statistical analysis will be performed by ICON under the direction of Calliditas.

With the exception of the unblinded statistician and programmers supporting the IDMC, all personnel involved with the analysis of the study will remain blinded until database lock and identification of protocol deviations. Analyses will be performed using SAS® (SAS Institute, Cary, NC, US) by the sponsor or its representatives.

A detailed description of all statistical analyses to be performed for this study and any deviations from the analysis detailed in the protocol will be outlined in the statistical analysis plan (SAP). A first version of the SAP will be prepared prior to the inclusion of the first study patient, and the SAP will be approved prior to database lock and unblinding of the study data.

All data will be presented by treatment group. For qualitative variables, the population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented. Quantitative variables will be summarised using descriptive statistics, including n, mean, standard deviation (SD), median, minimum, and maximum values. Graphical presentations of the data will be produced to aid interpretation.

Baseline is defined as the last nonmissing measurement before or on the date of first administration of IMP, unless otherwise stated in the SAP.

A strategy for dealing with data affected by protocol deviations will be agreed by the study sponsor physician, pharmacokineticist and statistician prior to database lock. Data from patients who discontinue from the study, or who have missing values for other reasons, will be included in the analysis in such a way as to minimise any possible bias.

An initial data cut-off will occur approximately 9 weeks after completion of enrolment, when all patients are expected to have had at least 3 cycles of pembrolizumab, at least one post-treatment scan, and the opportunity for a post-treatment tumour biopsy. At this point, the primary endpoint of best percentage change in tumour size and some secondary endpoints will be analysed. An updated analysis may be performed after 38 progression events have been reported. During ongoing review of the overall progression event count, if the predicted timing of the initial and updated analyses are expected to be close in proximity, one analysis may be performed.

Investigators and patients will continue to be blinded to randomised study treatment after initial unblinding of data for the primary analysis until the final database lock.

Safety and tolerability data will be regularly reviewed by an unblinded IDMC, with the first assessment after approximately 12 patients (6 per treatment group) have had the opportunity to complete at least 1 cycle of pembrolizumab +/- setanaxib. Safety data analyses will be descriptive only and will be described in the SAP and IDMC charter.

After approximately 12 patients (6 per treatment group) have completed their Baseline and post-treatment biopsy, initial gene expression and biomarker data in tumour tissue may be reviewed by the sponsor, who will remain masked to randomised treatment assignment. A second review may be performed, if required. Analyses will be descriptive only. Further details will be provided in the SAP.

8.2 Analysis Populations

The Full Analysis Set (FAS) will include all randomised patients who receive at least 1 full dose of IMP or placebo. Patients will be analysed according to randomised treatment regardless of the treatment they actually received. This analysis set will be the primary set used for all efficacy analyses, along with the summary of disposition, demographics, and Baseline characteristics.

The Safety Analysis Set will include all randomised patients who receive at least 1 tablet of IMP or placebo. Patients will be analysed according to treatment they actually received. This analysis set will be used for summaries of safety data.

The Per-Protocol Analysis Set will include all patients in the FAS who complied sufficiently with the protocol with respect to exposure to IMP, availability of tumour assessments, and absence of important protocol deviations likely to impact efficacy outcome. Important protocol deviations will be defined in the SAP and this analysis set will be finalised in a blinded manner prior to database lock.

The PK Analysis Set will include all patients who receive at least 1 dose of setanaxib and have at least 1 measured concentration at a scheduled PK time point post-dose.

The Biomarker Analysis Set will include all patients who received at least one tablet of IMP or placebo and have evaluable biomarker data.

8.3 Sample Size

An overall sample size of approximately 50 patients (25 per treatment group) is considered sufficient to assess the primary endpoint of the best percentage change in tumour size following treatment with setanaxib when administered with pembrolizumab, versus placebo when administered with pembrolizumab, in patients with recurrent or metastatic SCCHN. With 25 patients per treatment group, using a 2-sided t-test, there will be 85% power to detect a 20% mean difference between the treatment groups in best percentage change in tumour size, with an estimated SD of 30% and a 2-sided alpha of 20%. To mitigate risks from a higher than expected number of patients discontinuing the

study early or declining to have imaging or biopsies at Week 9, an additional up to 20 patients (making a maximum of 70 patients) may be randomised.

The key secondary endpoints of numbers of CAFs, $CD8^+$ TILs, and regulatory T-cells in tumour tissue, and gene expression analysis in tumour tissue will be used to determine proof-of-concept. With 25 patients per treatment group, there will be 90% power to detect a limit fold change (LFC) of more than 1.5 in gene sequencing endpoints measured in tumour tissue, assuming at least 20 patients have an evaluable Baseline and post-Baseline tissue sample.

For the key secondary endpoint of PFS, if the true hazard ratio for PFS is 0.5, at least 38 progression events as defined by RECIST v1.1 will be required to have >80% power to demonstrate a statistically significant difference in PFS with 2-sided $p<0.2$.

8.4 Statistical Methods

8.4.1 Statistical Hypothesis

The statistical hypothesis to be tested for the primary analysis with change in tumour size as the primary endpoint is as follows:

- H0: the average change in the tumour size between the treatment groups are the same
- HA: the average change in the tumour size between the treatment groups are different

The simple null hypotheses (H0) for the primary analysis using the t-test assumes that the observation for the difference in the best percentage change in tumour size for patients between the 2 treatment groups will follow a normal distribution with mean zero and a constant unknown variance. The composite alternative hypothesis (HA) assumes that the observation for the difference in the best percentage change in tumour size for patients between the 2 treatment groups will follow a normal distribution with an unknown mean and the same constant unknown variance which will be estimated from the data. This unknown mean under the distribution of the observations under the composite alternative hypothesis is the non-centrality parameter which determines the power of the statistical test on which the primary analysis is based. For the sample size calculation this non-centrality parameter was assumed to be 20%.

8.4.2 Primary Endpoint

The primary endpoint is the best percentage change in tumour size, defined as the percentage change from Baseline in the sum of diameters of target lesions, as assessed by RECIST v1.1.

For the primary endpoint of best percentage change in tumour size, the absolute values at Baseline and Week 9 and best percentage change in target lesion tumour size will be summarised using descriptive statistics and presented by treatment group in summary tables and waterfall plots. The primary endpoint will be used to assess the effect of the setanaxib + pembrolizumab versus placebo + pembrolizumab. The primary efficacy analysis will be based on the FAS and will evaluate the effect of setanaxib on best percentage change in tumour size from an analysis of covariance (ANCOVA) model including a term for the best percentage change in tumour size, a covariate for Baseline tumour size and a term for treatment. The number of patients, unadjusted mean, and adjusted least-square means (lsmeans) for each treatment group will be presented, together with the difference in adjusted lsmeans, 80% confidence interval, and corresponding p-value from the fitted ANCOVA model.

The primary estimand considered here is to compare the best percentage change in tumour size per RECIST v1.1 in recurrent or metastatic SCCHN adult patients treated with setanaxib and pembrolizumab versus patients treated with placebo and pembrolizumab.

The attributes of the primary estimand considered are listed as follows:

- Population: patients aged ≥18 years with recurrent or metastatic SCCHN who are eligible for treatment with pembrolizumab monotherapy

- Treatment: setanaxib + pembrolizumab versus placebo + pembrolizumab

- Variable: best percentage change in tumour size defined as the percentage change from Baseline in the sum of diameters of target lesions, as assessed by RECIST v1.1

- Population level summary: to evaluate the percentage mean difference in the tumour size between the competing treatment groups. The main results to ascertain the difference will be the p-value of treatment comparison obtained from the coefficient from the fitted ANCOVA model and the value of the coefficient as an estimate of the treatment effect of the percentage change between the competing treatment groups with its 80% confidence intervals

- Intercurrent events: premature study discontinuation, study drug interruption/premature discontinuation, use of certain alternative or additional therapy including a new anti-cancer therapy

The PFS follow-up will continue to objective progression regardless of the stated intercurrent events. Patients who withdraw completely from the study will be right-censored. For the patients who are right-censored, the time until which they were in the study from the randomisation would be recorded as the right-censored time. The treatment policy strategy used addresses the intercurrent events listed above. The occurrence of the intercurrent event in this case is considered irrelevant in defining the

treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent events occur. For example, when specifying how to address use of additional anti-cancer therapy prior to disease progression as an intercurrent event, the values of the variable of interest will be used whether or not the patient takes the additional anti-cancer therapy. In the case of premature study discontinuation, and whether or not a patient experiences changes in other treatments (eg, background or concomitant treatments), the intercurrent event will be considered to be part of the treatments being compared. In that case, this reflects the comparison under the usual intent-to-treat principle as the effect of a treatment policy.

8.4.3 Secondary Endpoints

The secondary endpoints are listed in Section 2.2.

An initial data cut-off will occur approximately 9 weeks after completion of enrolment, when all patients are expected to have had at least 3 cycles of pembrolizumab, at least one post-treatment scan, and the opportunity for a post-treatment tumour biopsy. At this point, the secondary endpoints (with the exception of PFS and OS) will be analysed. An updated analysis may be performed after 38 progression events have been reported. At the updated analysis, ORR, PFS, DoR, DCR, and OS will be summarised and safety data summaries will be updated as appropriate.

The key secondary endpoint of PFS will be summarised by Kaplan-Meier plots presented by treatment groups. Median PFS and the proportion of patients who are progression-free at 3, 6, and 12 months will be summarised along with 80% confidence intervals presented for each treatment group. Patients who have not progressed by the time of the data cut-off for the updated analysis will be censored. The comparison between the treatment groups of PFS will be performed by fitting a Cox proportional hazard model (Cox 1975) with treatment group as the only covariate. The hazard ratio for PFS, based on the profile partial likelihood from the fitted using Cox proportional hazards model, will be calculated as a measure of the treatment effect along with the respective 95% Wald confidence interval and the asymptotic p-value from the Wald test for the difference in the log hazards in the fitted model.

The secondary endpoint of OS will not be formally compared between the treatment groups but will be summarised in a Kaplan-Meier plot together with descriptive statistics, as described for PFS.

The secondary endpoints of ORR, DoR, and DCR will be summarised using descriptive statistics for each treatment group and associated 90% Agresti-Coull confidence interval.

For the key secondary endpoints of numbers of CAFs, $CD8^+$ TILs, and regulatory T-cells, and the secondary endpoint of PD-L1 expression analysis in tumour tissue, it is hypothesised based on the mode of action of setanaxib that there will be a reduction in CAFs level and an increase in the number of $CD8^+$ TILs. Data will be summarised

descriptively and will be graphically presented by boxplots displayed for each treatment group and individual patient profiles displaying pre- and post-doses counts. Changes within treatment groups (ie, across paired tissue samples) and between treatment groups will be summarised. An ANCOVA model will be used to assess for significant differences after adjustment for Baseline differences. The treatment effect from the fitted ANCOVA model will estimate the treatment difference based on mean score. A logarithmic transformation will be applied prior to analysis, if appropriate.

For the secondary endpoint of changes in patterns of gene expression and differential gene expression in tumour tissue, data will be displayed graphically and will be assessed by principal components analysis to identify distinction between clusters of genes. Detailed analysis methodology will be described in the SAP.

Changes in tumour biomarkers will be correlated with change in tumour size and other efficacy parameters.

8.4.4 Sensitivity Analysis

The proportionality of hazard will be examined in the sensitivity analysis for the fitted Cox proportional hazard model for PFS using the cumulative sums of martingale residuals for each treatment groups. The ASSESS statement with ODS Graphics in PROC PHREG step in SAS will perform this using both graphical and numerical methods of Lin, Wei, and Ying 1993 (Lin et al 1993). A violation of the proportional hazard assumption will indicate that the results obtained from the fitted Cox proportional hazard model will be invalid. In such circumstances, a modified max combo (Roychoudhury et al 2021) using the Fleming and Harrington 1981 weights (Fleming & Harrigton 1981) such as FH(0,0), FH(0.5,0.5), FH(0,0.5), FH(0.5,0) will be implemented for estimating the performance of the competing treatment groups for PFS. The p-value obtained from each of the modified max combo tests will be reported.

For each of the fitted ANCOVA models in the primary efficacy analysis and the secondary efficacy analyses, a plot of the residuals against the fitted values from the ANCOVA model will be produced to check for randomness in the plot. This is to check for the assumption of constant variance of the fitted model. Any systematic effect in this residual plot will indicate that a suitable transformation should be applied on the response of the model as appropriate to stabilise the variability of the error. A normal probability plot will also be plotted of the residuals of each of the fitted ANCOVA model to check if this fairly fits a straight line. Significant deviation from a straight line in this residual plot will indicate the violation of the ANCOVA model assumptions of the errors being normally distributed. In such cases, logarithmic transformations on the response will be applied, as appropriate, to normalise the data. The ANCOVA in such scenario will be fitted again on the log-normal response with log baseline values as the covariate, and the validity of the assumption of the fitted transformed model will be checked similarly. The response here for the fitted ANCOVA is the post-dose baseline ratio. If the assumptions

are not satisfied for the fitted transformed model, appropriate non-parametric method will be applied. Further details will be provided in the SAP.

The analysis of the primary endpoint will be repeated on the Per-Protocol Analysis Set to understand the effect of major protocol deviations on the treatment effect.

8.4.5 Supportive Analysis

Another method of handling the PFS data will be to consider death due to any other cause as a competing event. In such cases, patients who have not faced disease progression or not died until the end of the study or have dropped out prior to the event will be right-censored. A competing risk approach will therefore be implemented by fitting the Fine and Gray (1999) model (Fine & Gray 1999). A treatment effect in such cases will be estimated using the cumulative incidence function for a given cause. This is defined as the probability of a patient facing an event due to a given cause before a pre-specified time in the clinical study. The Fine and Gray (1999) model will be fitted considering time to disease progression as the main cause of interest and death due to any cause as the competing cause with treatment as the only explanatory variable. Similar to the Cox proportional hazard model, the placebo + pembrolizumab treatment group will be considered as the comparator group in the fitted model with the regression coefficient in the Fine and Gray (1999) model comparing the difference in the log-sub-distribution hazards between the competing treatment groups. The estimated ratio of the sub-distribution hazard for disease progression will be an estimator of the treatment effect and will be obtained by exponentiating the regression coefficient from the fitted Fine and Gray (1999) model. This estimate will be reported along with the 95% profile partial likelihood based Wald confidence interval for the estimated ratio of the sub-distribution hazard for disease progression.

A plot of the Cumulative Incidence Functions for facing disease obtained from the fitted Fine and Gray (1999) model at various time during the study will also be depicted, and the estimated quartiles along with its 95% confidence intervals will be presented to compare the treatment effects in regards to the cumulative incidence for disease progression after accounting for deaths as a competing event in the study.

8.4.6 Analysis of Safety

The safety endpoints are listed in Section 2.2.

The Safety Analysis Set will be used for the analysis of safety data (AEs, including AESIs, clinical laboratory tests, vital signs, 12-lead ECGs, and physical examination). The safety data will be presented descriptively and not formally analysed.

AEs that occur, having been absent before the date and time of the first dose of the IMP, or have worsened in severity or seriousness after initiating the IMP until 28 days after the date and time of last dose of IMP will be classified as TEAEs. The number of TEAEs and

number and percentage of patients experiencing TEAEs will be summarised by treatment group, severity, and relation to IMP. TEAEs will be summarised by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term. All AEs will be listed by patient and treatment group. Any AE occurring before treatment or more than 28 days after discontinuation of treatment will be flagged in the data listings but will not be included in the summary tables of AEs. Any AE occurring after a patient has received another anti-cancer therapy (after discontinuation of study treatment) will also be flagged in the listings.

SAEs will be listed by patients and summarised by treatment group, MedDRA SOC, and preferred term. Summaries will also be presented by severity and relationship to IMP.

Laboratory data (haematology, serum chemistry, thyroid function tests, and urinalysis) will be converted to Système International units for reporting and processing purposes. Absolute values and changes from Baseline will be presented descriptively. Laboratory data outside study-specific reference ranges will be listed.

Abnormal laboratory values will be listed by patient and summaries of the incidence and frequency by treatment group, scheduled visit, severity, and relationship to IMP will be presented. Shift tables of CTCAE grades from baseline to worst CTC grade post-baseline will be presented. Summary of clinically significant abnormalities and modified World Health Organisation ratings will also be presented. WBC and reticulocyte counts will be expressed in absolute values. Differential count will be expressed as both absolute count and percentage of WBCs.

Vital signs and ECG parameters will be presented descriptively. Vital signs including pulse rate, SBP, and DBP, and 12-lead ECG data will be summarised by treatment group and listed by patient.

A summary of abnormal physical examination findings by treatment group and scheduled visit will be presented. Demographic and Baseline Characteristics

Demographic characteristics (including age, sex, ethnicity, and race) and Baseline characteristics (including height, weight, and disease characteristics) will be presented descriptively.

Discrepancies between randomisation stratification information (obtained from IRT) and strata formed based on Screening factor collected on eCRFs (HPV status) will be summarised and listed.

8.4.7 Pharmacokinetic Endpoints

The PK Analysis Set will be used for PK analyses.

Plasma concentrations of setanaxib and GKT138184, along with blood sampling dates and actual blood sampling time relative to dosing time, will be listed by dose group, patient, and nominal sampling time. Pre-dose and post-dose plasma concentrations of setanaxib and GKT138184 will be summarised as appropriate. AUC(0-24)-ss, Cmin-ss and Cmax-ss will be estimated for each individual patient using non-linear mixed effect methodology and prior PK knowledge of the compound, and summarised as appropriate. More details regarding the PK analysis and exploratory PK/PD analyses will be provided in a separate pharmacokinetic analysis plan.

An interim pharmacokinetic analysis will be performed at the initial data cut-off approximately 9 weeks after completion of enrolment, when all patients are expected to have had at least 3 cycles of pembrolizumab, at least one post-treatment scan, and the opportunity for a post-treatment tumour biopsy. This analysis will result in an interim report.

The final pharmacokinetic analysis will be performed at the end of the study after database lock. If the predicted timing of the initial and final analyses are expected to be close in proximity, only one analysis may be performed. Only the final analysis will be reported formally and summarised for the CSR.

8.4.8 Handling of Missing Values

Rules for imputation of missing data will be detailed in the SAP.

9 ETHICS AND RESPONSIBILITIES

9.1 Good Clinical Practice

This study will be conducted in accordance with the Note for Guidance on ICH guidelines on GCP Harmonised Tripartite Guideline E6 (R1)/Integrated Addendum E6 (R2); United States Food and Drug Administration (US FDA) Code of Federal Regulations (Title 21 Parts 50, 56, 312), requirements for the conduct of clinical studies as provided in the European Directive 2001/20/EC; the general guidelines indicated in the Declaration of Helsinki; and all applicable regulatory requirements.

9.2 Institutional Review Board/Independent Ethics Committee

Before initiating a study, the investigator/institution must have written and dated approval/favourable opinion from the IRBs/IECs for the study protocol/amendment(s), written ICF, any ICF updates, patient recruitment procedures (eg, advertisements), and any written information to be provided to patients and a statement from the IRBs/IECs that these comply with GCP requirements (if applicable). A current copy of the IB should be included as part of the written application to the IRB/IEC.

The IRB/IEC approval(s) must identify the protocol version as well as the documents reviewed. Any amendments to the protocol will require IRB/IEC approval before the implementation of the changes made to the study, except for changes necessary to eliminate an immediate hazard to the study patients.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

- Notifying the IRB/IEC of SAEs or other significant safety findings, including adverse drug reactions that are both serious and unexpected, as required by IRB/IEC procedures

- Providing oversight of the conduct of the study at the site and adherence to the requirements of all applicable regulations

- Promptly reporting deviations from, or changes to, the protocol to eliminate immediate hazards to the study patients

9.3 Informed Consent

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to GCP and to the ethical

principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the study, the investigator should have the IRB/IEC's written approval/favourable opinion of the written ICF and any other written information to be provided to study patients.

- The investigator or his/her representative will explain the purpose and nature of the study as well as possible AEs to the patient or his/her legally acceptable representative and answer all questions regarding the study.

- Patients must be informed that their participation is voluntary, and consent can be withdrawn at any point.

- Patients or their legally acceptable representative will be required to sign a statement of informed consent that meets the requirements of local regulations, ICH guidelines, and the IRB/IEC or study site.

- Prior to a patient's participation in the study, the written ICF should be signed and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion.

- The medical record must include a study identifier and a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained.

- The original copy of the signed ICF will be retained at the study site.

- A copy of the ICF and any other written information must be provided to the patient or the patient's legally acceptable representative.

- If the ICF is revised, the revised ICF must have received the IRB/IEC's approval/favourable opinion in advance of its use. Patients must be informed of the changes to the ICF and must re-consent to the most current version during their participation in the study. The patient or the patient's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. The communication of this information should be documented.

A patient who is rescreened is not required to sign another ICF if the rescreening occurs within 35 days of the previous ICF signature date.

The ICF will contain a separate section that addresses the collection of a third optional tumour biopsy for an additional assessment of tumour biomarkers and gene expression analysis. The investigator (or authorised designee) will explain to each patient the objectives of this research. Patients will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason.

If a patient is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. The witness should sign and personally date the ICF after:

- The written ICF and any other written information to be provided to patients is read and explained to the patient or the patient's legally acceptable representative
- The patient or the patient's legally acceptable representative has orally consented to the patient's participation in the study
- The patient or the patient's legally acceptable representative has signed and personally dated the ICF, if they are capable of doing so

By signing the ICF, the witness attests that the information in the ICF and any other written information was accurately explained to, and apparently understood by, the patient or the patient's legally acceptable representative, and that informed consent was freely given by the patient or the patient's legally acceptable representative.

9.4 Independent Data Monitoring Committee

The IDMC will oversee the safety of participating patients.

Treatment safety and tolerability will be regularly reviewed, with the first assessment after approximately 12 patients (6 per treatment group) have had the opportunity to complete at least 1 cycle of pembrolizumab +/- setanaxib, followed by periodic assessments at a frequency defined in the IDMC Charter.

The IDMC may recommend change(s) to the setanaxib dose regimen or study conduct based on the safety data reviews, as defined in the IDMC Charter. The IDMC will include an unblinded statistician and 2 physicians (one of whom shall have expertise in head and neck cancer), and will be supported by an IDMC Specialist and programmers, as well as any other functions detailed in the IDMC Charter.

The role and responsibilities of the IDMC will be outlined in the IDMC Charter.

9.5 Financing and Insurance

9.5.1 Contractual and Financial Details

The investigator (and/or, as appropriate, the hospital administrative representative) and the CRO and/or sponsor (or designee) will sign a clinical trial agreement prior to the start of the study, outlining overall sponsor and investigator responsibilities in relation to the study. The contract should describe whether costs for pharmacy, laboratory, and other protocol-required services are being paid directly or indirectly.

9.5.2 Insurance, Indemnity, and Compensation

The sponsor will maintain an appropriate clinical study insurance policy.

9.5.3 Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

10 RECORDS MANAGEMENT

All clinical study information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification. This principle applies to all records referenced in this protocol, irrespective of the type of media used.

An eCRF will be used to store and transmit patient information. Information from the medical records (progress notes) and other source documents is to be promptly entered into the appropriate section of the eCRF. The eCRF must be reviewed and electronically signed and dated by the investigator on an ongoing basis. The investigator is responsible for verifying that the data entries are accurate and correct by signing the eCRF.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorised site personnel (eg, investigators and the study coordinator). The eCRF must be completed as soon as possible after any patient evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track these changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors.

During each study visit, a physician participating in the study will maintain progress notes in the patient's medical records to document all significant observations. At a minimum, these notes are to contain:

- The date of the visit and the corresponding day or visit in the study schedule
- General condition and status remarks by the patient, including any significant medical findings. The severity, frequency, duration, and resolution of any reported AE, and the investigator's assessment as to whether or not the reported AE is related to IMP
- Changes (including dosages) in concomitant medications/therapies (including medical foods) or procedures
- A general reference to the procedures completed
- Protocol deviations identified that could potentially affect safety and/or study results
- The signature or initials of all physicians making an entry in the medical record (progress notes)

In addition, any contact with the patient via telephone or other means that provides significant clinical information is to also be documented in the medical record (progress notes), as described above.

Changes to information in the medical record (progress notes) and other source documents are to be initialled and dated on the day the change is made by the investigator (or designee). If the reason for the change is not apparent, a brief explanation for the change is to be written adjacent to the change. Changes to the eCRF will be electronically tracked.

A data management plan will be written and finalised prior to performing any data validation.

10.1 Source Documentation

Source documents contain the results of original observations and activities of a clinical investigation. They are the original records in which raw data are first recorded. Source documents include, but are not limited to, medical records (progress notes), ECG and computer printouts, screening logs, completed scales, QoL questionnaires, and recorded data from automated instruments.

The investigator/site personnel should maintain adequate and accurate source documents and study records that include all pertinent observations on each of the site's study patients. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (eg, via an audit trail).

All source documents from this study are to be maintained by the investigator and made available for inspection by authorised persons. The investigator will provide direct access to source documents/data for study-related monitoring, audits, IRB/IEC review, and regulatory inspections. The sponsor should verify that each patient has consented, in writing, to direct access to his/her original medical records for study-related monitoring, audit, IRB/IEC review, and regulatory inspection.

10.2 Electronic Case Report Form Completion and Data Management

An eCRF will be used to store and transmit patient information. The file structure and format for the eCRF will be provided by the sponsor or its representative and should be handled in accordance with the instructions provided.

The eCRF must be reviewed and electronically signed and dated by the investigator.

Access to the eCRF will be strictly password protected and limited to personnel directly participating in the study. Data should be entered into the eCRF completely by authorised site personnel (eg, investigators and the study coordinator). The eCRF must be completed as soon as possible after any patient evaluation or communication. If data are to be changed due to erroneous input or other reason, an electronic audit trail will track the changes. The eCRFs and computers that store them must be accessible to study monitors and other regulatory auditors. Changes to the eCRF will be electronically tracked.

Data will be entered/loaded into a validated electronic database using a clinical data management system. Computerised data cleaning checks will be used in addition to manual review to check for discrepancies and to ensure consistency of the data.

10.3 Study Files and Record Retention

All data derived from the study will remain the property of the sponsor. The sponsor assumes accountability for actions delegated to other individuals, eg, the CRO.

Records must be retained in accordance with the current ICH guidelines on GCP. All essential study documents, including records of patients, source documents, eCRFs, and the IMP inventory, must be kept on file.

Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of setanaxib. However, essential documents may be retained for a longer period if required by the applicable regulatory requirements or by agreement with the sponsor. The sponsor is responsible for informing the investigator when these documents need no longer be retained.

The investigator is not to dispose of any records relevant to this study without written permission from the sponsor and is to provide the sponsor the opportunity to collect such records. The investigator shall take responsibility for maintaining adequate and accurate hard copy source documents of all observations and data generated during this study. Such documentation is subject to inspection by the sponsor, its representatives, and regulatory authorities.

If an investigator moves, withdraws from a study, or retires, the responsibility for maintaining the records may be transferred to another person who will accept responsibility. Notice of transfer must be made to and agreed by the sponsor.

11 AUDITING AND MONITORING

Sponsor-assigned monitors will conduct regular site visits to the investigational facilities for the purpose of monitoring various aspects of the study, such as verifying that the ICFs were signed and dated before any study-specific procedure was performed, assessing patient enrolment, compliance with protocol procedures, completeness and accuracy of data entered into the eCRFs, verification of eCRF data against original source documents, and occurrence of AEs. The investigator must agree to sponsor-authorised personnel having direct access to the clinical (or associated) files and clinical study supplies (dispensing and storage areas) to ensure compliance with applicable regulations, and the investigator will assist with the sponsor's monitoring activities.

Quality control will occur at each stage of data handling to ensure that all data are reliable and have been processed correctly. The sponsor should ensure oversight of any study-related duties and functions carried out on its behalf, including study-related duties and functions that are subcontracted to another party by the sponsor's contracted CRO(s).

The eCRFs should be completed in a timely manner and on an ongoing basis to allow regular review by the study monitor.

Details describing the strategy, responsibilities, and requirements of study monitoring are provided in the study Monitoring Plan.

The purpose of an audit is to assess whether ethics, regulatory, and quality requirements are being fulfilled. The sponsor or its representative may conduct audits at the investigative sites including, but not limited to, drug supply, presence of required documents, the informed consent process, and comparison of eCRFs with source documents. Government regulatory authorities may also inspect the investigator during or after the study. The investigator (or designee) should contact the sponsor/CRO immediately if this occurs. All medical records (progress notes) must be available for audit. The investigator must agree to participate with audits conducted at a convenient time in a reasonable manner.

11.1 Risk and Quality Tolerance Limits

Perceived risks and quality tolerance limits (QTLs) will be identified and documented in the Protocol Risk Evaluation Plan before the start of the study.

The sponsor will review risk control measures periodically to ascertain whether the implemented quality management activities remain effective and relevant. The quality management approach and any important deviations from the predefined QTLs (and remedial actions adopted) will be described in the clinical study report (CSR).

11.2 Protocol Adherence and Deviations

The investigator and site personnel should conduct the study in compliance with the protocol and should use continuous vigilance to identify and report protocol deviations.

A protocol deviation is any change, divergence, or departure from the study design or procedures defined in the protocol that may be on the part of the investigator, site personnel, or the patient.

Important protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a patient's rights, safety, or well-being. For example, important protocol deviations may include enrolling patients in violation of key eligibility criteria designed to ensure a specific patient population or failing to collect data necessary to interpret primary endpoints, as this may compromise the scientific value of the study.

The investigator should not implement any deviation from the protocol without agreement from the sponsor and prior review and approval from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard to a study patient, or when the change involves only logistical or administrative aspects of the study, such as a change in a monitor or telephone number.

In the event of an important protocol deviation, the investigator will discuss the deviation with the sponsor’s medical monitor and will come to an agreement as to whether the patient should be withdrawn from the study due to the important protocol deviation.

12 AMENDMENTS

Protocol modifications, except those intended to reduce immediate risk to study patients, may be made only by the sponsor. A protocol change intended to eliminate an apparent immediate hazard to patients should be implemented immediately.

Any permanent change to the protocol must be handled as a protocol amendment. The written amendment must be submitted to the IRB/IEC, and the investigator must await approval before implementing the changes. The sponsor will submit protocol amendments to the appropriate regulatory authorities for approval.

The current version of the ICF will require similar modification if the IRB/IEC, investigator, and/or sponsor, judge the amendment to the protocol to substantially change the study design and/or increase the potential risk to the patient and/or impact the patient's involvement as a study patient. In such cases, the ICF will be renewed for enrolled patients before their continued participation in the study.

13 STUDY REPORT AND PUBLICATIONS

This study will be registered on ClinicalTrials.gov in accordance with applicable laws or publication policy and may also be registered on other publicly accessible websites, such as EudraCT (EU Drug Regulating Authorities Clinical Trials), as necessary.

The sponsor is responsible for preparing and providing the appropriate regulatory authorities with the CSR according to the applicable regulatory requirements. The sponsor should ensure that the CSR meets the standards of the ICH Guideline for Structure and Content of Clinical Study Reports (ICH E3).

14 STUDY START AND TERMINATION

The study start date is the date on which the first patient provides informed consent.

The end of the study is defined as the last patient's last assessment.

Both the sponsor and the investigator reserve the right to terminate the study or the participation in the study at an investigator's site at any time. In terminating the study, the sponsor and the investigator will assure that adequate consideration is given to the protection of the patients' interests.

If the study is prematurely terminated or suspended for any reason, the sponsor/investigator/site personnel should promptly inform the study patients and should assure appropriate therapy and follow-up for the patients. Where required by the applicable regulatory requirements, the IRB/IEC should be informed promptly and be provided with a detailed written explanation of the termination or suspension.

If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the site personnel. The investigator/site personnel should promptly inform the sponsor and the IRB/IEC. The investigator/site personnel should also provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

15 CONFIDENTIALITY

All information generated in this study is considered highly confidential and must not be disclosed to any person or entity not directly involved with the study unless prior written consent is gained from the sponsor. However, authorised regulatory officials, IRB/IEC personnel, the sponsor and its authorised representatives are allowed full access to the records.

All study patients must be informed that their personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient, who will be required to give consent for their data to be used as described in the ICF. The patients must be informed that their medical records may be examined by auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities. In case of any data security breach, this will be reported to authorities in line with local requirements.

Identification of patients and eCRFs shall be by unique patient identification numbers (such as screening or randomisation number) only. All personal identifiers according to applicable regulations (eg, name, phone number) must be redacted permanently by the site personnel and replaced with the patient's unique identification number in all records and data before transfer to the sponsor (or designee).

All personal details will be treated as confidential by the investigator and staff at ICON.

16 REFERENCES

Argiris A, Karamouzis MV, Raben D, et al. Head and neck cancer. Lancet. 2008 May 17;371(9625):1695-709.

Arwert EN, Milford EL, Rullan A, et al. STING and IRF3 in stromal fibroblasts enable sensing of genomic stress in cancer cells to undermine oncolytic viral therapy. Nat Cell Biol. 2020 Jul;22(7):758-66.

Bauml J, Seiwert TY, Pfister DG, et al. Pembrolizumab for platinum- and cetuximab-refractory head and neck cancer: Results from a single-arm, Phase II study. J Clin Oncol. 2017 May 10;35(14):1542-9.

Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394-424.

Brown JA, Dorfman DM, Ma FR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. J Immunol. 2003 Feb 1;170(3):1257-66.

Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. Lancet. 2019 Nov 23;394(10212):1915-28.

Calvo F, Ege N, Grande-Garcia A, et al. Mechanotransduction and YAP-dependent matrix remodelling is required for the generation and maintenance of cancer-associated fibroblasts. Nat Cell Biol. 2013 Jun;15(6):637-46.

Catenacci DVT, Junttila MR, Karrison T, et al. Randomized Phase Ib/II study of gemcitabine plus placebo or vismodegib, a hedgehog pathway inhibitor, in patients with metastatic pancreatic cancer. J Clin Oncol. 2015 Dec 20;33(36):4284-92.

Chakravarthy A, Henderson S, Thirdborough SM, et al. Human papillomavirus drives tumor development throughout the head and neck: improved prognosis is associated with an immune response largely restricted to the oropharynx. J Clin Oncol. 2016 Dec;34(34):4132-41.

Chakravarthy A, Furness A, Joshi K, et al. Pan-cancer deconvolution of tumour composition using DNA methylation. Nat Commun. 2018 Aug 13;9(1):3220.

Chen X, Song E. Turning foes to friends: targeting cancer-associated fibroblasts. Nat Rev Drug Discov. 2019 Feb;18(2):99-115.

Chow LQM. Head and neck cancer. N Engl J Med. 2020 Jan; 382(1): 60-72.

Claret L, Girard P, Hoff PM, et al. Model-based prediction of phase III overall survival in colorectal cancer on the basis of phase II tumor dynamics. J Clin Oncol. 2009 Sep 1;27(25):4103-8.

Cohen EEW, Soulières D, Le Tourneau C, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. Lancet. 2019 Jan 12;393(10167):156-67.

Colevas AD. Chemotherapy options for patients with metastatic or recurrent squamous cell carcinoma of the head and neck. J Clin Oncol. 2006 Jun 10;24(17):2644-52.

Cox DR. Partial likelihood. Biometrika. 1975;62(2):269-76.

Disis ML. Immune regulation of cancer. J Clin Oncol. 2010 Oct 10;28(29):4531-8.

Dominguez CX, Müller S, Keerthivasan S, et al. Single-cell RNA sequencing reveals stromal evolution into LRRC15^{+} myofibroblasts as a determinant of patient response to cancer immunotherapy. Cancer Discov. 2020 Feb;10(2):232-53.

Dong H, Strome SE, Salomao DR, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med. 2002 Aug;8(8):793-800.

Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer. 2015 Mar 1;136(5):E359-86.

Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. N Engl J Med. 2016 Nov 10;375(19):1856-67.

Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. J Am Stat Assoc. 1999;94(446):496-509.

Fleming TR, Harrington DP. A class of hypothesis tests for one and two sample censored survival data. Commun Stat Theory Methods. 1981;10(8):763-94.

Ford K, Hanley CJ, Mellone M, et al. NOX4 inhibition potentiates immunotherapy by overcoming cancer-associated fibroblast-mediated CD8 T-cell exclusion from tumors. Cancer Res. 2020 May 1;80(9):1846-60.

Francisco LM, Sage PT, Sharpe AH. The PD-1 pathway in tolerance and autoimmunity. Immunol Rev. 2010 Jul;236:219-42.

Gaggioli C, Hooper S, Hidalgo-Carcedo C, et al. Fibroblast-led collective invasion of carcinoma cells with differing roles for RhoGTPases in leading and following cells. Nat Cell Biol. 2007 Dec;9(12):1392-400.

Gibson MK, Li Y, Murphy B, et al. Randomized phase III evaluation of cisplatin plus fluorouracil versus cisplatin plus paclitaxel in advanced head and neck cancer (E1395): an intergroup trial of the Eastern Cooperative Oncology Group. J Clin Oncol. 2005 May 20;23(15):3562-7.

Grauel A, Nguyen B, Ruddy D, et al. TGFβ-blockade uncovers stromal plasticity in tumors by revealing the existence of a subset of interferon-licensed fibroblasts. Nat Commun. 2020 Dec 9;11(1):6315.

Hanley CJ, Mellone M, Ford K, et al. Targeting the myofibroblastic cancer-associated fibroblast phenotype through inhibition of NOX4. J Natl Cancer Inst. 2018 Jan 1;110(1):109-20.

Hofheinz RD, al-Batran SE, Hartmann F, et al. Stromal antigen targeting by a humanised monoclonal antibody: an early phase II trial of sibrotuzumab in patients with metastatic colorectal cancer. Onkologie. 2003 Feb;26(1):44-8.

Kieffer Y, Hocine HR, Gentric G, et al. Single-cell analysis reveals fibroblast clusters linked to immunotherapy resistance in cancer. Cancer Discov. 2020 Sep;10(9):1330-51.

Kraman M, Bambrough PJ, Arnold JN, et al. Suppression of antitumor immunity by stromal cells expressing fibroblast activation protein-alpha. Science. 2010 Nov 5;330(6005):827-30.

Krause KH, Bedard K. NOX enzymes in immuno-inflammatory pathologies. Semin Immunopathol. 2008 Jul;30(3):193-4.

Liang S, Kisseleva T, Brenner DA. The role of NADPH oxidases (NOXs) in liver fibrosis and the activation of myofibroblasts. Front Physiol. 2016 Feb 2;7:17.

Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. Biometrika. 1993 Sep;80(3):557-72.

Mariathasan S, Turley S, Nickles D, et al. TGFβ attenuates tumour response to PD-L1 blockade by contributing to exclusion of T cells. Nature. 2018 Feb 22;554(7693):544-8.

Marsh D, Suchak K, Moutasim KA, et al. Stromal features are predictive of disease mortality in oral cancer patients. J Pathol. 2011 Mar;223(4):470-81.

Narra K, Mullins SR, Lee HO, et al. Phase II trial of single agent Val-boroPro (Talabostat) inhibiting Fibroblast Activation Protein in patients with metastatic colorectal cancer. Cancer Biol Ther. 2007 Nov;6(11):1691-9.

Öhlund D, Handly-Santana A, Biffi G, et al. Distinct populations of inflammatory fibroblasts and myofibroblasts in pancreatic cancer. J Exp Med. 2017 Mar 6;214(3):579-96.

Orimo A, Gupta PB, Sgroi DC, et al. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. Cell. 2005 May 6;121(3):335-48.

Ottensmeier C, Perry KL, Harden EL, et al. Upregulated glucose metabolism correlates inversely with $CD8^+$ T-cell infiltration and survival in squamous cell carcinoma. Cancer Res. 2016 Jul 15;76(14):4136-48.

Paik YH, Kim J, Aoyama T, et al. Role of NADPH oxidases in liver fibrosis. Antioxid Redox Signal. 2014 Jun 10;20(17):2854-72.

Roychoudhury S, Anderson KM, Ye J, et al. Robust design and analysis of clinical with trial non-proportional hazards: a straw man guidance. Stat Biopharm Res. Published online: 04 Mar 2021.

Sahai E, Astsaturov I, Cukierman E, et al. A framework for advancing our understanding of cancer-associated fibroblasts. Nat Rev Cancer. 2020 Mar;20(3):174-86.

Seiwert TY, Burtness B, Mehra R, et al. Safety and clinical activity of pembrolizumab for treatment of recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-012): an open-label, multicentre, phase 1b trial. Lancet Oncol. 2016 Jul;17(7):956-65.

Sharpe AH, Freeman GJ. The B7-CD28 superfamily. Nat Rev Immunol. 2002 Feb;2(2):116-26.

Teixeira G, Szyndralewiez C, Molango S, et al. Therapeutic potential of NADPH oxidase 1/4 inhibitors. Br J Pharmacol. 2017 Jun;174(12) :1647-69.

Thompson RH, Dong H, Lohse CM, et al. PD-1 is expressed by tumor-infiltrating immune cells and is associated with poor outcome for patients with renal cell carcinoma. Clin Cancer Res. 2007 Mar 15;13(6):1757-61.

Vermorken JB, Mesia R, Rivera F. Platinum-based chemotherapy plus cetuximab in head and neck cancer. N Engl J Med. 2008 Sep 11;359(11):1116-27.

Wang M, Chen C, Jemielita T, et al. Are tumor size changes predictive of survival for checkpoint blockade based immunotherapy in metastatic melanoma? J Immunother Cancer. 2019 Feb 8;7(1):39.

Ward MJ, Thirdborough SM, Mellows T, et al. Tumour-infiltrating lymphocytes predict for outcome in HPV-positive oropharyngeal cancer. Br J Cancer. 2014 Jan 21;110(2):489-500.

Wood O, Woo J, Seumois G, et al. Gene expression analysis of TIL rich HPV-driven head and neck tumors reveals a distinct B-cell signature when compared to HPV independent tumors. Oncotarget. 2016 Aug 30;7(35):56781-97.

17 APPENDICES

17.1 APPENDIX I – Study Administrative Structure

Sponsor:	Calliditas Therapeutics Suisse SA Chemin des Aulx 16 1228 Plan-les-Ouates Switzerland
Operationally responsible for study conduct, including certain sponsor obligations:	The sponsor is a controlled subsidiary of Calliditas Therapeutics AB, a Swedish corporation with its registered office and mailing address at PO Box 70351, SE-107 24 Stockholm, Sweden and its principal office and address for courier delivery at Kungsbron 1 C8, SE11122 Stockholm, Sweden ("Calliditas" and, with its controlled affiliates, the "Calliditas Group"). As such, the sponsor applies standard operating procedures relating to clinical development, medical affairs, manufacturing, quality assurance, quality control, and pharmacovigilance of the Calliditas Group. Certain Calliditas Group managers, including the Calliditas Group Chief Medical Officer, have been delegated responsibility by sponsor for sponsor's activities within their functional areas.
Sponsor's medical expert:	Chief Medical Officer c/o Calliditas Therapeutics AB Mailing address: PO Box 70351, SE-107 24 Stockholm, Sweden Principal office and address for courier delivery: Kungsbron 1 C8, SE11122 Stockholm, Sweden Telephone: +46 (0)8 411 3005
Medical monitor:	The names and contact details of the study Medical Monitor(s) will be provided in the Key Study Team Contact List.
CRO:	ICON Clinical Research Limited, South County Business Park, Leopardstown, Dublin 18, D18 X5R3, Ireland ICON is a corporate affiliate of PRA
Central laboratory:	ICON Laboratory Services (ILS) South County Business Park Leopardstown, Dublin 18 D18 X5R3 Ireland OR ICON Laboratory Services (ILS) 123 Smith St. Farmingdale New York 11735 USA OR ICON Speciality Lab 1341 SW Custer Dr. Portland Oregon, USA 97219

Pharmacokinetics laboratory:	Unilabs York Bioanalytical Solutions Cedar House Northminister Business Park Upper Poppleton York Y026 6QR UK
Central biomarker assessment (tumour biopsy):	University of Southampton Experimental Pathology Cancer Research UK Centre Southampton SO16 6YD UK
RNA sequencing central laboratory	WISH Lab LF110 Southampton General Hospital Tremona Road, Southampton S016 6YD United Kingdom
Setanaxib and placebo manufacturer:	Aptuit Via Alessandro Fleming, 4 37135 Verona VR Italy
Setanaxib and placebo distributor of drug supplies:	Almac Clinical Services 9 Charlestown Road Seagoe Industrial Estate Craigavon BT63 5PW UK OR Almac Clinical Services 4204 Technology Drive Durham, NC 27704 USA
IRT:	ICON PLC 2100 Pennbrook Pkwy Lansdale, PA 19446
eCRF:	Medidata 12 Hammersmith Grove, 9th Floor Hammersmith, London W6 7AP UK

A log of the name and title of the investigators who are responsible for conducting the study, and the address and telephone numbers of the study sites will be maintained.

The names and addresses of any other laboratories involved in the study (further to those stated above) will be provided in the laboratory manual.

17.2 APPENDIX II – Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed as outlined in Table 1 based on the following:

Score	Definition
0	Fully active, able to carry on pre-disease activities without restrictions.
1	Restricted in strenuous activity, but ambulatory and able to carry out light work or work of a sedentary nature (eg, light housework or office work).
2	Ambulatory and capable of 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; unable to carry out any self-care and totally confined to bed or chair.
5	Dead.

17.3 APPENDIX III – Medications or Substances to Be Avoided or Used with Caution During Treatment with Setanaxib

Based on regulatory guidelines for development of new investigational agents and/or results from nonclinical pharmacology studies with setanaxib, precautions will be adopted for use of specific types of concomitant medications or substances. The types of medications to be considered are listed in Table 4. Specific concomitant medications to be used with caution due to known risk of QT interval prolongation or increased risk of torsades de pointes are listed in Table 5. Medications to be avoided as being potent cytochrome P450 (CYP) 3A4 inhibitors or inducers, as well as uridine diphosphate (UDP)-glucuronosyltransferase 1A9 (UGT1A9) inhibitors or inducers are listed in Table 6. Sensitive CYP2C9, CYP2C19, OAT3, CYP2B6, BCRP and P-gp substrates to be co-administered with caution are listed in Table 7.

Table 4 Type of Concomitant Medications to Avoid or Use with Caution with Setanaxib

Concomitant Medication Types	Setanaxib Characteristics	Potential Effects of Co-Administration	Approach
Prolongs QT	Preclinical signal identified in vitro, and in vivo, but risk considered low; no clinical events or other evidence of QT prolongation identified in clinical studies conducted to date	Possible increased risk of torsades de Pointes	Caution
Potent CYP3A4 inhibitors	Metabolised by CYP3A4	Setanaxib levels may be increased if administered with CYP3A4 inhibitors	Avoid
Potent CYP3A4 inducers	Metabolised by CYP3A4	Setanaxib levels may be decreased if administered with CYP3A4 inducers	Avoid
Potent UGT1A9 inhibitors	Metabolised by UGT1A9	Setanaxib levels may be increased if administered with UGT1A9 inhibitors	Avoid
Potent UGT1A9 inducers	Metabolised by UGT1A9	Setanaxib levels may be decreased if administered with UGT1A9 inducers	Avoid
Sensitive CYP2C9 and CYP2C19 substrates	Weak inhibitor of CYP2C9 and CYP2C19	May increase drug levels of concomitant medications	Caution
Sensitive CYP2B6 substrates	Potential induction effects on CYP2B6	May decrease drug concentration of concomitant	Caution

		medications and reduce efficacy	
Sensitive OAT3 substrates	Weak inhibitor of OAT3	May increase drug levels of concomitant medications	Caution
Sensitive BCRP or P-gp substrates	Potential inhibitor of BCRP and P-gp	May increase drug levels of concomitant medications	Caution

Table 5 Use with Caution – Concomitant Medications with Known Risk of QT Interval Prolongation or Increased Risk of Torsades de Pointes

Aclarubicin (only on Non-US Market)	Haloperidol	Terfenadine (removed from US Market)
Amiodarone	Hydroquinidine (Dihydroquinidine) (Only on Non-US Market)	Terlipressin (only on Non-US Market)
Anagrelide	Hydroxychloroquine	Terodiline (only on Non-US Market)
Arsenic trioxide	Ibogaine (only on Non-US Market)	Thioridazine
Astemizole (removed from US Market)	Ibutilide	Vandetanib
Azithromycin	Levofloxacin	
Bepridil	Levomepromazine (Methotrimeprazine) (only on Non-US Market)	
Celsium Chloride	Levomethadyl acetate (removed from US Market)	
Chloroquine	Levosulpiride (only on Non-US Market)	
Chlorpromazine	Meglumine antimoniate (only on Non-US Market)	
Chlorprothixene (only on Non-US market)	Mesoridazine (removed from US Market)	
Cilostazol	Methadone	
Ciprofloxacin	Moxifloxacin	
Cisapride (removed from US market)	Nifekalant (only on Non-US Market)	
Citalopram	Ondansetron	
Clarithromycin	Oxaliplatin	
Cocaine	Papaverine HCl (Intracoronary)	
Disopyramide	Pentamidine	
Dofetilide	Pimozide	
Domperidone (only on Non-US Market)	Probucol (Removed from US Market)	
Donepezil	Procainamide	
Dronedarone	Propofol	
Droperidol	Quinidine	
Erythromycin	Roxithromycin (only on Non-US Market)	
Escitalopram	Sertindole (Only on Non-US Market)	
Flecainide	Sevoflurane	
Fluconazole	Sotalol	
Gatifloxacin (removed from US Market)	Sparfloxacin (removed from US Market)	
Grepafloxacin (removed from US Market)	Sulpiride (only on Non-US Market)	
Halofantrine (only on Non-US Market)	Sultopride (only on Non-US Market)	

Source: CredibleMeds.org website, most recent update May 03, 2021

Table 6 Avoid Usage – Guidance on Specific Concomitant Medications to Avoid with Setanaxib

Drug Name	Characteristic	Potential DDI Effect	Usage
avasimibe	Potent CYP3A4 inducer	Decreased IMP exposure	Avoid
belumosudil	UGT1A9 inhibitor/inducer	Increased IMP exposure	Avoid
boceprevir	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
cannabidiol, cannabinol and medical cannabis	UGT1A9 inhibitor/inducer	Increased IMP exposure	Avoid
carbamazepine	Potent CYP3A4 inducer	Decreased IMP exposure	Avoid
clarithromycin	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
conivaptan	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
deferasirox	UGT1A9 inhibitor/inducer	Increased IMP exposure	Avoid
diflunisal	UGT1A9 inhibitor/inducer	Increased IMP exposure	Avoid
eltrombopag	UGT1A9 inhibitor/inducer	Increased IMP exposure	Avoid
elvitegravir	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
enzalutamide	Potent CYP3A4 inducer	Decreased IMP exposure	Avoid
fluconazole	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
fosphenytoin	UGT1A9 inhibitor/inducer	Increased IMP exposure	Avoid
indinavir	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
isavuconazole	UGT1A9 inhibitor/inducer	Increased IMP exposure	Avoid
itonavir	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
itraconazole	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
ketoconazole	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
lopinavir	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
lopinavir/RIT	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
mefenamic acid	UGT1A9 inhibitor/inducer	Increased IMP exposure	Avoid
methylene blue	UGT1A9 inhibitor/inducer	Increased IMP exposure	Avoid
mibefradil	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid

Drug Name	Characteristic	Potential DDI Effect	Usage
mitotane	Potent CYP3A4 inducer	Decreased IMP exposure	Avoid
morniflumate	UGT1A9 inhibitor/inducer	Increased IMP exposure	Avoid
nefazodone	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
nelfinavir	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
nevirapine	Potent CYP3A4 inducer	Decreased IMP exposure	Avoid
niflumic acid	UGT1A9 inhibitor/inducer	Increased IMP exposure	Avoid
perampanel	UGT1A9 inhibitor/inducer	Increased IMP exposure	Avoid
phenobarbital	Potent CYP3A4 inducer	Decreased IMP exposure	Avoid
phenytoin	Potent CYP3A4 inducer; UGT1A9 inhibitor/inducer	Decreased IMP exposure	Avoid
posaconazole	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
regorafenib	UGT1A9 inhibitor/inducer	Increased IMP exposure	Avoid
rifabutin	Potent CYP3A4 inducer	Decreased IMP exposure	Avoid
rifampin	Potent CYP3A4 inducerUGT1A9 inhibitor/inducer	Decreased IMP exposure	Avoid
rifapentine	Potent CYP3A4 inducer	Decreased IMP exposure	Avoid
ritonavir	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
saquinavir	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
sorafenib	UGT1A9 inhibitor/inducer	Increased IMP exposure	Avoid
St John’s wort	CYP3A4 inducer	Decreased IMP exposure	Avoid
telaprevir	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
telithromycin	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
tipranavir/ritonavir	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
troleandomycin	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid
umifenovir	UGT1A9 inhibitor/inducer	Increased IMP exposure	Avoid
voriconazole	Potent CYP3A4 inhibitor	Increased IMP exposure	Avoid

800 mg BID of setanaxib has been shown to increase the plasma concentration of sensitive CYP2C9, CYP2C19 and OAT3 transporter substrates less than two-fold. Caution should be exercised during concomitant use of such drugs with setanaxib due to risk of increased drug concentrations. Setanaxib has potential induction effects on CYP2B6. Sensitive substrates of CYP2B6 should be used with caution due to risk of decreased drug concentration and reduced efficacy. In addition, setanaxib inhibited BCRP and MDR1 (P-gp) in vitro. This may result in increased exposures of applicable concomitant medications, and hence caution should be exercised with use of sensitive BCRP and P-gp substrates.

Some examples of sensitive CYP2C9, CYP2C19, CYP2B6, OAT3, BCRP, and P-gp substrates are included in Table 7, however the list is not comprehensive.

Table 7 Use with Caution – Sensitive CYP2C9, CYP2C19, CYP2B6, OAT3, BCRP, and P-gp Substrates

Drug Name	Characteristic	Potential DDI Effect	Usage
acyclovir	Sensitive OAT3 substrate	May increase the drug level of concomitant medications	Caution
amitriptyline	Sensitive CYP2B6 substrate	May decrease the drug level of concomitant medications and reduce efficacy	Caution
carbamazepine	Sensitive CYP2B6 substrate	May decrease the drug level of concomitant medications and reduce efficacy	Caution
cefaclor	Sensitive OAT3 substrate	May increase the drug level of concomitant medications	Caution
ceftizoxime	Sensitive OAT3 substrate	May increase the drug level of concomitant medications	Caution
cyclophosphamide	Sensitive CYP2B6 substrate	May decrease the drug level of concomitant medications and reduce efficacy	Caution
diazepam	Sensitive CYP2C19 substrate	May increase the drug level of concomitant medications	Caution
digoxin	Sensitive BCRP and P-gp substrate	May increase the drug level of concomitant medications	Caution
dosulepin	Sensitive CYP2B6 substrate	May decrease the drug level of concomitant medications and reduce efficacy	Caution
enasidenib	Sensitive CYP2B6 substrate	May decrease the drug level of concomitant	Caution

Drug Name	Characteristic	Potential DDI Effect	Usage
		medications and reduce efficacy	
famotidine	Sensitive OAT3 substrate	May increase the drug level of concomitant medications	Caution
furosemide	Sensitive OAT3 substrate	May increase the drug level of concomitant medications	Caution
glimepiride	Sensitive CYP2C9 substrate	May increase the drug level of concomitant medications	Caution
ifosfamide	Sensitive CYP2B6 substrate	May decrease the drug level of concomitant medications and reduce efficacy	Caution
imipramine	Sensitive CYP2B6 substrate	May decrease the drug level of concomitant medications and reduce efficacy	Caution
irinotecan	Sensitive CYP2B6 substrate	May decrease the drug level of concomitant medications and reduce efficacy	Caution
ixazomib	Sensitive CYP2B6 substrate	May decrease the drug level of concomitant medications and reduce efficacy	Caution
losartan	Sensitive CYP2C9 substrate	May increase the drug level of concomitant medications	Caution
methotrexate	Sensitive OAT3 substrate	May increase the drug level of concomitant medications	Caution
omeprazole	Sensitive CYP2C19 substrate	May increase the drug level of concomitant medications	Caution
oseltamivir carboxylate	Sensitive OAT3 substrate	May increase the drug level of concomitant medications	Caution
penicillin G	Sensitive OAT3 substrate	May increase the drug level of concomitant medications	Caution
phenytoin	Moderate sensitive CYP2C9 substrate; sensitive CYP2B6 substrate	May increase the drug level of concomitant medications	Caution
romidepsin	Sensitive CYP2B6 substrate	May decrease the drug level of concomitant medications and reduce efficacy	Caution
S-mephenytoin	Sensitive CYP2C19	May increase the drug	Caution

Drug Name	Characteristic	Potential DDI Effect	Usage
	substrate	level of concomitant medications	
tamoxifen	Sensitive CYP2B6 substrate	May decrease the drug level of concomitant medications and reduce efficacy	Caution
valproic acid	Sensitive CYP2B6 substrate	May decrease the drug level of concomitant medications and reduce efficacy	Caution
voriconazole	Sensitive CYP2C19 substrate	May increase the drug level of concomitant medications	Caution
warfarin	Moderate sensitive CYP2C9 substrate	May increase the drug level of concomitant medications	Caution
zanubrutinib	Sensitive CYP2B6 substrate	May decrease the drug level of concomitant medications and reduce efficacy	Caution

Additionally, examples of potent CYP3A4 or UGT1A9 inhibitors and inducers, and sensitive CYP2C9, CYP2C19, CYP2B6, OAT3, BCRP and P-gp substrates may be found on the following websites; note that the published lists are not comprehensive. Refer to the specific product information for an intended concomitant drug.

- FDA.gov: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm (FDA 2016)
- Pharmacytimes.com: http://www.pharmacytimes.com/publications/issue/2015/december2015/drug-interactions-with-cyp3a4-an-update (Horn and Hansen 2015)
- DrugBank Online: https://go.drugbank.com/
- Drug Interaction Database (referred to as DIDB) from the University of Washington: https://www.druginteractionsolutions.org/

17.4 APPENDIX IV – RECIST v1.1 Methodology

Response evaluation criteria in solid tumours: Revised RECIST criteria (Eisenhauer et al 2009) are summarised below.

Measurable/Non-Measurable Lesions. Each tumour lesion or site of disease identified at baseline is categorised as either a measurable lesion or a non-measurable lesion according to the following definitions.

Lesion Type	Qualifying Definition
Measurable	Tumour lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of 10 mm by CT or MRI scan (CT scan slice thickness no greater than 5 mm.). Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be 15 mm in short axis when assessed by CT or MRI scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.
Non-Measurable	All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with 10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability:

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above.

However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

Tumour lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 35 days before the beginning of the treatment.

Target Lesions. Target lesions are selected from measurable lesions at baseline on the basis of their size and suitability for accurate repeated measurements by imaging techniques or clinical judgment. The sum of the longest diameter (LD) for all target lesions provides a quantitative means of characterising objective tumour response to treatment as follows:

Evaluation Criteria Used for Categorising Treatment Response of Target Lesions	
Response Category	**Definition**
Complete Response (CR)	Disappearance of all target lesions
Partial Response (PR)	>30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD)	>20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Non-Target Lesions. Non-target lesions are other lesions (or sites of disease) not identified as target lesions at baseline. These include both non-measurable lesions as well as measurable lesions exceeding the maximum number allowed per organ or in total. The response of non-target lesions to treatment is evaluated on the basis of their presence or absence as follows:

Evaluation Criteria Used for Categorising Treatment Response of Non-Target Lesions	
Response Category	**Definition**
Complete Response (CR)	Disappearance of all non-target lesions and normalisation of tumour marker levels initially above upper limits of normal
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions
Non-CR/Non-PD	Persistence of one or more non-target lesion(s) or/and maintenance of tumour marker level above the normal limits

To achieve “unequivocal progression” on the basis of non-target lesions, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target lesions, the overall tumour burden has increased sufficiently to merit

unequivocal progression by non-target lesions. A modest "increase" in the size of 1 or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PD of target disease will therefore be exceptional.

New Lesions. New lesions not present at baseline should be recorded at time of occurrence.

Overall Response. The 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). For example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR. In the case of SD, follow-up measurements must have met the SD criteria at least once with a minimum interval of at least 6 weeks from randomisation.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
PD	Any	Yes or No	PD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR=complete response; NE=not evaluable; PD=progressive disease; PR=partial response; SD=stable disease.

Duration of Response. The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). Stable disease is measured from the start of the treatment until the criteria for progression

are met, taking as reference the smallest measurements recorded since the treatment started.

Response review

For studies where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible.

All of the patients who met the eligibility criteria should be included in the main analysis of the response rate.

All conclusions should be based on all eligible patients.

Sub-analyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (eg, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.