CLINICAL STUDY PROTOCOL

Protocol Number:	**VIC-1911-01**
Protocol Title:	A Phase 1a/1b Study of Aurora Kinase A Inhibitor VIC-1911 as Monotherapy and in Combination with Sotorasib for the Treatment of *KRAS G12C*-Mutant Non-Small Cell Lung Cancer
Sponsor:	**VITRAC Therapeutics, LLC** 27 Strathmore Road Natick, MA 01760
Original Protocol	**Date: 10 May 2022**
Amendment 1	**Date: 14 September 2022**
Amendment 2	**Date: 11 November 2022**

INVESTIGATOR SIGNATURE PAGE

I have reviewed the above-titled protocol and agree that it contains all the information necessary to conduct the study as required. I will conduct the trial in accordance with the principles of the International Conference on Harmonisation (ICH) Good Clinical Practice, the Declaration of Helsinki and the applicable U.S. Food and Drug Administration (FDA) regulations.

I will maintain as confidential all written and verbal information provided to me by the Sponsor, including but not limited to, the protocol, electronic case report forms (eCRFs), investigator's brochure, material supplied at investigator meetings, minutes of teleconferences, etc. Such material will only be provided as necessary to site personnel involved in the conduct of the trial, the Institutional Review Board (IRB) or local regulatory authorities.

I will obtain written informed consent from each prospective trial subject or each prospective trial subject's legal representative prior to conducting any protocol-specified procedures. The Informed Consent Document (ICD) used will have the approval of the IRB.

I will maintain adequate source documents and record all observations, treatments and procedures pertinent to trial subjects in their medical records. I will accurately complete and submit the eCRFs supplied by the Sponsor in a timely manner. I will ensure that my facilities and records will be available for inspection by representatives of the Sponsor, the IRB or local regulatory authorities. I will ensure that I and my staff are available to meet with representatives of the Sponsor during regularly scheduled monitoring visits.

I will report all serious adverse events (SAEs) according to the guidelines stipulated in the protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

1. SYNOPSIS

Protocol Number: VIC-1911-01

Name of Sponsor/Company:
VITRAC Therapeutics, LLC

Name of Investigational Product:
VIC-1911

Name of Active Ingredient: $C_{23}H_{22}Cl_2FN_5O_3$ HCl

Title of Study: A Phase 1a/1b Study of Aurora Kinase A Inhibitor VIC-1911 Monotherapy and in Combination with Sotorasib for the Treatment of *KRAS G12C*-Mutant Non-Small Lung Cancer

Principal Investigators: The study will be conducted at Yale Cancer Center, Sarah Goldberg, MD, MPH, Principal Investigator (PI) and Study Chair; New York University Perlmutter Cancer Center, Vamsidhar Velcheti, MD, PI; University of California Davis Comprehensive Cancer Center, Jonathan Reiss, MD, PI; University of Maryland Cancer Center, Katherine Scilla, MD, PI; Emory University Winship Cancer Center, Jennifer Carlisle, MD, PI. Additional clinical sites may be added to complete enrollment in a timely manner.

Study Period (42 months): **Estimated Date First Subject Enrolled:** October 2022 **Estimated Date Last Subject Completed:** March 2026	**Phase of Development:** 1

Objectives:

***Primary*:**

- **<u>Phase 1a (Dose Escalation Phase)</u>:** To determine the safety, tolerability, maximum tolerated dose (MTD) and Recommended Phase 2 Dose (RP2D) of:
  - VIC-1911 monotherapy in subjects previously treated with KRAS G12C inhibitor therapy,
  - VIC-1911 in combination with sotorasib (LUMAKRAS™) in subjects previously treated with KRAS G12C inhibitor therapy, and
  - VIC-1911 in combination with sotorasib in subjects naïve to KRAS G12C inhibitor therapy
- **<u>Phase 1b (Expansion Phase)</u>**: To determine the objective response rate (ORR), defined as complete response (CR) or partial response (PR), for:
  - VIC-1911 monotherapy in subjects previously treated with KRAS G12C inhibitor therapy,
  - VIC-1911 in combination with sotorasib in subjects previously treated with KRAS G12C inhibitor therapy, and
  - VIC-1911 in combination with sotorasib in subjects naïve to KRAS G12C inhibitor therapy

***Secondary*:**

The following parameters will be evaluated for VIC-1911 monotherapy and in combination with sotorasib:

- **<u>Phase 1a (Dose Escalation Phase)</u>:**
  - ORR
  - Duration of response (DoR)
  - Time to response (TTR)

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- Disease control rate (DCR), defined as stable disease (SD), CR or PR
- Progression-free survival (PFS)
- Overall survival (OS)
- Pharmacokinetics (PK) of VIC-1911 monotherapy and in combination with sotorasib
- Pharmacodynamics of tumor biomarker determinations pre- and on-study summarized and correlated with clinical outcome
- In subjects refractory to or relapsed on prior KRAS G12C inhibitor therapy, the effect of prior KRAS G12C *de novo* resistance (KRAS G12C inhibitor treatment ≤ 3 months) versus KRAS G12C acquired resistance (KRAS G12C inhibitor treatment > 3 months) on clinical outcome

- **Phase 1b (Expansion Phase):**
  - Safety and tolerability of VIC-1911 as monotherapy and in combination with sotorasib
  - Duration of response (DoR)
  - Time to response (TTR)
  - Disease control rate (DCR), defined as SD, CR or PR
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - Pharmacodynamics of circulating tumor DNA (ctDNA) and tumor biomarker determinations pre- and on-study summarized and correlated with clinical outcome
  - In subjects refractory to or relapsed on prior KRAS G12C inhibitor therapy, the effect of prior KRAS G12C *de novo* resistance (KRAS G12C inhibitor treatment ≤ 3 months) versus KRAS G12C acquired resistance (KRAS G12C inhibitor treatment > 3 months) on clinical outcome

Methodology:

This is a non-randomized, open-label Phase 1a/1b study of aurora kinase A inhibitor VIC-1911 administered as monotherapy and in combination with sotorasib for the treatment of locally advanced or metastatic *KRAS G12C*-mutant non-small cell lung cancer (NSCLC).

Selected subjects will include males and females age ≥18 years with histologically confirmed locally advanced or metastatic *KRAS G12C*-mutated NSCLC, received at least 1 prior line of cancer therapy with a PD-1 or PD-L1 inhibitor with or without platinum-based chemotherapy (unless subject is not eligible or refuses chemotherapy or PD-1/PD-L1 therapy), previously treated with or naïve to KRAS G12C inhibitor therapy, recovered from all acute toxicities (≤ Grade 1) due to prior therapy, have adequate hematologic, renal and hepatic function and no known history of significant cardiac, hepatic or ocular disease.

Phase 1a (Dose Escalation Phase):

Following screening, a total of up to 36 subjects are anticipated to establish the MTDs of VIC-1911 monotherapy and VIC-1911 in combination with sotorasib therapy.

Cohort 1a: Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will receive VIC-1911 monotherapy. Up to 24 subjects are anticipated in this cohort.

VIC-1911 monotherapy will be administered orally twice daily (b.i.d.) at doses of 25, 50, 75 and 90 mg (total daily doses of 50, 100, 150 and 180 mg) repeated every 28 days (=1 cycle). Subjects will take their VIC-1911 b.i.d. doses in the fasted state (1 hour before or 2 hours after the morning and evening meal), with the two doses approximately 12 hours apart.

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VIC-1911 Monotherapy Dose Escalation Levels:

Dose Level	VIC-1911 (PO b.i.d.)
1	25 mg
2	50 mg
3	75 mg
4	90 mg

VIC-1911-related adverse events (AEs) will lead to dose reductions as indicated in Section 5.5.1.2.

Cohort 1b: Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy or are naïve to KRAS G12C inhibitor therapy will receive VIC-1911 plus sotorasib combination therapy. Up to 12 subjects are anticipated in this cohort.

VIC-1911 will be administered orally twice daily (b.i.d.) at the doses indicated below on Days 1-4, 8-11, and 15-18, repeated every 28 days (=1 cycle), and sotorasib will be administered once daily at the doses indicated below. Both VIC-1911 and sotorasib will be taken together in the fasted state (1 hour before or 2 hours after the morning meal and after the evening meal [VIC-1911 only]) with the VIC-1911 b.i.d. doses approximately 12 hours apart.

Combination VIC-1911 Plus Sotorasib Dose Escalation Levels:

Dose Level	VIC-1911 (PO b.i.d.)[a]	Sotorasib (PO q.d.)
1	75 mg	960 mg
2	150 mg	960 mg
3	200 mg	960 mg
[a] Days 1-4 x 3 weeks q 28 days		

VIC-1911-related or sotorasib-related AEs will lead to individual dose reductions as indicated in Section 5.5.1.2.

Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will be enrolled alternatingly into Cohort 1a (VIC-1911 monotherapy) and Cohort 1b (VIC-1911 plus sotorasib) by dose level (e.g., Dose Level 1 in Cohort 1a will be filled, then Dose Level 1 in Cohort 1b, then Dose Level 2 in Cohort 1a, etc.). In Cohort 1b, VIC-1911 pharmacokinetics will be analyzed from Dose Level 1 before Dose Level 2 is initiated to assess the impact of co-administration of VIC-1911 plus sotorasib on the pharmacokinetics of VIC-1911. If necessary, a dose adjustment to VIC-1911 will be made prior to initiating Dose Level 2. This information will be used to make a dose adjustment for Dose Level 3, if necessary.

A 3+3 dose escalation schema will be followed for each cohort. A total of 3 subjects per cohort will be dosed and followed for 28 days through Cycle 1 for dose limiting toxicity (DLT). If 0 of 3 subjects experiences a DLT in Cycle 1, the next higher dose level cohort will open. However, if a DLT is experienced in 1 of 3 subjects, the cohort will be expanded to 6 subjects. If 2 or more of 6 subjects per cohort experience DLT, further dose escalation will be subject to Safety Review Committee (SRC) review and recommendation. The highest dose level below the dose level eliciting DLT in ≥ 2 of 6 subjects will be declared the VIC-1911 monotherapy MTD or the combination VIC-1911 plus sotorasib MTDs. A total of 6 subjects will be treated at the MTD(s) in each cohort.

For dose de-escalation, if 1 of 3 subjects experiences a DLT at the de-escalated dose level, the cohort will be expanded to 6 subjects. If ≥ 2 of 6 subjects at that dose level experience a DLT, no further subjects will be treated at that dose level and the next lower dose level to enroll 0 of 3 or < 2 of 6 subjects without DLT will be declared the MTD.

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Subjects in all cohorts who demonstrate clinical benefit (CR, PR or SD) will be allowed to continue therapy with VIC-1911 monotherapy or VIC-1911 and sotorasib combination therapy until progression of disease (unless the subject is still benefiting clinically in the opinion of the treating physician, after discussion with the Medical Monitor, as described in Section 7.1.1.), observation of unacceptable AEs, intercurrent illness or changes in the subject's condition that prevents further study participation.

DLT is defined as any one of the following events considered at least possibly related to VIC-1911 and/or sotorasib occurring within the first 28 days of study treatment (=DLT evaluation period):

- Grade 4 hematologic toxicity for > 1 day
- Grade 3 febrile neutropenia (defined as absolute neutrophil count (ANC) < 1000/mm^3 with a single temperature of ≥ 38.3°C [≥ 101°F] or sustained temperature of ≥ 38.0°C [≥ 100.4°F] for more than 1 hour)
- Grade 3 hematologic toxicity with complications (e.g., thrombocytopenia with bleeding)
- Failure of Grade 3 thrombocytopenia, ANC or hemoglobin (Hb) to recover to Grade ≤ 1 within 4 weeks despite the use of platelet and red blood cell (RBC) transfusions and/or growth factors
- ≥ Grade 3 non-hematologic toxicity not due to disease progression (excluding nausea, vomiting, constipation, pain, diarrhea or rash that is adequately controlled with supportive care and resolves to ≤ Grade 2 within 48 hours), or electrolyte disturbances unresponsive to correction within 24 hours
- Laboratory abnormalities that satisfy the 3 components of Hy's Law of drug-induced liver injury: 1) ALT or AST elevation ≥ 3 times the upper limit of normal (ULN), 2) total bilirubin elevation > 2 times the ULN without initial findings of cholestasis (i.e., absence of alkaline phosphatase activity > 2 times the ULN), and 3) no other reason to explain the combination of increased ALT/AST and total bilirubin, such as viral hepatitis, preexisting or acute liver disease, or another drug capable of causing the observed injury
- A treatment interruption for ≥ Grade 3 drug-related toxicity in Cycle 1 exceeding 7 days or inability to begin Cycle 2 for > 7 days due to drug-related toxicity.
- Other important medical event not clearly due to underlying disease or extraneous causes

A DLT evaluable subject is one who receives study treatment and does not meet the criteria for subject replacement during the DLT evaluation period.

No intra-subject dose escalation will be allowed from previous dose levels until the subject has received ≥ 3 cycles of their assigned dose, and all subjects at the higher dose level have completed Cycle 1 at that dose level (e.g., 3 – 6 subjects, as required to establish safety of the higher dose level) and no ≥ Grade 3 toxicity, irrespective of causality, was observed during the previous treatment cycle. Subjects who experience a DLT may continue treatment in subsequent cycles at the next lower dose level(s) until disease progression (or until no longer benefiting clinically) or unacceptable toxicity.

Subjects who experience DLT at the first dose level in each cohort will not be dose-reduced and will be discontinued.

A total of at least 6 subjects will be treated at the MTD in each group before initiating the Expansion Phase.

An SRC, consisting of the actively recruiting investigators, Sponsor Medical Monitor, and study staff, will review safety and efficacy data from each cohort monthly or more often as necessary. Intermediate dose levels may be added if it is recommended to do so by the SRC.

Phase 1b (Expansion Phase): Following screening, a total of 104 subjects with *KRAS G12C*-mutated locally advanced or metastatic NSCLC are anticipated to expand the disease treatment settings of VIC-

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1911 as monotherapy or in combination with sotorasib. VIC-1911 monotherapy and VIC-1911 plus sotorasib combination therapy will be administered orally at the MTDs/RP2Ds established during the Dose Escalation Phase.

VIC-1911 and sotorasib will be taken in the fasted state, 1 hour before or 2 hours after a meal. VIC-1911 dose reductions for suspected VIC-1911-related toxicity will be followed in accordance with those established in the Dose Escalation Phase. Sotorasib dose reductions for suspected sotorasib-related toxicity will be 480 mg q.d. (Dose Level -1) and 240 mg q.d. (Dose Level -2) in accordance with the LUMAKRAS U.S. Product Label. Further detail on dose reduction guidelines for VIC-1911 and sotorasib are found in Section 5.5.1.2.

Subjects who demonstrate clinical benefit (CR, PR or SD) will be allowed to continue therapy with VIC-1911 and sotorasib until progression of disease (unless the subject is still benefiting clinically in the opinion of the treating physician, after discussion with the Medical Monitor, as described in Section 7.1.1.), observation of unacceptable AEs, intercurrent illness or changes in the subject's condition that prevents further study participation.

The statistical objective is the evaluation of the ORR, defined as CR or PR. The sample sizes are based on Simon's 2-stage optimal design.

Cohort 2a: Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will receive VIC-1911 monotherapy. The null hypothesis that the true OR rate (p_0) $\leq$ 5% will be tested against a one-sided alternative true OR rate (p_1) $\geq$ 20%. In the first stage, 10 subjects will be accrued. If there are 0 ORs in these 10 subjects, the cohort will be terminated due to futility. If there is at least 1 OR in these 10 subjects, 19 additional subjects will be accrued for a total of n = 29 evaluable subjects. The null hypothesis will be rejected if 4 or more responses are observed in a total of 29 evaluable subjects. The design yields a type 1 error rate of 0.05% and power of 80% when the true response rate is at least 20% and provides evidence of clinical utility to move forward with continued clinical development in this patient population.

Cohort 2b: Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will receive VIC-1911 plus sotorasib combination therapy. The null hypothesis that the true OR rate (p_0) $\leq$ 5% will be tested against a one-sided alternative true OR rate (p_1) $\geq$ 20%. In the first stage, 10 subjects will be accrued. If there are 0 ORs in these 10 subjects, the cohort will be terminated due to futility. If there is at least 1 OR in these 10 subjects, 19 additional subjects will be accrued for a total of n = 29 evaluable subjects. The null hypothesis will be rejected if 4 or more responses are observed in a total of 29 evaluable subjects. The design yields a type 1 error rate of 0.05% and power of 80% when the true response rate is at least 20% and provides evidence of clinical utility to move forward with continued clinical development in this patient population.

Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will be enrolled alternatingly into Cohort 2a (VIC-1911 monotherapy) and Cohort 2b (VIC-1911 plus sotorasib) (e.g., one subject in Cohort 2a, next subject in Cohort 2b, next subject in Cohort 2a, etc.).

Cohort 2c: Subjects who are naïve to KRAS G12C inhibitor therapy will receive VIC-1911 plus sotorasib combination therapy. The null hypothesis that the true OR rate (p_0) $\leq$ 30% will be tested against a one-sided alternative true OR rate (p_1) $\geq$ 50%. In the first stage, 15 subjects will be accrued. If there are 5 or fewer ORs in these 15 subjects, the cohort will be terminated due to futility. If there is at least 6 ORs in these 15 subjects, 31 additional subjects will be accrued for a total of n = 46 evaluable subjects. The null hypothesis will be rejected if 19 or more responses are observed in a total of 46 evaluable subjects. The design yields a type 1 error rate of 0.05% and power of 80% when the true response rate is at least 50% and provides evidence of clinical utility to move forward with continued clinical development in this patient population.

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A sample size of n = 46 evaluable subjects also yields a type 1 error rate of 0.05% and power of 79% when the median PFS is 10 months (from 6 months historical) based on a one-sample log-rank test.

During the Expansion Phase, we will use continuous monitoring for excess toxicity using a Popcock-type boundary,[32] with the following assumptions: DLT event probability = 0.30 (30%) with 0.05 (5%) desired probability of stopping early.

The maximum planned sample sizes for the Expansion Phase Cohorts 2a and 2b are n = 29 each. In each of these cohorts, sequential boundaries will be used to monitor the rates of DLTs. The accrual will be halted if excessive DLTs are seen, that is, if the number of subjects with a DLT is equal to or exceeds $\mathbf{b_n}$ out of **n** subjects with full follow-up through C1D28. This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most (probability of early stopping) when the rate of DLT is equal to the acceptable rate (event probability θ). For the maximum planned samples sizes of n = 29 for each Cohorts 2a and 2b, the boundary is equivalent to testing the null hypothesis, after each subject, that the event rate is equal to 0.3, using a one-sided test level of 0.017846.

The maximum planned sample size for the Expansion Phase Cohort 2c is n = 46. In this cohort, sequential boundaries will be used to monitor the rates of DLTs. The accrual will be halted if excessive DLTs are seen, that is, if the number of subjects with a DLT is equal to or exceeds $\mathbf{b_n}$ out of **n** subjects with full follow-up through C1D28. This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most (probability of early stopping) when the rate of DLT is equal to the acceptable rate (event probability θ). For the maximum planned samples size of n = 46 for Cohort 2c, the boundary is equivalent to testing the null hypothesis, after each subject, that the event rate is equal to 0.3, using a one-sided test level of 0.011900.

Each cohort in the Expansion Phase will be stopped if the number of subjects with a DLT is equal to or exceeds $\mathbf{b_n}$ out of **n** subjects with completed follow up through C1D28. See Section 11.2.

An SRC, consisting of the actively recruiting investigators, Sponsor Medical Monitor, and study staff, will review safety and efficacy data from each cohort monthly or more often as necessary.

Study Assessments:

Blood for hematology, coagulation parameters and serum chemistry determinations will be collected within 28 days prior to Cycle 1 Day 1; on Days 1 and 15 of Cycles 1-3; on Day 1 of each subsequent cycle and at the End of Treatment Visit.

Urine will be collected for urinalysis within 28 days prior to Cycle 1 Day 1, on Day 1 of each subsequent cycle and at the End of Treatment visit.

Electrocardiograms (ECGs) will be taken within 28 days prior to Cycle 1 Day 1, pre-dose and approximately 2 hours post-dose on Cycle 1 Day 1 and Day 15, and at the End of Treatment visit.

Ophthalmic exams will be conducted within 28 days prior to Cycle 1 Day 1 and at the End of Treatment visit. Additional ophthalmologic examinations will be conducted during the study, if clinically indicated. Subjects should be educated on, and be instructed to, immediately report any signs of potential ocular toxicity so that the toxicity is identified and managed in a timely fashion.

Blood for PK assessment of VIC-1911 plasma concentrations will be collected at Cycle 1 Day 1 and Day 15 pre-dose, 15 and 30 minutes, 1, 2, 4, 8 and 24 hours following the first daily dose, and pre-first dose Cycles 2, 4 and 6. On Cycle 1 Day 1 and Day 15, the evening dose of VIC-1911 will be held and subjects will receive only a single morning dose of VIC-1911 to collect a full pharmacokinetic profile following a single dose of study drug at steady state (*Dose Escalation Phase only*).

Blood for assessment of ctDNA will be collected in the Expansion Phase Cohorts 2b and 2c pre-dose Cycle 1 Day 1 and at progression of disease for biomarker assessment.

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If clinically feasible, tumor biopsies will be collected on all subjects (Dose Escalation and Expansion phases) at Screening (archived or fresh) and on subjects in the Expansion Phase only at Cycle 3 Day 1 and at time of progression for biomarker assessment.

Results of ctDNA and tumor biomarker assessment also will be correlated with clinical outcome (e.g., objective response, disease progression, resistance development).

Disease assessments will be based on computed tomography (CT) or magnetic resonance imaging (MRI). Assessments will be obtained every 8 weeks until documented progressive disease (PD).

Number of Subjects and Centers (planned): Phase 1a (Dose Escalation Phase): Up to 36 subjects are anticipated. Phase 1b (Expansion Phase): Up to 104 subjects are anticipated. The total number of subjects anticipated for the study is up to 140 across 5 clinical sites. Additional clinical sites may be added to complete enrollment in a timely manner.

Duration of Study: Accrual in the Dose Escalation Phase is expected to be 18 months. Accrual in the Expansion Phase is expected to be 18 months, with the last subject followed for up to 6 months. The total study duration is expected to be 42 months. The anticipated accrual rate in the Dose Escalation Phase is ~ 2 – 3 subjects per month, and in the Expansion Phase is ~6 subjects per month.

Inclusion Criteria:

1. Males and females ≥ 18 years of age
2. Have locally advanced or metastatic histologically or cytologically confirmed NSCLC, *KRAS G12C*-mutated
3. The presence of a *KRAS G12C* mutation should be established prior to entry as assessed in a CLIA qualified laboratory. Testing may be done on tumor tissue (archival or fresh) or on ctDNA from blood.
4. Have received at least 1 prior line of cancer therapy with a PD-1 or PD-L1 inhibitor with or without platinum-based chemotherapy (unless subject is not eligible or refuses chemotherapy or PD-1/PD-L1 therapy) and have documented progression of disease on all prior cancer therapies
5. Phase 1a (Dose Escalation Phase):
   - 5.1 Cohort 1a: (VIC-1911 monotherapy): Locally advanced or metastatic NSCLC refractory to or relapsed on at least 1 prior cancer therapy as noted above, and relapsed/refractory on KRAS G12C inhibitor therapy as the most recent cancer therapy prior to study
   - 5.2 Cohort 1b: (VIC-1911 plus sotorasib): Locally advanced or metastatic NSCLC:
     - 5.2.1 Refractory to or relapsed on at least 1 prior cancer therapy as noted above, and relapsed/refractory on KRAS G12C inhibitor therapy as the most recent cancer therapy prior to study, or
     - 5.2.2 Refractory to or relapsed on at least 1 prior cancer therapy as noted above, and naïve to KRAS G12C inhibitor therapy
6. Phase 1b (Expansion Phase):
   - 6.1 Cohort 2a: (VIC-1911 monotherapy): Locally advanced or metastatic NSCLC refractory to or relapsed on at least 1 prior cancer therapy as noted above, and relapsed/refractory on KRAS G12C inhibitor therapy as the most recent cancer therapy prior to study
   - 6.2 Cohort 2b: (VIC-1911 plus sotorasib): Locally advanced or metastatic NSCLC refractory to or relapsed on at least 1 prior cancer therapy as noted above, and relapsed/refractory on KRAS G12C inhibitor therapy as the most recent cancer therapy prior to study

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6.3 Cohort 2c: (VIC-1911 plus sotorasib): Locally advanced or metastatic NSCLC refractory to or relapsed on at least 1 prior cancer therapy as noted above, and naïve to KRAS G12C inhibitor therapy

7. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
8. Have discontinued previous treatments for cancer, except for sotorasib for subjects to receive VIC-1911 plus sotorasib combination treatment, and have resolution, except where otherwise stated in the inclusion criteria, of all clinically significant toxic effects of prior cancer treatment, surgery, or radiotherapy to Grade ≤ 1
9. Adequate performance status: Eastern Cooperative Oncology Group (ECOG) ≤ 2
10. Life expectancy of ≥ 3 months
11. Subjects with brain metastases:
    - 11.1 KRAS G12C inhibitor naïve: Subjects with clinically stable (i.e., no increase in corticosteroid requirement) asymptomatic brain metastases are allowed without prior local therapy, as long as all lesions are each ≤ 1 cm. Prior local therapy is required (e.g., stereotactic radiosurgery [SRS], stereotactic body radiation therapy [SBRT], or surgery) for any lesion > 1 cm or any lesion that is symptomatic
    - 11.2 KRAS G12C inhibitor pretreated: Subjects with clinically stable (i.e., no increase in corticosteroid requirement) asymptomatic brain metastases following prior local therapy (e.g., SRS, SBRT or surgery) are allowed
12. Adequate hematologic without ongoing transfusion support:
    - 12.1 Hemoglobin (Hb) ≥ 8 g/dL
    - 12.2 Absolute neutrophil count (ANC) ≥ 1.0 x 10^9 cells/L
    - 12.3 Platelets ≥ 75 x 10^9 cells/L
13. Adequate renal and hepatic function:
    - 13.1 Calculated creatinine clearance ≥ 50 mL/minute x 1.73 m^2 per the Cockcroft-Gault formula
    - 13.2 Total bilirubin ≤ 1.5 times the ULN, unless due to Gilbert's disease, or < 3 times the ULN for subjects with liver metastases
    - 13.3 ALT/AST ≤ 2 times the ULN, or < 3 times the ULN for subjects with liver metastases
14. Negative serum pregnancy test within 14 days prior to the first dose of study therapy for women of child-bearing potential (WCBP), defined as a sexually mature woman who has not undergone a hysterectomy or who has not been naturally post-menopausal for at least 24 consecutive months (i.e., who has had menses any time in the preceding 24 consecutive months). Sexually active WCBP and male subjects must agree to use adequate methods to avoid pregnancy (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study and for 28 days after the completion of study treatment.
15. Ability to provide written informed consent

Exclusion Criteria:

1. Serious cardiac condition within the last 6 months, such as uncontrolled arrhythmia, myocardial infarction, unstable angina or heart disease defined by the New York Heart Association (NYHA) Class III or Class IV
2. QT interval corrected for rate (QTc) > 480 msec on the ECG obtained at Screening using Fridericia method for QTc calculation

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3. Medications that are inhibitors or inducers of UDP-glucuronosyltransferases (UGTs) are prohibited in the Dose Escalation Phase
4. History of corneal epithelial cysts or other ocular events leading to blurred vision, or has medically relevant abnormalities identified on screening ophthalmologic examination
5. Symptomatic pneumonitis/interstitial lung disease requiring medical intervention
6. Symptomatic central nervous system metastasis
7. Leptomeningeal carcinomatosis
8. Inability to swallow oral medication
9. Gastrointestinal conditions that could impair absorption or tolerance of study drugs
10. Current hematologic malignancies
11. Second, active primary solid tumor malignancy that, in the judgement of the Investigator or Sponsor Medical Monitor, may affect the interpretation of results, with the exception of carcinoma *in situ* of any origin, non-muscle invasive bladder cancer, and Gleason $\leq$ 3+3 prostate cancer
12. Active infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) requiring treatment within the last week prior to study treatment
13. Other active infection requiring IV antibiotic usage within the last week prior to study treatment
14. Unable to tolerate marketed dose of KRAS G12C inhibitor on prior therapy for subjects to be enrolled in the combination VIC-1911 plus sotorasib treatment cohorts. Alternatively, these subjects may be able to enroll in the VIC-1911 monotherapy treatment cohort, upon discussion with the Medical Monitor and Study Chair.
15. Previous MEK or EGFR inhibitor therapy
16. Any other medical intervention or other condition which, in the opinion of the Principal Investigator, could compromise adherence to study requirements or confound the interpretation of study results
17. Receipt of an investigational product on a clinical trial within 5 elimination half-lives or within 28 days, whichever is shorter, prior to C1D1 on this study, or currently enrolled in a clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study
18. Previously completed or withdrawn from any other study investigating an aurora kinase A inhibitor
19. Known hypersensitivity to VIC-1911 or its components
20. If female, pregnant, breast-feeding, or planning to become pregnant

Criteria for Evaluation:

***Safety*:** Safety will be assessed through the monitoring of AEs, clinical laboratory parameters (hematology, coagulation parameters, serum chemistry, urinalysis), vital sign measurements, electrocardiograms (ECGs), ophthalmologic examinations and physical examinations. AEs will be classified according to the Medical Dictionary for Regulatory Affairs (MedDRA, version 24.0 or higher) and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE, version 5.0 or higher).

***Efficacy*:** Efficacy assessments will be determined on the basis of CT and/or MRI scans with best ORR at protocol-specified time points. DoR, TTR, DCR, PFS, and OS will be determined.

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Pharmacokinetics: Pharmacokinetic determinations of VIC-1911 will be made. Additionally, any identified drug-drug interactions (DDIs) between VIC-1911 and sotorasib will be characterized. ***Pharmacodynamics*****:** The results of ctDNA and tumor biomarker determinations will be correlated with clinical outcome (e.g., objective response, disease progression, resistance development).
Investigational Product, Dosage and Mode of Administration: VIC-1911 is an inhibitor of aurora kinase A (AURA kinase). VIC-1911 is supplied in 10 mg and 25 mg tablets for oral administration. VIC-1911 should be stored at room temperature (15 - 25°C), protected from light. Sotorasib (LUMAKRAS) is commercially available and will be provided by the investigational site.
Reference Therapy: None
Statistical Methods: ***Efficacy Endpoints and Analyses*****:** Response rates (ORR [CR+PR]) and DCR [CR+PR+SD]) will be summarized using number and percentage of subjects with a best response of CR, PR, SD or PD assessed by RECIST v 1.1, along with 2-sided, 95% confidence intervals for the proportions. In subjects refractory to or relapsed on prior KRAS G12C inhibitor therapy, the effect of KRAS G12C *de novo* resistance (prior KRAS G12C inhibitor treatment ≤ 3 months) versus KRAS G12C acquired resistance (prior KRAS G12C inhibitor treatment > 3 months) on clinical outcome will be determined. Determinations of DoR, TTR, PFS and OS will be made using the Kaplan-Meier product- limit method. Subjects who do not have disease response (for TTR) or progression (for PFS, OS) will be censored at the last follow-up time. DoR will be calculated from the date of first response to the date of progression or death. TTR will be calculated from the date of first treatment to the date of first response. PFS will be calculated from the date of first treatment to the date of first evidence of progression or death. OS will be calculated from the date of first treatment to the date of death from any cause; subjects who do not experience death will be censored at the last follow-up time. SAS Version 9.4 for Windows (SAS Institute, Cary, NC) or higher will be used for all analyses. ***Pharmacokinetic Endpoint Analyses*****:** Because plasma concentrations will be determined at a limited number of time points during the study, a complete pharmacokinetic profile of VIC-1911 at each dose level may not be possible. Limited pharmacokinetic analyses will be performed, as VIC-1911 monotherapy and when given in combination with sotorasib. Additionally, any identified DDIs between VIC-1911 and sotorasib will be characterized. ***Pharmacodynamic Endpoint Analyses*****:** Results of ctDNA and tumor biomarker assessment will be summarized and correlated with clinical outcome (e.g., objective response, disease progression, resistance development). ***Safety Endpoints and Analyses*****:** Safety endpoints for AEs include the following: incidences of all treatment-emergent adverse events (TEAEs) and all serious adverse events (SAEs); incidences of TEAEs and SAEs by severity; incidences of TEAEs and SAEs by relationship to study medications; incidences of all Grade 3 and 4 TEAEs and by severity and relationship to study medications; and discontinuation of subjects from the study due to AEs or death. Safety endpoints for AEs, clinical laboratory tests, vital signs, ECGs, ophthalmologic examinations and physical examinations will be specified in the statistical analysis plan. All safety endpoints will be summarized using descriptive statistics.

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and specialist terms are used in this study protocol.

Table 1: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AKT	Protein kinase B
ALT	Alanine transaminase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area under the concentration-time curve (exposure)
AurA	Aurora A
AurB	Aurora B
AurC	Aurora C
BCRP	Breast cancer resistance protein
b.i.d.	Twice daily
BRAF, B-Raf	*BRAF* is the human proto-oncogene that encodes the serine/threonine-protein kinase B-Raf
BUN	Blood urea nitrogen
C	Centigrade
C_{max}	Maximum plasma concentration
CLIA	Clinical Laboratory Improvement Amendments
CR	Complete response
CT	Computed tomography
ctDNA	Circulating tumor DNA
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450
DCR	Disease control rate
DDI	Drug-drug interaction
DLT	Dose limiting toxicity
DoR	Duration of response
ECG	Electrocardiogram

Abbreviation or Specialist Term	Explanation
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ED_{50}	Concentration for 50% effectiveness
EDTA	Ethylenediaminetetraacetic acid
EGFR	Epidermal growth factor receptor
ERK	Extracellular signal-regulated kinase
F	Bioavailability
FAS	Full analysis set
FDA	Food and Drug Administration
GALT	Gut-associated lymphoid tissue
G protein	guanine nucleotide-binding proteins
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GDP	Guanosine diphosphate
GI	Gastrointestinal
GLP	Good Laboratory Practice
GM-CSF	Granulocyte-macrophage colony-stimulating factor
GPT	Guanosine triphosphate
GVHD	Graft versus host disease
Hb	Hemoglobin
HBV	Hepatitis B virus
HCG	Human chorionic gonadotropin
HCV	Hepatitis C virus
HDPE	High density polypropylene
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HSCT	Hematopoietic stem cell transplantation
HRAS	Harvey RAS
IC_{50}	Concentration for 50% maximal inhibition
ICD	Informed consent document

Abbreviation or Specialist Term	Explanation
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
ILD	Interstitial lung disease
IND	Investigational New Drug
IOP	Intraocular pressure
IV	Intravenous
IRB	Institutional Review Board
Kg	Kilogram
K_i	Inhibition constant
K_{inact}	Rate of inactivation
K_m	Binding affinity or Michaelis-Menten constant
KRAS	Kirsten RAS
L	Liter
LDH	Lactate dehydrogenase
LFT	Liver function test
LOF	Loss of function
MDR1	Multidrug resistance protein 1
MedDRA	Medical Dictionary for Regulatory Activities
MEK	Mitogen-activated protein kinase kinase
Mg	Milligram
mL	Milliliter
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTORC1	Mammalian target of rapamycin complex 1
NCI	National Cancer Institute
nM	Nanomolar
NOAEL	No adverse effect level
NRAS	Neuroblastoma rat sarcoma
NSCLC	Non-small cell lung cancer
NYHA	New York Heart Association
OCT	Optical coherence tomography

Abbreviation or Specialist Term	Explanation
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death protein 1
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
P-gp	P-glycoprotein
pHH3	Phospho-histone H3
PI	Principal Investigator
PI3K	Phosphoinositide 3-kinase
PK	Pharmacokinetic
PO	Per os (oral)
PPS	Per protocol set
PR	Partial response
PT (INR)	Prothrombin time (international normalized ratio)
PTX	Paclitaxel
q.d.	Once daily
q.o.d.	Every other day
QTc	QT interval corrected for rate
RAF	Rapidly accelerated fibrosarcoma
RAL/RALGDS	Ras-like/Ral guanine nucleotide dissociation stimulator
RAS	Rat sarcoma
RASA1	Gene encoding RAS-GAP activating protein
RAS-GAP	*RAS* oncogene GTP-ase activating protein
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RET	Ret proto-oncogene
ROS	Proto-oncogene encoding receptor tyrosine kinase protein
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event

Abbreviation or Specialist Term	Explanation
SCLC	Small cell lung cancer
SD	Stable disease
SRC	Safety Review Committee
STD_{10}	Severely toxic dose in 10% of animals
$T_{1/2}$	Half-life
T_{max}	Time to maximum plasma concentration
T/C	Tumor growth inhibition ratio
TEAE	Treatment-emergent adverse event
TGD	Tumor growth delay
TK	Toxicokinetic
TRKA	Tropomyosin receptor kinase A
TRKB	Tropomyosin receptor kinase B
TRKC	Tropomyosin receptor kinase C
UGT	Uridine 5'-diphospho (UDP)-glucuronosyltranferase
ULN	Upper limit of normal
V_d	Volume of distribution
WCBP	Woman of child-bearing potential

3. INTRODUCTION

3.1. VIC-1911 Summary

VIC-1911 is a novel, selective, and orally active small molecular inhibitor of Aurora A (AurA) kinase under development for the treatment of solid tumors, hematologic malignancies and the prevention of acute graft versus host disease (GVHD) following hematopoietic stem cell transplantation (HSCT). AurA kinase, a key regulator in mitotic cell division, is associated with spindle assembly checkpoint and regulation of the transition from G2 to M phase.[1] AurA gene amplification and/or overexpression are reported in various tumor types, including breast, lung, gastro-esophageal, bladder, ovary, prostate, pancreas and hematologic malignancies.[2,3,4,5] Overexpression of AurA kinase also is associated with disease progression and survival in various cancers.[6,7,8,9] Elevated levels of AurA kinase are reported to override the mitotic spindle checkpoint activated by treatment with chemotherapeutic agents like taxanes, and are linked to taxane resistance.[10,11]

VIC-1911 has demonstrated activity in nonclinical studies at concentrations and doses which have been shown to selectively inhibit AurA, a pharmacokinetic profile supportive of twice daily administration with either a daily b.i.d. continuous 28-day cycle or a Day 1-4, 8-11, 15-18 b.i.d. intermittent 28-day cycle. An acceptable safety profile was demonstrated in nonclinical (both continuous and intermittent regimens) and clinical studies (intermittent regimen), including combination treatment with paclitaxel and docetaxel. Additional information is found in the VIC-1911 Investigator's Brochure.[12]

3.1.1. Preclinical Pharmacology

3.1.1.1. *In Vitro*

VIC-1911 selectively inhibited human recombinant AurA kinase (half maximal inhibitory concentration [IC_{50}] 1.04 nM) versus Aurora B (AurB) kinase (IC_{50} 95 nM) or Aurora C (AurC) kinase (IC_{50} 36.5 nM), with 91- and 35-fold higher selectively, respectively, for AurA (Table 2).

Table 2: VIC-1911 IC_{50} Values Against Aurora Kinases A, B and C

Aurora Kinase	AurA*	AurB	AurC
IC_{50} (nM)	1.04 ± 0.09	95 ± 11	36.5 ± 6.2

VIC-1911 inhibited AurA kinase autophosphorylation in cervical cancer HeLa (IC_{50}: 13.9 nM) and non-small cell cancer (NSCLC) NCI-H460 cells (IC_{50}:13.7 nM) showing selectivity for AurA over AurB of > 720-fold in HeLa cells and > 730-fold in NCI-H460 cells (Table 3).

Table 3: VIC-1911 IC_{50}s for AurA Kinase and AurB Kinase in HeLa and NCI- H460 Cells

Cell Line	IC_{50} (pAurA)	IC_{50} (pAurB)	Ratio*
HeLa	13.9	>10000	>720
NCI-H460	13.7	>10000	>730

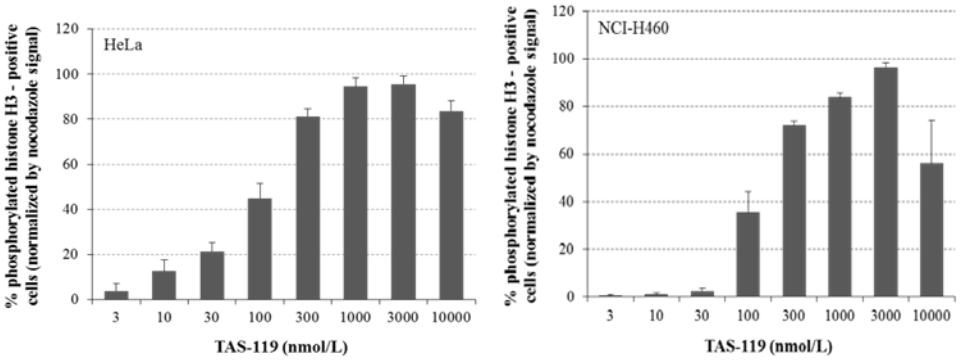
*Ratio of the IC_{50} (i.e., IC_{50} AurB / IC_{50} AurA)

VIC-1911 showed no significant inhibition against a panel of 301 other human protein kinases except for recombinant human Ret proto-oncogene (RET) (S891A) (IC_{50} 25.8 nM), proto-oncogene tyrosine protein kinase ROS (ROS) (IC_{50} 29.3 nM), tropomyosin receptor kinase A (TRKA) (IC_{50} 1.46 nM), tropomyosin receptor kinase B (TRKB) (IC_{50} 1.53 nM) and tropomyosin receptor kinase C (TRKC) (IC_{50} 1.47 nM).

Incubation of both HeLa and NCI-H460 cells with VIC-1911 dose-dependently increased the number of phosphorylated histone H3 (pHH3)-positive cells (a selective marker of AurA inhibition) with ED_{50} values of 105.8 and 132.1 nM, in HeLa and H460 cells, respectively (Figure 1). VIC-1911 also induced the accumulation of pHH3-positive cells in both OCUM- 2M and MDA-MB-231 cells (data not shown).

Figure 1: Accumulation of Phospho-histone H3 in VIC-1911 (TAS-119) Treated HeLa Cells (A) and NCI-H460 cells (B)

(A) **(B)**



In a 240 human tumor cell line study, VIC-1911 inhibited cell growth, with most potency (IC_{50}) demonstrated against lung NCI-H69 (14 nM), neuroblastoma IMR-32 (14 nM) and colon SW48 (18.9 nM). Among the 10 most sensitive cell lines, 4 possessed *MYC* amplification (*N- myc* or *c-myc*) and 4 other cell lines showed *CTNNB1* (*β-catenin*) mutation (Table 4).

Table 4:VIC-1911 Cell Line Sensitivity: Gene Abnormality Status of *MYC* Amplification and *CTNNB1* Mutation

Rank Order	Cell line	IC_{50} (µmol/L)	*CTNNB1*	*MYC*	Tumor Type
1	NCI-H69	0.014	wt	*N-myc* amp	Lung
2	IMR-32	0.014	wt	*N-myc* amp	Neuroblastoma
3	SW48	0.0189	mut	wt	Colon
4	AGS	0.0204	mut	wt	Stomach
5	CHP-212	0.0262	wt	*N-myc* amp	Neuroblastoma
6	HCT-116	0.0265	mut	wt	Colon
7	SW-13	0.0269	wt	wt	Endocrine
8	MC-IXC	0.0274	wt	*c-myc* amp	Neuroblastoma
9	CRO-AP2	0.0287	wt	wt	Hematopoietic
10	A427	0.0291	mut	wt	Lung
11	MDA MB 453	0.0304	wt	wt	Breast
12	KPL-1	0.0327	wt	wt	Breast
13	CEM-C1	0.0337	unknown	unknown	Hematopoietic
14	SR	0.0343	wt	wt	Hematopoietic
15	Daoy	0.0349	wt	wt	CNS
16	G-401	0.0363	wt	wt	Kidney
17	BeWo	0.0378	unknown	unknown	Placenta
18	CAMA-1	0.0384	wt	wt	Breast
19	KHOS-240S	0.0396	unknown	unknown	Soft Tissue
20	NCI-H520	0.0432	wt	*L-myc* amp	Lung

VIC-1911 exhibited nM potency against an additional 12 human cancer cell lines, 9 with Rb LOF mutation, reported to be more sensitive to AurA kinase inhibition. Specific AurA kinase inhibitors VIC-1911 and LY3295668 showed similar potency against all cell lines tested, different from AurB kinase inhibitor, barasertib, and AurA kinase selective inhibitor, alisertib (Table 5).

Table 5: VIC-1911 IC_{50}s in Human Cancer Cell Lines vs. Other Aurora Kinase Inhibitors

Cell Line	Tumor Type	Compound (IC_{50}. nM)				
		Control	Barasertib[a]	Alisertib[b]	LY3295668[c]	VIC-1911[c]
NCI-H524	SCLC	447	2.7	9.6	19.8	6.1
DU-4475	Breast	15.7	21.3	13.9	86.1	39.4
NCI-H446	SCLC	10,000	8.7	1.5	12.1	3.8
NCI-H82	SCLC	1858	1.2	2.6	17.9	24.8
U-266	Plasma cell myeloma	354	10,000	8.2	44.7	26.1
NCI-H69	SCLC	1535	19.1	6.6	16.1	5.3
NCI-H1734	NSCLC	242	224	15.1	45.5	61.8
SW48	Large Intestine	14.0	2.3	0.3	6.3	3.6
HCT-116	Large Intestine	63.0	10,000	0.4	8.3	26.7
MDA-MB468	Breast (TNBC)	34.8	5,531	0.8	7.9	7.0
MDA-MB231	Breast (TNBC)	164	3964	1953	23.2	26.8

NSCLC = non-small cell lung cancer
SCLC = small cell lung cancer
TNBC = triple negative breast cancer
[a] AurB kinase inhibitor
[b] Selective AurA kinase inhibitor
[c] Specific AurA kinase inhibitor

VIC-1911 enhanced the antiproliferative effect in osimertinib-acquired resistant cells, and VIC-1911 plus osimertinib treatment enhanced the magnitude of the response in osimertinib-resistant cells (Table 6).

Table 6: IC_{50}s (nM) for VIC-1911 and Osimertinib Against Osimertinib-Resistant NSCLC Human Cancer Cell Lines

	IC_{50} (nM)			
Drug	**NCI-H1975**	**NCI-1975-OR**	**HCC827**	**HCC827-OR**
VIC-1911	38	81	192	219
Osimertinib	7	2589	5.8	5097

OR = Osimertinib-resistant

Combination VIC-1911 and sotorasib demonstrated synergy in *KRAS G12C*-mutated NSCLC cell lines with intrinsic and acquired sotorasib resistance (Figure 2 and Figure 3).[13]

Figure 2: Activity of VIC-1911 Plus Sotorasib Against Intrinsic Resistance to *KRAS G12C*-Mutant NSCLC Human Cell Lines

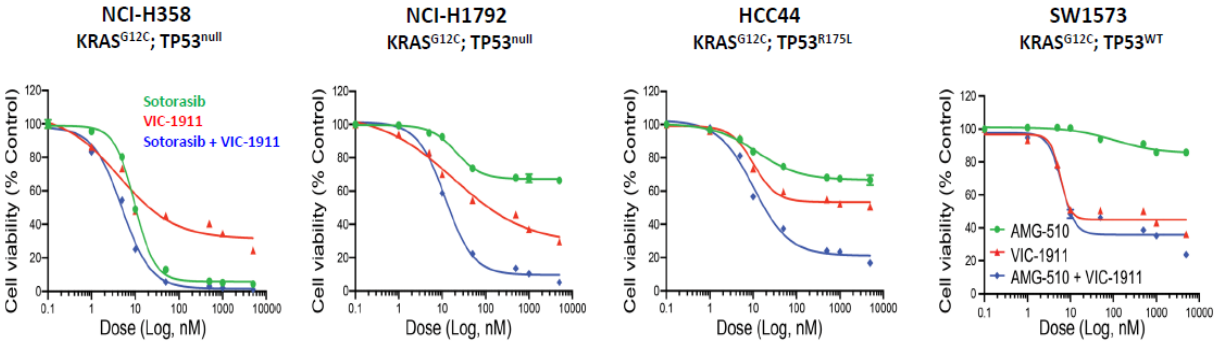
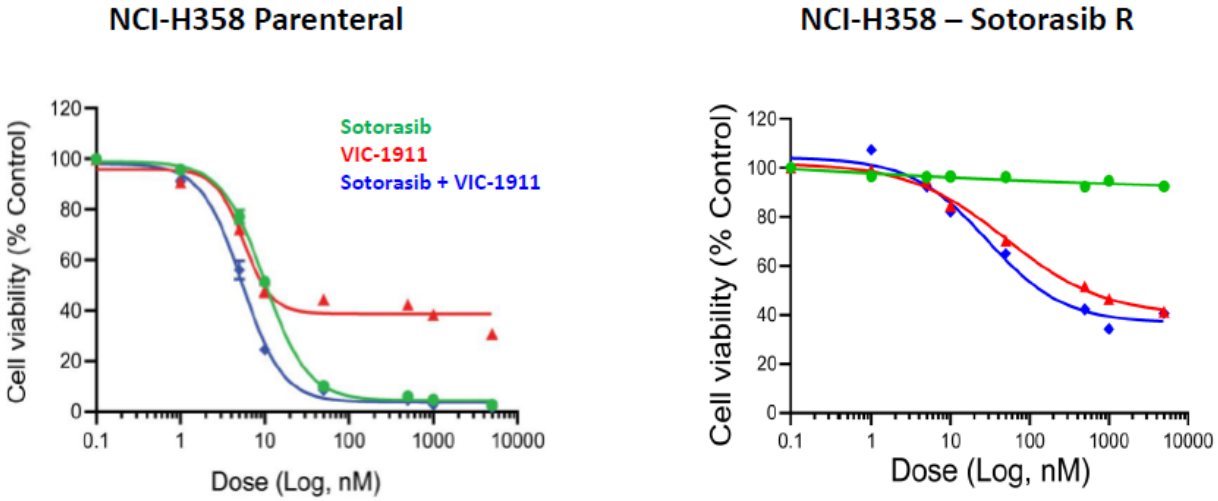


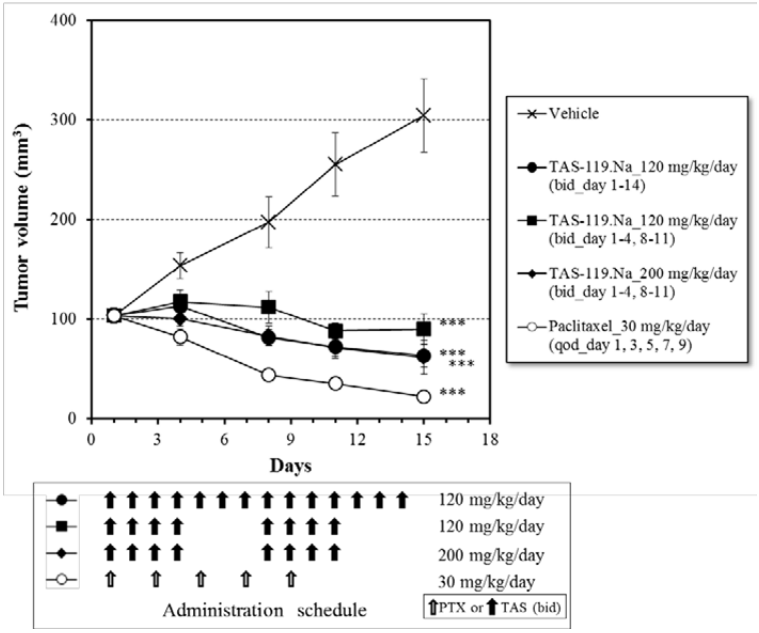
Figure 3: Activity of VIC-1911 Plus Sotorasib Against Acquired Resistance to KRAS *G12-C*-Mutant NSCLC Human Cell Line NCI-H358



3.1.1.2. *In Vivo*

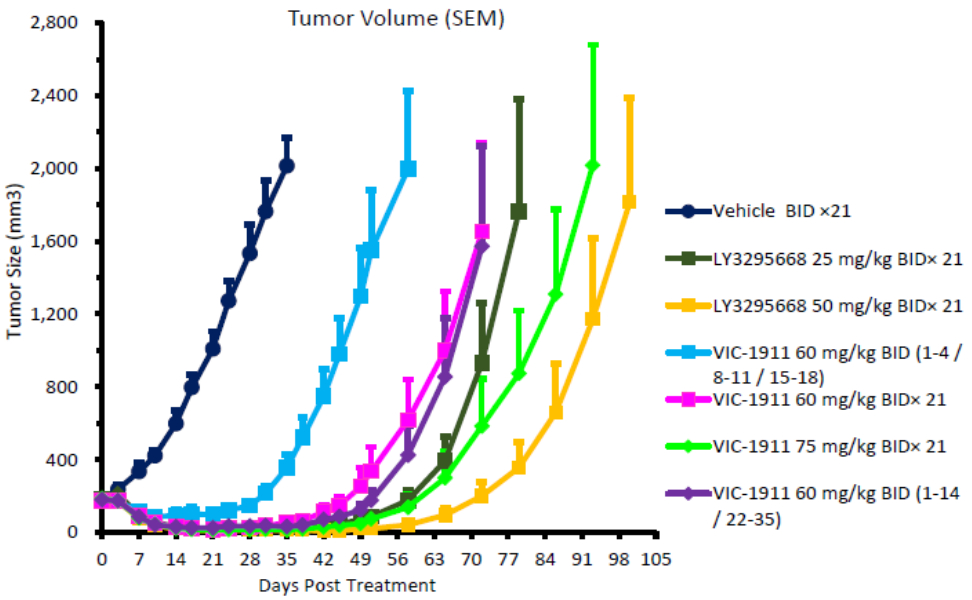
In athymic nude mice bearing human NSCLC *KRAS*-mutant A427 cell line xenografts, VIC-1911 (100 mg/kg PO, b.i.d. x 4 days starting on D1 and D8) demonstrated maximum tumor growth delay (TGD) and overall survival benefit ($p<0.006$) vs. lower doses of 60 mg/kg PO, b.i.d. continuously for 14 days and 60 mg/kg p.o, b.i.d. x 4 days starting on D1 and D8. Evaluation of maximum tumor volume at D15 showed VIC-1911 (60 mg/kg PO, b.i.d x 14 days) significantly reduced tumor volume versus vehicle control (T/C; 21%) ($p<0.01$). VIC-1911 (60 mg/kg and 100 mg/kg) administered intermittently (cycled PO, b.i.d. x 4 days) was also efficacious with T/C; 30% and 20% respectively ($p<0.001$). Positive control paclitaxel (PTX) (30 mg/kg IV, every other day [q.o.d.] x5), was efficacious, resulting in maximum TGD, 100% regression and a significant survival benefit compared to vehicle control ($p<0.001$) (Figure 4).

Figure 4: Anti-tumor Efficacy of VIC-1911 (formerly TAS-119.Na) Against A427 Human Lung Carcinoma Xenografts in a Nude Mouse Model



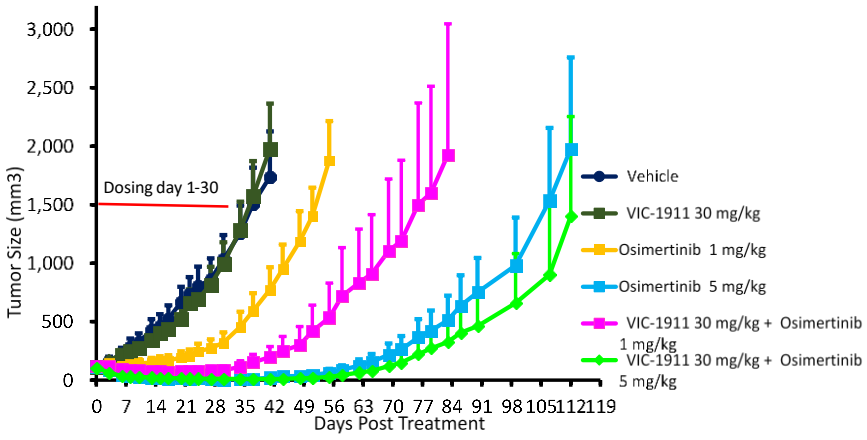
The growth of small cell lung cancer (SCLC) NCI-H69 lung cancer xenografts was inhibited by treatment with AurA kinase inhibitors LY3295668 or VIC-1911. Continuous dosing of VIC-1911 demonstrated more potent anti-tumor effect, with further reduction in tumor volume and longer time to tumor regrowth compared to the intermittent VIC-1911 dosing ($p<0.0001$ for all VIC-1911 and LY3295668 dose groups versus vehicle control) (Figure 5).

Figure 5: Anti-tumor Efficacy of VIC-1911 or LY3295668 Against NCI-H69 Human SCLC in a Nude Mouse Xenograft Model



In athymic nude mice bearing NSCLC NCI-H1975 osimertinib-resistant xenografts with VIC-1911 (30 mg/kg b.i.d.) plus osimertinib (1 or 5 mg/kg q.d.) daily for 30 days demonstrated more potent antitumor effects and kept the tumors from regrowth for longer duration than VIC-1911 or osimertinib treatment alone ($p<0.001$) (Figure 6).

Figure 6: Anti-tumor Efficacy of VIC-1911 Plus Osimertinib Against NCI-H1975-OR Human NSCLC in a Nude Mouse Xenograft Model



VITRAC in-house preclinical studies demonstrated synergy with VIC-1911 and sotorasib on a continuous dosing schedule compared with their respective monotherapies in *KRAS G12C*-mutated NSCLC xenograft models, NCI-H358 (Figure 7).[14] VIC-1911 also demonstrated synergy with sotorasib on a continuous dosing schedule in a *KRAS G12C*-mutant patient-derived xenograft

(PDX) model (LU-01-0030) (Figure 8).[15] These findings suggest that combination VIC-1911 and sotorasib may be more active than sotorasib and VIC-1911 alone in *KRAS G12C*-mutated NSCLC that is naïve to G12C inhibitors.

Figure 7: Synergistic Activity of VIC-1911 and Sotorasib Combination Treatment in *KRAS G12C*-Mutant Human Cell Line NCI-H358

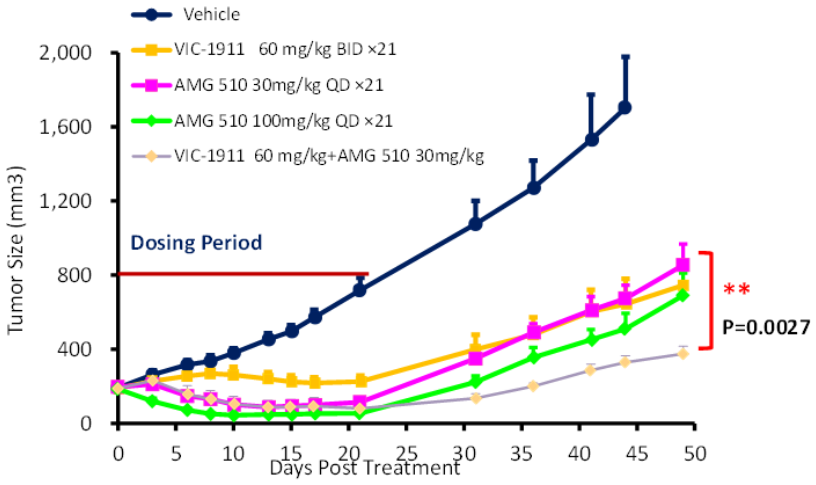
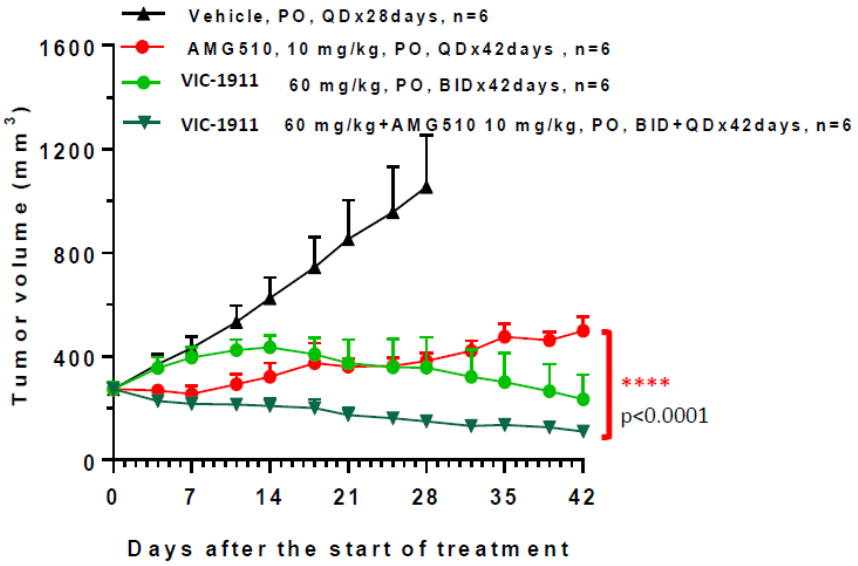


Figure 8: Synergistic Activity of VIC-1911 and Sotorasib Combination Treatment in NSCLC KRAS G12C-Mutant PDX Xenograft Model



Safety pharmacology core battery studies showed that VIC-1911 had little to no effect on behavioral or physiological functions. Repeat daily dosing of VIC-1911 had no effect on cardiovascular function.

3.1.2. Preclinical Pharmacokinetics

Nonclinical pharmacokinetic (PK) profiles of VIC-1911 have been characterized in rats and dogs in single-dose and repeat-dose studies after IV and p.o. administrations. Absorption of VIC-1911 after oral dosing occurred rapidly in all species studied at doses up to 112 mg/kg b.i.d. with time to maximum plasma concentration (T_{max}) 0.5 – 4.0 hours post-dose in rat and dog.

Following repeat oral administration of VIC-1911 to the rat over the dose range 21-84 mg/kg/b.i.d. for durations up to 3 weeks (cyclical dosing, with 4 days dosing and 3 days off dosing per week), mean exposure to VIC-1911 was broadly dose proportional or greater than dose proportional (particularly at higher doses). VIC-1911 was rapidly absorbed after oral dosing to rats, and maximum concentrations (C_{max}) was 0.5 – 1.0 hours post-dose (T_{max}).

Following a single oral gavage administration of VIC-1911 to dogs over the dose range 28-112 mg/kg, rapid drug absorption was seen at all dose levels, however, there was no obvious trend in increased exposure with increasing dose level. For example, dogs given a single dose at 42 mg/kg had plasma exposure substantially higher than those dosed at 56 mg/kg. b.i.d. Following repeated cyclical dosing, with 4 days dosing and 3 days off dosing per week, or 28-42 mg/kg b.i.d. (continuous dosing) for durations up to 3 weeks, exposure was, in general, of the same order of magnitude compared with that following a single administration. Exposures in males and females were broadly similar after gavage dosing, although individual variability was observed. There was little evidence of accumulation of VIC-1911 with repeated administration.

In vitro investigations indicated that VIC-1911 is highly bound to plasma proteins in rat (98%), dog (94%) and human (99.4%). There was no evidence of saturation of protein binding over the concentration range 1-20 μM in plasma from all species andhuman plasma fractions. VIC-1911 had low distribution to human blood cells *in vitro*.

In vitro studies indicated that VIC-1911 is a substrate of human multidrug resistance protein 1 (MDR1), but not breast cancer resistance protein (BCRP), and is not an inhibitor of either transporter. In addition, VIC-1911 is a substrate of OATP1B1 andOATP1B3, but not of OCT1. The K_m of VIC-1911 for OATP1B1 is 0.6 μmol/L. The OATP1B1-mediated uptake of VIC-1911 was inhibited by PTX and DTX. Although VIC-1911 inhibited the OATP1B1 and OATP1B3-mediated transport of PTX and DTX, the impact of VIC-1911 on plasma levels of PTX and DTX was predicted to be low due to their high passive membrane permeability.

In vitro incubations of VIC-1911 in human, rat and dog hepatocytes indicated a single major metabolite in all three species. Analysis of this component characterized it as the acyl glucuronide of VIC-1911.

After oral dosing of radiolabeled VIC-1911 to rats, drug-related radioactivity was excreted primarily in the feces with 97.4% of the dose recovered by 72 hours, with < 1% recovered in urine. No quantifiable radioactivity was detected by 72 hours after dosing. In bile duct-cannulated rats, 57.6% of administered radioactivity was excreted in bile after oral dosing.

In vitro studies with human liver microsomes have shown that VIC-1911 has the potential to inhibit CYPP2C8 (IC_{50} = 25 μM) and CP3A4/5 (IC_{50} = 180 μM) including metabolism-dependent inhibition (CYP2C8 IC_{50} = 14 μM; CYP3A4/5 (IC_{50} = 72 μM). Human hepatocyte studies demonstrated VIC-1911 has induction potential for CYP3A4 at a concentration of 10 μM.

3.1.3. Preclinical Toxicology

AurA kinase regulates the correct development of the various phases of mitosis, and in humans is expressed at detectable levels in all somatic cells undergoing mitotic cell division. VIC-1911 acts to reduce or block AurA kinase activity and therefore prevent normal cell cycling at mitosis. Aberrations of the mitotic processes make it possible for apoptosis or single cell necrosis to occur. The treatment-related histopathological findings observed in these studies (widespread lymphoid atrophy and epithelial cell degeneration/regeneration) could therefore be directly or indirectly associated with the pharmacological effects of VIC-1911 in disruption of the mitotic process.

In the rat, following VIC-1911 cyclical dosing (4 days on followed by 3 days off) for 3 cycles, or daily b.i.d. dosing for 21 days continuously, the severely toxic dose in 10% of the animals (STD_{10}) was 63 mg/kg b.i.d. Major findings included body weight loss, reduced food consumption, reduction in hemoglobin, red blood cell (RBC) counts, packed cell volume and reticulocytes, elevated liver enzymes, total bilirubin and decreased albumin, degeneration and regeneration or hyperplasia of epithelial tissue (liver, eye, skin, tongue, esophagus, pancreas, parotid salivary gland, GI tract, adrenal, kidney, lung and heart), atrophy of lymphoid and/or hemopoietic tissues (bone marrow, spleen, thymus, GALT/Peyer's patch, mesenteric and popliteal lymph nodes) and generally atrophic findings in reproductive tissues (testis, epididymis, seminal vesicle, prostate, ovary and uterus). These findings showed evidence of reversibility during the 2-week recovery period.

In the dog, following VIC-1911 cyclical dosing (4 days on followed by 3 days off) for 3 cycles, or daily b.i.d. dosing for 21 days continuously, the highest non-severely toxic dose (HNSTD) was > 84 mg/kg b.i.d. Major findings included vomiting, diarrhea, decreased food consumption, body weight loss, elevated liver enzymes, total bilirubin, widespread lymphoid atrophy, scattered individual epithelial cell degeneration/regeneration in a range of tissues, mucosal atrophy/inflammation in the gut and pyloric gastritis, bile duct hyperplasia/inflammation in liver and gall bladder inflammation, right atrial epicarditis and myocarditis, pulmonary alveolitis and minor metaphyseal congestion/trabecular atrophy in bone. These findings showed evidence of reversibility during the 2-week recovery period.

The no adverse effect level (NOAEL) in rat and dog was 21 and 28 mg/kg b.i.d., respectively.

VIC-1911 was not phototoxic. No genotoxicity or specific reproductive or developmental toxicology studies have been conducted.

3.2. Rationale for Targeting RAS Mutations in NSCLC

Lung cancer is the leading cause of cancer death in the United States.[16] In the US, 228,820 new cases and 135,720 deaths were projected for lung cancer in 2020.[16]

Rat Sarcoma (*RAS*) is the most commonly mutated gene in human malignancies, including NSCLC.[17,18] RAS genes encode a family of small, membrane-bound, guanine nucleotide-binding proteins (G proteins), including Kirsten RAS (KRAS), neuroblastoma RAS (NRAS), and Harvey RAS (HRAS). *KRAS* mutation is the most common RAS gene mutation, accounting for approximately 80% of *RAS* mutations.[19] RAS proteins are binary switches that cycle between an active guanosine triphosphate (GTP)-bound conformation and an inactive guanosine diphosphate (GDP)-bound conformation.[17] GTP-bound RAS activates multiple downstream effector protein

pathways, including rapidly accelerated fibrosarcoma/ mitogen-activated protein kinase kinase/extracellular signal-regulated kinase (RAF/MEK/ERK), phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin complex 1 (PI3K/AKT/mTORC1), and Ras-like/Ral guanine nucleotide dissociation stimulator (RAL/RALGDS). *RAS* mutations stabilize or "lock in" the active, GTP-bound mutant protein. These constitutively active GTP-bound mutant RAS proteins continuously activate downstream signaling and lead to uncontrolled cell proliferation and survival. As a result, *RAS* mutations are oncogenic drivers. *KRAS* gene mutations can occur at codon 12 due to a single point mutation with a glycine-to-cysteine substitution (*KRAS G12C*). In Western populations, approximately one-quarter to one-third of patients with NSCLC have a *KRAS* mutation.[17] *KRAS G12C* mutations occur in 12%-16% of patients with NSCLC (approximately 40% of all *KRAS* mutations).[17,18] NSCLC with *KRAS G12C* mutations represents diseases with a poor prognosis.[17,20,21]

Recently, a new class of KRAS G12C small molecule kinase inhibitors have been successfully developed.[20,22] Sotorasib is the most advanced of these KRAS G12C inhibitors. Sotorasib is a highly selective, irreversible, oral inhibitor composed of a pyridine ring with two conformations that produce up to 25 covalent interactions with cysteine 12 in the KRAS G12C mutant protein.[17,20,22] Sotorasib inhibition occurs by irreversibly locking the KRAS G12C protein in its inactive GDP-bound state, thus preventing its oncogenic activity. In preclinical studies, sotorasib inhibited KRAS signaling and impaired viability of KRAS G12C-mutated cell lines.

Sotorasib received FDA accelerated approval in May 2021[23] based on results of the single-group, open-label, phase 2 CodeBreaK100 trial.[24] In this trial, sotorasib was administered at a dose of 960 mg orally once daily in 124 evaluable patients with *KRAS G12C*-mutated, locally advanced or metastatic NSCLC with disease progression after receiving standard first-line therapy. The majority (81%) of patients had previously received both platinum-based chemotherapy and inhibitors of programmed death 1 (PD-1) or programmed death ligand 1 (PD-L1). The objective response rate was 37%, the median duration of response 11.1 months, the median progression-free survival 6.8 months, and the median overall survival 12.5 months. The most common adverse events (occurring in ≥ 20% of patients) were diarrhea, nausea, fatigue, arthralgia, and increases in aspartate or alanine aminotransferase levels. Sotorasib is now FDA indicated for the treatment of adult patients with *KRAS G12C*-mutated locally advanced or metastatic non-small cell lung cancer, as determined by an FDA-approved test, who have received at least one prior systemic therapy. This indication was obtained under accelerated approval based on ORR and DOR.[23]

While sotorasib monotherapy has been rightfully heralded as a significant breakthrough with an objective response rate of 37%, still nearly two-thirds of patients have intrinsic resistance to sotorasib and most responding patients will develop acquired resistance after approximately 12 months.[18] Thus, new therapeutic strategies are required to overcome intrinsic/*de novo* and acquired resistance to sotorasib.[17]

3.3. Rationale for Targeting AURA Kinase in NSCLC

AURA kinase is a key mitotic cell cycle regulator and is associated with spindle assembly checkpoint and regulation of the transition from G2 to M phase.[1] *AURA* kinase gene amplification and/or overexpression are reported in multiple tumor types, including NSCLC.[2,4] AURA kinase has been shown to be a mediator of intrinsic and acquired resistance to KRAS G12C inhibitors,

such as sotorasib, in *G12C*-mutated NSCLC.[13,17,24,25] Augmented upstream AURA kinase signaling maintains or stabilizes the mutant KRAS G12C protein in an inhibitor-insensitive state, possibly by AURA kinase complexing with the mutant KRAS G12C protein. This complex then facilitates the interaction between mutated KRAS G12C protein and downstream CRAF protein.[25] This interaction induces cell-cycle progression and cell proliferation. Therefore, AURA kinase inhibition may disrupt these interactions between AURA kinase, mutant KRAS G12C and CRAF.[19]

Preclinical studies have evaluated the impact of AURA kinase inhibition on intrinsic and acquired resistance to KRAS G12C inhibitors, such as sotorasib.[13,25] AURA kinase expression was found to be increased in *KRAS G12C*-mutated NSCLC cells resistant to G12C inhibitors, including sotorasib.[13,25] Combination AURA kinase and KRAS G12C inhibitors showed synergistic *in vitro* antiproliferative and *in vivo* antitumor effects in *KRAS G12C*-mutant models with acquired resistance to the G12C inhibitor.[25] This confirmed the dependence of KRAS G12C inhibitor acquired resistance on AURA kinase and suggested that the addition of AURA kinase inhibition could overcome acquired resistance to G12C inhibition.

As noted above, VIC-1911 is a highly selective, small molecular inhibitor of AURA kinase. AURA kinase inhibition with VIC-1911 demonstrated monotherapy activity in *KRAS G12C*-mutated human NSCLC cells with intrinsic and acquired resistance to the G12C inhibitor sotorasib, and combination VIC-1911 and sotorasib showed synergy in *KRAS G12C*-mutated NSCLC cell lines with intrinsic and acquired sotorasib resistance (Figure 2 and

Figure 3).[13] Interestingly, NSCLC cells with intrinsic resistance to sotorasib showed the most profound synergistic effects with the combination of VIC-1911 and sotorasib. These findings suggested that 1) AURA kinase activation led to both intrinsic and acquired resistance to sotorasib in *KRAS G12C*-mutated NSCLC and 2) the addition of VIC-1911 AURA kinase inhibition with sotorasib may be a potential therapeutic approach for intrinsic and acquired resistance to sotorasib.

Additionally, VITRAC in-house preclinical studies showed synergy with VIC-1911 and sotorasib compared with their respective monotherapies in *KRAS G12C*-mutated NSCLC xenograft models, NCI-H358 (Figure 7) and in a *KRAS G12C*-mutated PDX) model (LU-01-0030) (Figure 8).[15] These findings suggest that combination VIC-1911 and sotorasib may be more active than sotorasib alone in *KRAS G12C*-mutated NSCLC that is naïve to G12C inhibitors.

New therapeutic strategies are needed to overcome intrinsic and acquired sotorasib (KRAS G12C inhibitor) resistance, especially due to increased AURA kinase activity.[13,17,25,26] Preclinical mechanistic and therapeutic studies suggest that the combination of VIC-1911 AURA kinase inhibition and sotorasib KRAS G12C inhibition may be a promising therapeutic approach in sotorasib resistant KRAS G12C mutated NSCLC.[13,25] This combination may potentially overcome or delay sotorasib primary resistance and overcome sotorasib acquired resistance. In addition, preclinical studies suggest that VIC-1911 monotherapy may be a potential therapeutic approach in sotorasib resistant NSCLC and could be compared with the combination of VIC-1911 and sotorasib.[13] Finally, preclinical synergy results support the combination of VIC-1911 AURA kinase inhibition and sotorasib KRAS G12C inhibition in sotorasib (G12C inhibitor) naive *KRAS G12C*-mutated NSCLC.[13,25] This combination may potentially provide superior results to sotorasib alone based on these studies. This provides sufficient rationale to evaluate VIC-1911 monotherapy

and combination VIC-1911 plus sotorasib in patients with sotorasib intrinsic and acquired resistance and combination VIC-1911 plus sotorasib in *KRAS G12C*-mutated NSCLC naïve to sotorasib (KRAS G12C inhibitor) therapy, as proposed in this Phase 1a/1b study.

3.4. Possible Risks and Side Effects

3.4.1. VIC-1911 Monotherapy Phase 1 Study in Advanced Solid Tumors

A Phase 1, open-label, non-randomized, dose-escalation study of VIC-1911 was conducted evaluating the safety, tolerability, PK, pharmacodynamics, pharmacogenomics and preliminary anti-tumor activity in patients with advanced, unresectable solid tumors.[27] The study consisted of two phases, a Dose Escalation Phase to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of VIC-1911 given orally (PO) b.i.d., and an Expansion Phase, with VIC-1911 at the RP2D. In the Dose Escalation Phase, VIC-1911 doses were administered PO b.i.d. Days 1 – 4, 8 – 11 and 15 – 18 of a 28-day cycle in DL1, 2, 2.1, 2.2 and 3. In an expanded DL 2.1 (200 mg b.i.d.), doses were administered PO b.i.d. Days 1 – 4, 8 – 11, 15 – 18 and 22 – 25 of a 28-day cycle (DL 2.1 continuous).

A total of 74 patients were enrolled and treated in the study, 34 patients in the Dose Escalation portion and 40 patients in the Expansion portion. In the Dose Escalation Phase, the MTD was determined to be DL 2.2 (250 mg b.i.d.) and the RP2D was established at 200 mg b.i.d. administered on Days 1-4, 8-11 and 15-18 of a 28-day cycle. The Expansion portion included 10 patients with SCLC, 9 patients with breast cancer, 13 patients with a *MYC*-amp/*B-cat* mutation, and 8 patients with other tumor types. All Expansion Phase patients received VIC-1911 at the RP2D of 200 mg PO b.i.d. Days 1 – 4, 8 – 11 and 15 – 18 of a 28-day cycle.

In the Dose Escalation Phase, no patient had a confirmed complete response (CR) or a confirmed partial response (PR). A total of 14 (41.2%) patients had SD: 6 patients in DL 2 (150 mg b.i.d.), 4 patients in DL 2.1 (200 mg b.i.d.), and 4 patients in DL 2.1 continuous (200 mg b.i.d. continuous). One patient in DL 2 (150 mg b.i.d.) had an unconfirmed PR.

In the Expansion Phase, no patients had a confirmed CR or PR. A total of 14 (35.0%) patients had SD: 5 patients with SCLC, 1 patient with breast cancer, 5 patients with *MYC*-amp/*B- cat* mutation, and 3 patients with other solid tumors (2 patients with mesothelioma and 1 patient with colon cancer. The target ORR of ≥ 20% for each specific indication (or ≥ 10% for patients who were *MYC*+) for any indication was not met. Therefore, the study was discontinued.

VIC-1911 mean maximum observed plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increased with increasing dose in a dose proportional manner.

The rate of phospho-histone H3 (pHH3) positive cells to total cells in paired skin samples was assessed. The mean pHH3 positive rate increased after VIC-1911 administration, thus confirming the mechanism of action of AurA kinase inhibition, with cell cycle arrest in mitotic assembly.

In the Dose Escalation Phase, the most frequently reported treatment emergent adverse events (TEAEs) were fatigue (52.9%), diarrhea (41.2%), cough (29.4%), dyspnea (26.5%), and decreased appetite (26.5%). The most frequently reported TEAEs considered to be treatment-related were fatigue (32.4%), diarrhea (23.5%), nausea (14.7%), corneal epithelial microcysts (14.7%), vomiting (11.8%), vision blurred (11.8%), and decreased appetite (11.8%).

In the Expansion Phase, the most frequently reported TEAEs were diarrhea (45.0%), fatigue (35.0 %), nausea (30.0%), ALT increased (25.0%), anemia (35.0%), and decreased appetite (32.5%). The most frequently reported TEAEs considered to be treatment-related were diarrhea (32.5%), decreased appetite (17.5%), ALT increased (15.0%), AST increased (15.0%), vision blurred (15.0%), anemia (15.0%), fatigue (15.0 %), nausea (12.5%), lipase increased (12.5%), and vomiting (12.5%).

In the Dose Escalation Phase, the most frequently reported Grade 3 or higher TEAEs were diarrhea (14.7%) and lipase increased (11.8%). The most frequently reported Grade 3 or higher TEAEs considered to be treatment-related were diarrhea and lipase increased, each reported for 3 patients (8.8%).

In the Expansion Phase, the most frequently reported Grade 3 or higher AEs were lipase increased (12.5%), and anemia (10.0%). The most frequently reported Grade 3 or higher TEAEs considered to be treatment-related was lipase increased, which occurred in 3 patients (7.5%).

Despite > 97% of patients experiencing AEs in both the Dose Escalation and Expansion Phases of the study, VIC-1911 was well tolerated, as evidenced by the low frequency of treatment discontinuations due to AEs. Serious adverse events (SAEs) were reported for approximately 40% of patients in each Phase. One death on Day 30 was reported in the Dose Escalation Phase, which was due to rapid disease progression. Few patients experienced Grade 3 and 4 laboratory test results or deterioration of ECOG performance status from baseline.

Nine patients experienced 11 ocular-related AEs (conjunctival hemorrhage [200 mg b.i.d.], corneal epithelial microcysts [200, 250 and 300 mg b.i.d.], keratitis [200 mg b.i.d.], and blurred vision [150 – 250 mg b.i.d.]). Expert review of the events determined that, as with other oncolytic agents, VIC-1911 may cause dose-dependent, temporary, and reversible ocular effects.

3.4.2. Clinical Studies of Other AurA Kinase Inhibitors

In Phase 1 and 2 clinical trials in advanced solid tumors with alisertib (N = 273), the most frequently reported TEAEs in ≥ 10% of subjects were neutropenia, alopecia, diarrhea, leucopenia, nausea, stomatitis, fatigue, decreased appetite, somnolence, vomiting, oral candidiasis, thrombocytopenia, anemia, febrile neutropenia and confusional state (memory impairment). The most frequently reported Grade ≥ 3 TEAEs were neutropenia, leucopenia, febrile neutropenia, anemia, diarrhea, fatigue, nausea, stomatitis and vomiting.[28,29]

3.4.3. Sotorasib (LUMAKRAS™)

3.4.3.1. Warnings and Precautions[23]

- Hepatotoxicity: Monitor liver function tests every 3 weeks for the first 3 months of treatment than once monthly as clinically indicated. Withhold, reduce dose, or permanently discontinue LUMAKRAS based on the severity.
- Interstitial Lung Disease (ILD)/Pneumonitis: Monitor for new or worsening pulmonary symptoms. Immediately withhold LUMAKRAS for suspected ILD/pneumonitis and permanently discontinue if no other potential causes of ILD/pneumonitis are identified.

3.4.3.2. Adverse Reactions

The most common adverse reactions (≥ 20%) for LUMAKRAS are diarrhea, musculoskeletal pain, nausea, fatigue, hepatoxicity, and cough. The most common laboratory abnormalities ≥ 25% are decreased lymphocytes, decreased hemoglobin, increased AST, increased ALT, decreased calcium, increased alkaline phosphatase, increased urine protein and decreased sodium.[23]

3.4.4. Potential Overlapping Toxicities of VIC-1911 in Combination with Sotorasib

Based on the clinical toxicities of AurA kinase inhibitors, VIC-1911 and alisertib, and KRAS G12C inhibitor, sotorasib, potential overlapping toxicities of VIC-1911 in combination with sotorasib may include diarrhea, nausea, vomiting, decreased appetite, anemia, and increased liver enzymes (ALT and AST).

3.5. Dose Rationale

3.5.1. VIC-1911

In the VIC-1911 Phase 1 study in advanced solid tumors, the MTD was 250 mg b.i.d. and the RP2D was 200 mg b.i.d., Days 1-4, 8-11 and 15-18 (e.g., 4 days on, 3 days off) for 3 weeks of a 28-day cycle.

For the combination VIC-1911 plus sotorasib dose groups in Phase 1a (Dose Escalation) and Phase 1b (Expansion) of the study, VIC-1911 will be administered on the 4 days on, 3 days off schedule as described in Section 5.1 below.

For the VIC-1911 monotherapy dose groups in the Dose Escalation and Expansion Phases of the study, VIC-1911 will be administered on a continuous dosing schedule. The rationale for continuous dosing is supported by preclinical studies in which continuous dosing was found to be more effective than intermittent dosing, and to maximize the potential for clinical benefit while reducing the potential for C_{max}-related toxicities that were observed on the 4 days on 3 days off dosing schedule in the previous Phase 1 study (TO-TAS-119-102). To support the continuous dosing schedule, pharmacokinetic modeling was performed to predict exposure over a 1-month period under a continuous dosing regimen vs. the RP2D of 200 mg b.i.d. 4 days on 3 days off for 3 weeks, repeated every 28 days. The exposure (AUC_{0-672}) at 200 mg b.i.d. 4/3 for 3 weeks vs. 75 mg and 100 mg b.i.d. continuous daily dosing was 437,000 vs. 374,000 and 498,000 h*ng/mL respectively. For the current study, we have set the threshold for observed cumulative exposure not to exceed the RP2D of 200 mg b.i.d. 4 days on, 3 days off for 3 weeks, repeated every 28 days cumulative exposure (AUC) of 437,000 h*ng/mL. Thus, the VIC-1911 doses in this study will start at 25 mg b.i.d. and escalate to 50, 75 and 90 mg b.i.d. in the Dose Escalation Phase, and the RP2D determined on the continuous schedule will be utilized in the Expansion Phase. See Section 5.1.

3.5.2. Sotorasib

Sotorasib will be evaluated at the approved dose and schedule for treatment *KRAS G12C*-mutated locally advanced or metastatic NSCLC, 960 mg q.d., with dose reductions for toxicity.[23]

Therefore, in the combination Dose Escalation Phase of this study, VIC-1911 will be administered twice daily starting at Dose Level -1 from the MTD established in an earlier monotherapy Phase 1 study (TO-TAS-119-102) on Days 1-4, 8-11 and 15-18 for 3 weeks repeated every 28 days in combination with sotorasib at a dose of 960 mg orally once daily continuously, with VIC-1911 and sotorasib dose reduction criteria for management of toxicity. In the combination Expansion Phase, VIC-1911 plus sotorasib will be administered at the MTDs established for both drugs in the combination Dose Escalation Phase of the study.

4. TRIAL OBJECTIVES AND PURPOSE

4.1. Primary Objectives

- **Phase 1a (Dose Escalation Phase):** To determine the safety, tolerability, maximum tolerated dose (MTD) and Recommended Phase 2 Dose (RP2D) of:
  - VIC-1911 monotherapy in subjects previously treated with KRAS G12C inhibitor therapy,
  - VIC-1911 in combination with sotorasib (LUMAKRAS™) in subjects previously treated with KRAS G12C inhibitor therapy, and
  - VIC-1911 in combination with sotorasib in subjects naïve to KRAS G12C inhibitor therapy
- **Phase 1b (Expansion Phase)**: To determine the objective response rate (ORR), defined as complete response (CR) or partial response (PR), for:
  - VIC-1911 monotherapy in subjects previously treated with KRAS G12C inhibitor therapy,
  - VIC-1911 in combination with sotorasib in subjects previously treated with KRAS G12C inhibitor therapy, and
  - VIC-1911 in combination with sotorasib in subjects naïve to KRAS G12C inhibitor therapy

4.2. Secondary Objectives

The following parameters will be evaluated for VIC-1911 monotherapy and in combination with sotorasib:

- Phase 1a (Dose Escalation Phase):
  - ORR
  - Duration of response (DoR)
  - Time to response (TTR)
  - Disease control rate (DCR), defined as SD, CR or PR
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - Pharmacokinetics (PK) of VIC-1911 monotherapy and in combination with sotorasib
  - Pharmacodynamics of tumor biomarker determinations pre- and on-study summarized and correlated with clinical outcome
  - In subjects with refractory to or relapsed on prior KRAS G12C inhibitor therapy, the effect of prior KRAS G12C de novo resistance (KRAS G12C inhibitor treatment ≤ 3

months) versus KRAS G12C acquired resistance (KRAS G12C inhibitor treatment > 3 months) on clinical outcome

- Phase 1b (Expansion Phase):
  - Safety and tolerability of VIC-1911 monotherapy and in combination with sotorasib
  - Duration of response (DoR)
  - Time to response (TTR)
  - Disease control rate (DCR), defined as SD, CR or PR
  - Progression-free survival (PFS)
  - Overall survival (OS)
  - Pharmacodynamics of ctDNA and tumor biomarker determinations pre- and on-study summarized and correlated with clinical outcome
  - In subjects with refractory to or relapsed on prior KRAS G12C inhibitor therapy, the effect of prior KRAS G12C de novo resistance (KRAS G12C inhibitor treatment ≤ 3 months) versus KRAS G12C acquired resistance (KRAS G12C inhibitor treatment > 3 months) on clinical outcome

5. INVESTIGATIONAL PLAN

5.1. Overall Study Design

This is a non-randomized, open-label Phase 1a/1b study of aurora kinase A inhibitor VIC-1911 administered as monotherapy and in combination with sotorasib for the treatment of locally advanced or metastatic *KRAS G12C*-mutant non-small cell lung cancer (NSCLC).

Selected subjects will include males and females age ≥18 years with histologically confirmed locally advanced or metastatic *KRAS G12C*-mutated NSCLC, received at least 1 prior line of cancer therapy with a PD-1 or PD-L1 inhibitor with or without platinum-based chemotherapy (unless subject is not eligible or refuses chemotherapy or PD-1/PD-L1 therapy), previously treated with or naïve to G12C inhibitor therapy, recovered from all acute toxicities (≤ Grade 1) due to prior therapy, have adequate hematological, renal and hepatic function and no known history of significant cardiac, hepatic or ocular disease.

Phase 1a (Dose Escalation Phase):

Following screening, a total of up to 36 subjects are anticipated to establish the MTDs of VIC-1911 monotherapy and VIC-1911 in combination with sotorasib therapy.

Cohort 1a: Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will receive VIC-1911 monotherapy. Up to 24 subjects are anticipated in this cohort.

VIC-1911 will be administered orally twice daily (b.i.d.) at doses of 25, 50, 75 and 90 mg (total daily doses of 50, 100, 150 and 180 mg) repeated every 28 days (=1 cycle) (Table 7). Subjects will take their VIC-1911 b.i.d. doses in the fasted state (1 hour before or 2 hours after the morning and evening meal), with the two doses approximately 12 hours apart.

Table 7: VIC-1911 Monotherapy Dose Escalation Levels

Dose Level	VIC-1911 (PO b.i.d.)
1	25 mg
2	50 mg
3	75 mg
4	90 mg

VIC-1911-related AEs will lead to individual dose reductions as indicated in Section 5.5.1.2.

Cohort 1b: Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy or are naïve to KRAS G12C inhibitor therapy will receive VIC-1911 plus sotorasib combination therapy. Up to 12 subjects are anticipate in this cohort.

VIC-1911 will be administered orally twice daily (b.i.d.) at the doses indicated below on Days 1-4, 8-11, and 15-18 repeated every 28 days (=1 cycle) and sotorasib will be administered once daily at the doses indicated in Table 8. Both VIC-1911 and sotorasib will be taken together in the fasted state (1 hour before or 2 hours after the morning meal and after the evening meal [VIC-1911 only]), with the VIC-1911 b.i.d. doses approximately 12 hours apart.

Table 8: Combination VIC-1911 Plus Sotorasib Dose Escalation Levels

Dose Level	VIC-1911 (PO b.i.d.)[a]	Sotorasib (PO q.d.)
1	75 mg	960 mg
2	150 mg	960 mg
3	200 mg	960 mg
[a] Days 1-4 x 3 weeks q 28 days		

VIC-1911 and sotorasib (LUMAKRAS)-related AEs will lead to individual dose reductions as indicated in Section 5.5.1.2.

Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will be enrolled alternatingly into Cohort 1a (VIC-1911 monotherapy) and Cohort 1b (VIC-1911 plus sotorasib) by dose level (e.g., Dose Level 1 in Cohort 1a will be filled, then Dose Level 1 in Cohort 1b, then Dose Level 2 in Cohort 1a, etc.). In Cohort 1b, VIC-1911 pharmacokinetics will be analyzed from Dose Level 1 before Dose Level 2 is initiated to assess the impact of co-administration of VIC-1911 plus sotorasib on the pharmacokinetics of VIC-1911. If necessary, a dose adjustment to VIC-1911 will be made prior to initiating Dose Level 2. This information will be used to make a dose adjustment for Dose Level 3, if necessary.

A 3+3 dose escalation schema will be followed for each cohort. A total of 3 subjects per cohort will be dosed and followed for 28 days through Cycle 1 for DLT. If 0 of 3 subjects experiences a DLT in Cycle 1, the next higher dose level cohort will open. However, if a DLT is experienced in 1 of 3 subjects, the cohort will be expanded to 6 subjects. If 2 or more of 6 subjects per cohort experience DLT, further dose escalation will be subject to SRC review and recommendation. The highest dose level below the dose level eliciting DLT in ≥ 2 of 6 subjects will be declared the VIC-1911 monotherapy MTD or the combination VIC-1911 plus sotorasib MTDs. A total of 6 subjects will be treated at the MTD(s) in each cohort.

For dose de-escalation, if 1 of 3 subjects experiences a DLT at the de-escalated dose level, the cohort will be expanded to 6 subjects. If ≥ 2 of 6 subjects at that dose level experience a DLT, no further subjects will be treated at that dose level and the next lower dose level to enroll 0 of 3 or < 2 of 6 subjects without DLT will be declared the MTD.

Subjects in all cohorts who demonstrate clinical benefit (CR, PR or SD) will be allowed to continue therapy with VIC-1911 monotherapy or VIC-1911 plus sotorasib combination therapy until progression of disease (unless the subject is still benefiting clinically in the opinion of the treating physician, after discussion with the Medical Monitor, as described in Section 7.1.1.), observation of unacceptable AEs, intercurrent illness or changes in the subject's condition that prevents further study participation.

DLT is defined in Section 5.5.1.2.

No intra-subject dose escalation will be allowed from previous dose levels until the subject has received ≥ 3 cycles of their assigned dose, all subjects at the higher dose level have completed Cycle 1 at that dose level (e.g., 3 – 6 subjects, as required to establish safety of the higher dose level) and no ≥ Grade 3 toxicity, irrespective of causality, was observed during the previous treatment cycle. Subjects who experience a DLT may continue treatment in subsequent cycles at

the next lower dose level(s) until disease progression (or until no longer benefiting clinically) or unacceptable toxicity.

Subjects who experience DLT at the first dose level in each cohort will not be dose-reduced and will be discontinued.

A total of at least 6 subjects will be treated at the MTD in each group before initiating the Expansion Phase.

A Safety Review Committee (SRC), consisting of the actively recruiting investigators, Sponsor Medical Monitor, and study staff, will review safety and efficacy data from each cohort monthly more often as necessary. Intermediate dose levels may be added it is recommended to do so by the SRC.

Phase 1b (Expansion Phase): Following screening, a total of 104 subjects with *KRAS G12C*-mutated locally advanced or metastatic NSCLC are anticipated to expand the disease treatment settings of VIC-1911 as monotherapy or in combination with sotorasib. VIC-1911 monotherapy and VIC-1911 plus sotorasib combination therapy will be administered orally at the MTDs/RP2Ds established during the Dose Escalation Phase.

VIC-1911 and sotorasib will be taken in the fasted state, 1 hour before or 2 hours after a meal. VIC-1911 dose reductions for suspected VIC-1911-related toxicity will be followed in accordance with those established in the Dose Escalation Phase. Sotorasib dose reductions for suspected sotorasib-related toxicity will be 480 mg q.d. (Dose Level -1) and 240 mg q.d. (Dose Level -2) in accordance with the LUMAKRAS U.S. Product Label. Further detail on dose reduction guidelines for VIC-1911 and sotorasib are found in Section 5.5.1.2.

Subjects who demonstrate clinical benefit (CR, PR or SD) will be allowed to continue therapy with VIC-1911 and sotorasib until progression of disease (unless the subject is still benefiting clinically in the opinion of the treating physician, after discussion with the Medical Monitor, as described in Section 7.1.1.), observation of unacceptable AEs, intercurrent illness or changes in the subject's condition that prevents further study participation.

The statistical objective is the evaluation of ORR, defined as CR or PR. The sample sizes are based on Simon's 2-stage optimal design.[30]

Cohort 2a: Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will receive VIC-1911 monotherapy. The null hypothesis that the true OR rate (p_0) ≤ 5% will be tested against a one-sided alternative true OR rate (p_1) ≥ 20%. In the first stage, 10 subjects will be accrued. If there are 0 ORs in these 10 subjects, the cohort will be terminated due to futility. If there is at least 1 OR in these 10 subjects, 19 additional subjects will be accrued for a total of n = 29 evaluable subjects. The null hypothesis will be rejected if 4 or more responses are observed in a total of 29 evaluable subjects. The design yields a type 1 error rate of 0.05% and power of 80% when the true response rate is at least 20% and provides evidence of clinical utility to move forward with continued clinical development in this patient population.

Cohort 2b: Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will receive VIC-1911 plus sotorasib combination therapy. The null hypothesis that the true OR rate (p_0) ≤ 5% will be tested against a one-sided alternative true OR rate (p_1) ≥ 20%. In the first stage, 10 subjects will be accrued. If there are 0 ORs in these 10 subjects, the cohort will be terminated

due to futility. If there is at least 1 OR in these 10 subjects, 19 additional subjects will be accrued for a total of n = 29 evaluable subjects. The null hypothesis will be rejected if 4 or more responses are observed in a total of 29 evaluable subjects. The design yields a type 1 error rate of 0.05% and power of 80% when the true response rate is at least 20% and provides evidence of clinical utility to move forward with continued clinical development in this patient population.

Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will be enrolled alternatingly into Cohort 2a (VIC-1911 monotherapy) and Cohort 2b (VIC-1911 plus sotorasib) (e.g., one subject in Cohort 2a, next subject in Cohort 2b, next subject in Cohort 2a, etc).

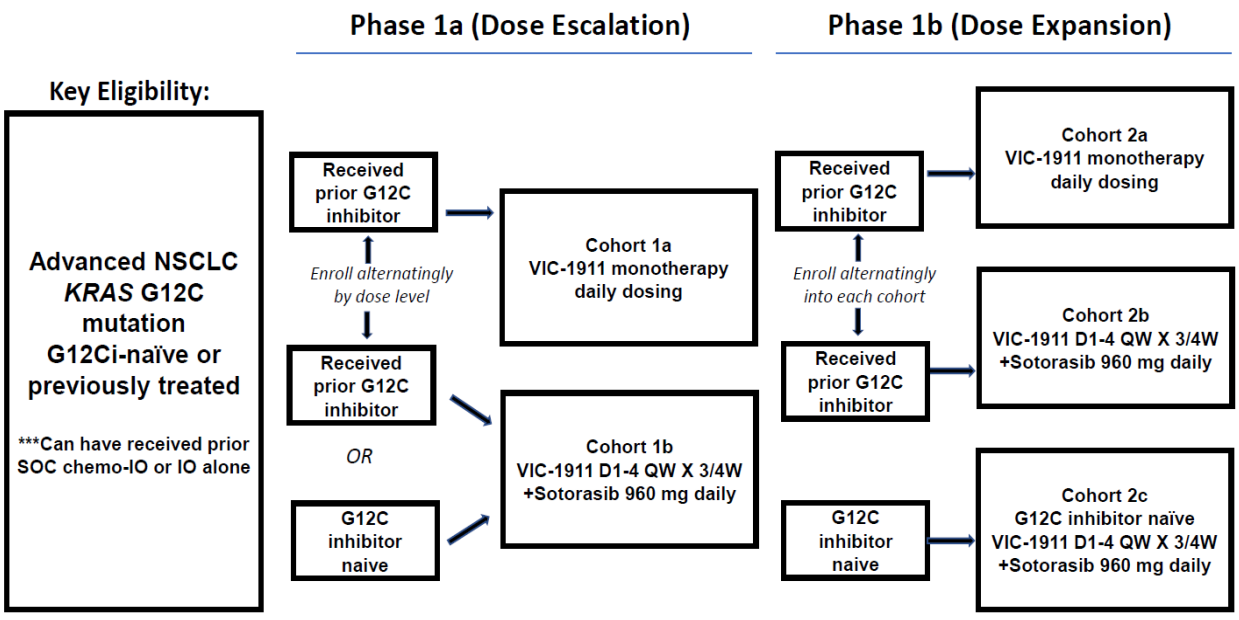
Cohort 2c: Subjects who are naïve to KRAS G12C inhibitor therapy will receive VIC-1911 plus sotorasib combination therapy. The null hypothesis that the true OR rate (p_0) ≤ 30% will be tested against a one-sided alternative true OR rate (p_1) ≥ 50%. In the first stage, 15 subjects will be accrued. If there are 5 or fewer ORs in these 15 subjects, the cohort will be terminated due to futility. If there is at least 6 ORs in these 15 subjects, 31 additional subjects will be accrued for a total of n = 46 evaluable subjects. The null hypothesis will be rejected if 19 or more responses are observed in a total of 46 evaluable subjects. The design yields a type 1 error rate of 0.05% and power of 80% when the true response rate is at least 50% and provides evidence of clinical utility to move forward with continued clinical development in this patient population.

A sample size of n = 46 evaluable subjects also yields a type 1 error rate of 0.05% and power of 79% when the median PFS is 10 months (from 6 months historical) based on a one-sample log-rank test.

Monitoring guidelines for DLTs (= excess toxicity) are found in Section 11.2.

An SRC, consisting of the actively recruiting investigators, Sponsor Medical Monitor, and study staff, will review safety and efficacy data from each cohort monthly or more often as necessary.

The study design schema is depicted below.



Study Assessments:

Blood for hematology, coagulation parameters and serum chemistry determinations will be collected within 28 days prior to Cycle 1 Day 1; on Days 1 and 15 of Cycles 1-3; on Day 1 of each subsequent cycle and at the End of Treatment Visit.

Urine will be collected for urinalysis within 28 days prior to Cycle 1 Day 1, on Day 1 of each subsequent cycle and at the End of Treatment visit.

Electrocardiograms (ECGs) will be taken within 28 days prior to Cycle 1 Day 1, pre-dose and approximately 2 hours post-dose on Cycle 1 Day 1 and Day 15, and at the End of Treatment visit.

Ophthalmic exams will be conducted within 28 days prior to Cycle 1 Day 1 and at the End of Treatment visit. Additional ophthalmologic examinations will be conducted during the study, if clinically indicated. Subjects should be educated on, and be instructed to, immediately report any signs of potential ocular toxicity so that the toxicity is identified and managed in a timely fashion.

Blood for PK assessment of VIC-1911 plasma concentrations will be collected at Cycle 1 Day 1 and Day 15 pre-dose, 15 and 30 minutes, 1, 2, 4, 8 and 24 hours following the first daily dose, and pre-first dose Cycles 2, 4 and 6. On Cycle 1 Day 1 and Day 15, the evening dose of VIC-1911 will be held and subjects will receive only a single morning dose of VIC-1911 to collect a full pharmacokinetic profile following a single dose of study drug at steady state (*Phase 1a [Dose Escalation Phase] only*).

Blood for assessment of ctDNA will be collected for Expansion Phase Cohorts 2b and 2c pre-dose Cycle 1 Day 1 and at progression of disease for biomarker assessment.

If clinically feasible, tumor biopsies will be collected on all subjects (Dose Escalation and Expansion phases) at Screening (archived or fresh) and on subjects in the Expansion Phase only at Cycle 3 Day 1 and at time of progression for biomarker assessment.

Results of ctDNA and tumor biomarker assessment also will be correlated with clinical outcome (e.g., objective response, disease progression, resistance development).

Disease assessments will be based on computed tomography (CT) or magnetic resonance imaging (MRI). Assessments will be obtained every 8 weeks until documented progressive disease (PD).

5.2. Number of Subjects and Centers

Phase 1a (Dose Escalation Phase): Up to 36 subjects are anticipated. Phase 1b (Expansion Phase): Up to 104 subjects are anticipated. The total number of subjects anticipated for the study is up to 140 across 5 clinical sites. Additional clinical centers may be added to complete enrollment in a timely manner.

5.3. Treatment Assignment

This is a non-randomized, open-label Phase 1a/1b study.

In Phase 1a (Dose Escalation Phase), subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will receive either VIC-1911 monotherapy or VIC-1911 plus sotorasib combination therapy. Subjects who are naïve to KRAS G12C inhibitor therapy will receive VIC-1911 plus sotorasib combination therapy. The VIC-1911 monotherapy group will receive VIC-

1911 orally twice daily and the VIC-1911 plus sotorasib combination groups will receive VIC-1911 orally twice daily and sotorasib orally once daily. Dose regimens for all cohorts are repeated every 28 days (= 1 cycle).

Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will be enrolled alternatingly into Cohort 1a (VIC-1911 monotherapy) and Cohort 1b (VIC-1911 plus sotorasib) by dose level (e.g., Dose Level 1 in Cohort 1a will be filled, then Dose Level 1 in Cohort 1b, then Dose Level 2 in Cohort 1a, etc.).

In Phase 1b (Expansion Phase), subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will receive VIC-1911 monotherapy (Cohort 2a) or VIC-1911 plus sotorasib combination therapy (Cohort 2b). Subjects who are naïve to KRAS G12C inhibitor therapy will receive VIC-1911 plus sotorasib (Cohort 2c). The VIC-1911 monotherapy group will receive VIC-1911 orally twice daily and the VIC-1911 plus sotorasib combination group will receive VIC-1911 orally twice daily and sotorasib orally once daily. Dose regimens for all cohorts are repeated every 28 days (= 1 cycle).

Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will be enrolled alternatingly into Cohort 2a (VIC-1911 monotherapy) and Cohort 2b (VIC-1911 plus sotorasib) (e.g., one subject in Cohort 2a, next subject in Cohort 2b, next subject in Cohort 2a, etc.).

5.4. Duration of Study

Accrual in the Dose Escalation Phase is expected to be 18 months. Accrual in the Expansion Phase is expected to be 18 months, with the last subject followed for up to 6 months. The total study duration is expected to be 42 months. The anticipated accrual rate in the Dose Escalation Phase is ~ 2 – 3 subjects per month, and in the Expansion Phase is ~6 subjects per month.

5.5. Dose Adjustment Criteria

Subjects who experience a toxicity requiring dose reduction of either drug may continue at the next lower dose level until disease progression, unacceptable toxicity or changes in the subject's condition that prevents further study participation. AEs considered for dose reduction should not include the events assessed by the investigator as exclusively related to the underlying disease, other medical condition or a concomitant medication/treatment.

5.5.1. Safety Criteria for Adjustment or Stopping Doses

5.5.1.1. Toxicity Grading Criteria

Toxicity grading is based on NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 or higher; http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

5.5.1.2. Dose Modifications and Dose Reductions

Dose-limiting toxicity (DLT) is defined as any one of the following events considered at least possibly related to VIC-1911 and/or sotorasib occurring within the first 28 days of study treatment (=DLT evaluation period):

- Grade 4 hematologic toxicity for > 1 day

- Grade 3 febrile neutropenia (defined as absolute neutrophil count (ANC) < 1000/mm^3 with a single temperature of ≥ 38.3°C [≥ 101°F] or sustained temperature of ≥ 38.0°C [≥ 100.4°F] for more than 1 hour)
- Grade 3 hematologic toxicity with complications (e.g., thrombocytopenia with bleeding)
- Failure of Grade 3 thrombocytopenia, ANC or hemoglobin (Hb) to recover to Grade ≤ 1 within 4 weeks despite the use of platelet and RBC transfusions and/or growth factors
- ≥ Grade 3 non-hematologic toxicity not due to disease progression (excluding nausea, vomiting, constipation, pain, diarrhea or rash that is adequately controlled with supportive care and resolves to ≤ Grade 2 within 48 hours), or electrolyte disturbances unresponsive to correction within 24 hours
- Laboratory abnormalities that satisfy the 3 components of Hy's Law of drug-induced liver injury[31]: 1) ALT or AST elevation ≥ 3 times the upper limit of normal (ULN), 2) total bilirubin elevation > 2 times the ULN without initial findings of cholestasis (i.e., absence of alkaline phosphatase activity > 2 times the ULN), and 3) no other reason to explain the combination of increased ALT/AST and total bilirubin, such as viral hepatitis, preexisting or acute liver disease, or another drug capable of causing the observed injury
- A treatment interruption for ≥ Grade 3 drug-related toxicity in Cycle 1 exceeding 7 days or inability to begin Cycle 2 for > 7 days due to drug-related toxicity
- Other important medical event not clearly due to underlying disease or extraneous causes

A DLT evaluable subject is one who receives study treatment and does not meet the criteria for subject replacement during the DLT evaluation period.

The VIC-1911 monotherapy dose modification guidelines are outlined in Table 9. These guidelines are based on the toxicity profile of VIC-1911 established in preclinical toxicology studies, in which the most adverse findings were reversible following withdrawal of the drug, and on the emerging safety profile of VIC-1911 in previous Phase 1 studies as monotherapy and in combination with paclitaxel. Provisions are not made for dose levels below 25 mg b.i.d. If 25 mg b.i.d. is determined to be unsuitable based on toxicity as defined above, the subject will be permanently discontinued from VIC-1911 treatment.

All AEs should be considered related to VIC-1911 and/or sotorasib except those with known causality outside of treatment with VIC-1911 or sotorasib, or those known to be associated with the subject's disease state, other medical condition or a concomitant medication/procedure. Best attempts should be made by the treating physician to attribute each drug-related AE to VIC-1911, sotorasib or both (e.g., overlapping toxicity, such as diarrhea with both agents). If causality is assessed as related to both sotorasib and VIC-1911, the most conservative action for the toxicity based on both dose modification guidelines should be undertaken for both study drugs (e.g., for a specific toxicity, if either guideline states to interrupt study treatment, then both VIC-1911 and sotorasib should be interrupted).

See Section 10.3.1 for the definition of an AE and Section 10.3.1.5.2 for assessment of study drug relationship to the AE. Use of supportive medications (e.g., anti-emetic, anti-diarrheal

medications) to manage AEs does not negate the need to first record the initial finding as an AE, with associated intensity and causality.

Table 9: VIC-1911 Dose Modification Guidelines

VIC-1911-Related Toxicity	During a Cycle	Dose Adjustment for Next Treatment Day
Grade 1		
	Continue treatment	Maintain b.i.d. dose at 100%
Grade 2		
First incidence	Interrupt until resolved to Grade 0-1	Maintain b.i.d. dose at 100%
Second incidence	Interrupt until resolved to Grade 0-1	Reduce dose by 1 dose level[a]
Third incidence despite dose reduction	Interrupt until resolved to Grade 0-1	Reduce dose by 2 dose levels[a]
Fourth incidence despite dose reduction	Discontinue treatment permanently	Discontinue treatment
Grade 3		
First incidence	Interrupt until resolved to Grade 0-1	Reduce dose by 1 dose level[a]
Second incidence	Interrupt until resolved to Grade 0-1	Reduce dose by 2 dose levels[a]
Third incidence despite dose reduction	Discontinue treatment permanently	Discontinue treatment
Grade 4		
First incidence	Discontinue treatment permanently	Discontinue treatment
[a] Excluding Grade 2 or 3 nausea and vomiting controlled by antiemetics, insomnia, obesity/weight gain, infertility, amenorrhea, galactorrhea, glucose intolerance due to dexamethasone used as an antiemetic, asymptomatic hypercholesterolemia or hypertriglyceridemia, any Grade 2 non-clinically significant laboratory findings and any ≥ Grade 3 nonhematological toxicities due to disease and disease progression.		

Sotorasib dose reduction guidelines are outlined in Table 10.

Table 10: Sotorasib (LUMAKRAS) Dose Reduction Guidelines[23]

Action	Recommended Dose
First Dose Reduction	480 mg (4 tablets) once daily
Second Dose Reduction	240 mg (2 tablets) once daily

Recommended sotorasib dose modification guidelines outlined in the U.S. Product Label are found in Table 11.

Table 11: Sotorasib (LUMAKRAS) Dose Modification Guidelines[23]

Adverse Reaction	Severity[a]	Dosage Modification
Hepatotoxicity[b]	Grade 2 AST or ALT with symptoms or Grade 3 to 4 AST or ALT	• Withhold LUMAKRAS until recovery to ≤ Grade 1 or baseline • Resume LUMAKRAS at the next lower dose level
	AST or ALT > 3 times the ULN with total bilirubin > 2 times the ULN in the absence of alternative causes	• Permanently discontinue LUMAKRAS
Interstitial Lung Disease (ILD)/pneumonitis[c]	Any Grade	• Withhold LUMAKRAS if ILD/pneumonitis is suspected • Permanently discontinue LUMAKRAS if ILD/pneumonitis is confirmed
Nausea or vomiting despite appropriate supportive care (including anti-emetic therapy)[d]	Grade 3 to 4	• Withhold LUMAKRAS until recovery to ≤ Grade 1 or baseline • Resume LUMAKRAS at the next lower dose level
Diarrhea despite appropriate supportive care (including anti-diarrheal therapy)[d]	Grade 3 to 4	• Withhold LUMAKRAS until recovery to ≤ Grade 1 or baseline • Resume LUMAKRAS at the next lower dose level
Other adverse reactions[d]	Grade 3 to 4	• Withhold LUMAKRAS until recovery to ≤ Grade 1 or baseline • Resume LUMAKRAS at the next lower dose level

ALT = alanine aminotransferase, AST - aspartate aminotransferase, ULN = upper limit of normal
[a] National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 5.0 or higher.
[b] See Warnings and Precautions (5.1), LUMAKRAS U.S. Product Label
[c] See Warnings and Precautions (5.2) LUMAKRAS U.S. Product Label
[d] See Adverse Reactions (6.1) LUMAKRAS U.S. Product Label

5.5.1.3. Schedule Adjustments for Toxicity

- For each AE that occurs in a subject enrolled in VIC-1911 plus sotorasib combination cohorts, instructions for assessment and management of VIC-1911 and sotorasib doses should be followed, as provided in Table 9, Table 10 and Table 11.
- The maximum delay allowed between treatment cycles for either VIC-1911 or sotorasib is 2 weeks. If toxicity has not resolved after 2 weeks of delay, the Medical Monitor should be contacted to discuss permission for resuming treatment after a longer delay for subjects who are experiencing clinical benefit.
- Subjects in the combination dose cohorts (Cohorts 1b, 2b or 2c) who require a dose delay or dose reduction for either VIC-1911 or sotorasib may continue the other drug uninterrupted.

5.5.2. Supportive Care Guidelines

- Medications may be administered for the management of symptoms associated with the administration of VIC-1911 or sotorasib, as required.

- Prophylactic pre-medication will not be used routinely. Adequate treatment for nausea and/or vomiting and diarrhea is permitted during Cycle 1. After Cycle 1, prophylaxis of nausea and/or vomiting and diarrhea is permitted.
- Granulocyte stimulating growth factors (e.g., G-CSF or GM-CSF) are allowed according to standard ASCO guidelines.
- Erythropoiesis-stimulating agents, transfusions, etc. are permitted for management of hematologic toxicities.

5.6. Criteria for Study Termination

If the Sponsor, investigators, study monitor or regulatory officials discover conditions arising during the study that indicate that the study should be halted or that the study site should be terminated, this action may be taken after appropriate consultation between the Sponsor and investigators.

Conditions that may warrant termination include, but are not limited to, the following:

- The discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product
- Failure of an investigator to enroll subjects into the study at an acceptable rate
- Failure of an investigator to comply with pertinent FDA regulations
- Submission of knowingly false information from the study site to the Sponsor, study monitor or the FDA
- Insufficient adherence to protocol requirements
- Study termination and follow-up would be performed in compliance with the conditions set forth in 21 CFR 312.50 and 21 CFR 312.56.

6. STUDY POPULATION

6.1. Subject Inclusion Criteria

Subjects must meet all the following criteria to participate in the study:

Inclusion Criteria:

1. Males and females ≥ 18 years of age
2. Have locally advanced or metastatic histologically or cytologically confirmed NSCLC, *KRAS G12C*-mutated
3. The presence of a *KRAS G12C* mutation should be established prior to entry as assessed in a CLIA qualified laboratory. Testing may be done on tumor tissue (archival or fresh) or on ctDNA from blood.
4. Have received at least 1 prior line of cancer therapy with a PD-1 or PD-L1 inhibitor with or without platinum-based chemotherapy (unless subject is not eligible or refuses chemotherapy or PD-1/PD-L1 therapy) and have documented progression on all prior cancer therapies
5. Phase 1a (Dose Escalation Phase):

   5.1 Cohort 1a: (VIC-1911 monotherapy): Locally advanced or metastatic NSCLC refractory to or relapsed on at least 1 prior cancer therapy as noted above, and relapsed/refractory on KRAS G12C inhibitor therapy as the most recent cancer therapy prior to study

   5.2 Cohort 1b: (VIC-1911 plus sotorasib): Locally advanced or metastatic NSCLC:

   5.2.1 Refractory to or relapsed on at least 1 prior cancer therapy as noted above, and relapsed/refractory on KRAS G12C inhibitor therapy as the most recent cancer therapy prior to study, or

   5.2.2 Refractory to or relapsed on at least 1 prior cancer therapy as noted above, and naïve to KRAS G12C inhibitor therapy
6. Phase 1b (Expansion Phase):

   6.1 Cohort 2a: (VIC-1911 monotherapy): Locally advanced or metastatic NSCLC refractory to or relapsed on at least 1 prior cancer therapy as noted above, and relapsed/refractory on KRAS G12C inhibitor therapy as the most recent cancer therapy prior to study

   6.2 Cohort 2b: (VIC-1911 plus sotorasib): Locally advanced or metastatic NSCLC refractory to or relapsed on at least 1 prior cancer therapy as noted above, and relapsed/refractory on KRAS G12C inhibitor therapy as the most recent cancer therapy prior to study

   6.3 Cohort 2c: (VIC-1911 plus sotorasib): Locally advanced or metastatic NSCLC refractory to or relapsed on at least 1 prior cancer therapy as noted above, and naïve to KRAS G12C inhibitor therapy
7. Measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
8. Have discontinued previous treatments for cancer, except for sotorasib for subjects to receive VIC-1911 plus sotorasib combination treatment, and have resolution, except where

otherwise stated in the inclusion criteria, of all clinically significant toxic effects of prior cancer treatment, surgery, or radiotherapy to Grade ≤ 1

9. Adequate performance status: Eastern Cooperative Oncology Group (ECOG) ≤ 2 (Appendix A)
10. Life expectancy of ≥ 3 months
11. Subjects with brain metastases:

    11.1 KRAS G12C inhibitor naïve: Subjects with clinically stable (i.e., no increase in corticosteroid requirement) asymptomatic brain metastases are allowed without prior local therapy, as long as all lesions are each ≤ 1 cm. Prior local therapy is required (e.g., stereotactic radiosurgery [SRS], stereotactic body radiation therapy [SBRT], or surgery) for any lesion > 1 cm or any lesion that is symptomatic.

    11.2 KRAS G12C inhibitor pretreated: Subjects with clinically stable (i.e., no increase in corticosteroid requirement) asymptomatic brain metastases following prior local therapy (e.g., SRS, SBRT or surgery) are allowed

12. Adequate hematologic without ongoing transfusion support:

    12.1 Hemoglobin (Hb) ≥ 8 g/dL

    12.2 Absolute neutrophil count (ANC) ≥ 1.0 x 10^9 cells/L

    12.3 Platelets ≥ 75 x 10^9 cells/L

13. Adequate renal and hepatic function:

    13.1 Calculated creatinine clearance ≥ 50 mL/minute x 1.73 m^2 per the Cockcroft-Gault formula (Appendix B)

    13.2 Total bilirubin ≤ 1.5 times the ULN, unless due to Gilbert's disease, or < 3 times the ULN for subjects with liver metastases

    13.3 ALT/AST ≤ 2 times the ULN, or < 3 times the ULN for subjects with liver metastases

14. Negative serum pregnancy test within 14 days prior to the first dose of study therapy for women of child-bearing potential (WCBP), defined as a sexually mature woman who has not undergone a hysterectomy or who has not been naturally post-menopausal for at least 24 consecutive months (i.e., who has had menses any time in the preceding 24 consecutive months). Sexually active WCBP and male subjects must agree to use adequate methods to avoid pregnancy (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study and for 28 days after the completion of study treatment.
15. Ability to provide written informed consent

6.2. Subject Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study:

Exclusion Criteria:

1. Serious cardiac condition within the last 6 months, such as uncontrolled arrhythmia, myocardial infarction, unstable angina or heart disease defined by the New York Heart Association (NYHA) Class III or Class IV (Appendix C)
2. QT interval corrected for rate (QTc) > 480 msec on the ECG obtained at Screening using Fridericia method for QTc calculation
3. Medications that are inhibitors or inducers of UDP-glucuronosyltransferase (UGT) are prohibited in the Dose Escalation Phase
4. History of corneal epithelial cysts or other ocular events leading to blurred vision, or has medically relevant abnormalities identified on screening ophthalmologic examination
5. Symptomatic pneumonitis/interstitial lung disease requiring medical intervention
6. Symptomatic central nervous system metastasis
7. Leptomeningeal carcinomatosis
8. Inability to swallow oral medication
9. Gastrointestinal conditions that could impair absorption or tolerance of study drugs
10. Current hematologic malignancies
11. Second, active primary solid tumor malignancy that, in the judgement of the Investigator or Sponsor Medical Monitor, may affect the interpretation of results, with the exception of carcinoma in situ of any origin, non-muscle invasive bladder cancer, and Gleason ≤ 3+3 prostate cancer
12. Active infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) requiring treatment within the last week prior to study treatment
13. Other active infection requiring IV antibiotic usage within the last week prior to study treatment
14. Unable to tolerate marketed dose of KRAS G12C inhibitor on prior therapy for subjects to be enrolled in combination VIC-1911 plus sotorasib treatment cohorts. Alternatively, these subjects may be able to enroll in the VIC-1911 monotherapy treatment cohort, upon discussion with the Medical Monitor and Study Chair.
15. Previous MEK or EGFR inhibitor therapy
16. Any other medical intervention or other condition which, in the opinion of the Principal Investigator, could compromise adherence to study requirements or confound the interpretation of study results
17. Receipt of an investigational product on a clinical trial within 5 elimination half-lives or within 28 days, whichever is shorter, prior to C1D1 on this study, or currently enrolled in a

clinical trial involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study

18. Previously completed or withdrawn from any other study investigating an aurora kinase A inhibitor
19. Known hypersensitivity to VIC-1911 or its components
20. If female, pregnant, breast-feeding, or planning to become pregnant

6.3. Discontinuation of Subjects

Any subject may be removed from study treatment for the following reasons:

- Subject withdrawal of the informed consent
- Subject noncompliance
- An increasing or unexpected pattern of unacceptable toxicity
- Disease progression or confirmed loss of clinical response
- Pregnancy
- Investigator judgment when the well-being and best interest of the subject is compromised

Subjects experiencing unacceptable toxicity should be removed from the study treatment and followed until complete resolution of toxicity, return to baseline or until stable and no further resolution is expected, and the End of Treatment visit (28 days after the last dose of study drugs) has been completed, whichever is later. Subjects will then enter the Long-term Follow-up Period.

Individual subjects may be discontinued from the study by the investigator or Sponsor at any time if either person determines that it is not in the best interest of the subject to continue.

Any subject who becomes pregnant during the study must be discontinued from the study treatment immediately but should be followed through delivery or termination of the pregnancy. Subjects should also notify the investigator if they become pregnant within 28 days following the last dose of study drug. The Sponsor also must be notified if a subject becomes pregnant on study.

When a subject is discontinued from study treatment, they should complete the end-of-study assessments and report any SAEs for 28 days following the last dose of study drug. The date and the primary reason for discontinuation from treatment will be recorded on the electronic case report form (eCRF).

6.3.1. Replacement of Study Subjects

Subjects in the Dose Escalation and Expansion phases will be replaced in the following circumstance only:

- Subjects who are screened but do not receive at least one dose of study drug (VIC-1911 or for the combination cohorts, VIC-1911 or sotorasib)

Subjects in the Dose Escalation phase will be replaced in the following circumstances only:

- Subjects treated in Cycle 1 who do not complete 75% of their prescribed daily doses of VIC-1911 or sotorasib
- Subjects who withdraw consent during Cycle 1
- Subjects who do not complete Cycle 1 due to progression of disease or non-drug-related AEs

7. TREATMENT OF SUBJECTS

7.1. Description of Treatment Plan

7.1.1. Treatment Duration

Treatment will continue until confirmation of disease progression, unacceptable toxicity, or subject decision to discontinue therapy.

Subjects may continue treatment with study drugs beyond progressive disease if they are determined by the treating physician to be deriving clinical benefit from treatment and meet the following criteria: no decline in performance status, absence of rapid disease progression with threat to vital organs or critical anatomical sites, and no significant, unacceptable or irreversible toxicities related to study treatment. The decision to continue treatment beyond initial progression should be discussed with the Sponsor Medical Monitor. Additionally, in cases where the majority of the disease is stable or responding, progressing lesions may be treated with local therapy (e.g., resection or radiotherapy) and the subject may be continued on trial following local therapy.

7.2. Concomitant Medications

7.2.1. Permitted Medications

All medications and other treatments taken by subjects 4 weeks before and throughout the study period will be recorded in the eCRF module. Any changes in documented, permitted concomitant medications being taken at the beginning of the clinical trial or added during the time the subject is participating in this study (through the End of Treatment Visit) must be recorded in the CRF module.

7.2.2. Prohibited Medications and Medications to be Avoided

- Concurrent anti-tumor therapy of any kind or any other investigational agent is prohibited.
- VIC-1911 coadministration with inhibitors or inducers of UGTs is prohibited in the Dose Escalation Phase
- Per LUMAKRAS U.S. Product Label[23], the following medications should be avoided for coadministration:
    - Coadministration of sotorasib with proton pump inhibitors (PPIs) and histamine H2 receptor antagonists. If an acid-reducing agent cannot be avoided, administer sotorasib 4 hours before or 10 hours after a local antacid
    - Coadministration of sotorasib with strong CYP3A4 inducers. See https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-3
    - Coadministration of sotorasib with strong CYP3A4 substrates for which minimal concentration changes may lead to therapeutic failures of the substrate. If coadministration cannot be avoided, adjust the substrate dosage in accordance with its Prescribing Information. See https://www.fda.gov/drugs/drug-interactions-

labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table3-2

- Coadministration of sotorasib with P-gp substrates for which minimal concentration changes may lead to serious toxicities. If coadministration cannot be avoided, decrease the substrate dosage in accordance with its Prescribing Information. See https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers#table4-1

7.3. Treatment Compliance

VIC-1911 will be dispensed by the clinical site pharmacy for the subject to take on an outpatient basis between visits.

Sotorasib (LUMAKRAS) will be supplied by prescription to the subject by the Investigator or trained designee for the subject to take on an outpatient basis between visits.

All subjects will be supplied with Dosing Diaries to record their daily VIC-1911 and sotorasib treatment (as applicable), and any missed doses. The Diaries will be reviewed by the clinic staff at each study visit to assess treatment compliance.

7.4. Randomization and Blinding

Not applicable. Subjects who are refractory to or relapsed on prior KRAS G12C therapy will be enrolled alternatingly into Cohort 1a (VIC-1911 monotherapy) or Cohort 1b (VIC-1911 plus sotorasib) during the Dose Escalation Phase and into Cohort 2a (VIC-1911 monotherapy) or Cohort 2b (VIC-1911 plus sotorasib) during the Expansion Phase, as described above.

8. STUDY DRUG MATERIALS AND MANAGEMENT

8.1. VIC-1911

8.1.1. Study Drug Description

VIC-1911 is a selective and orally active small molecule inhibitor of AurA kinase. VIC-1911 drug product is supplied as an immediate release, film coated tablet in 2 strengths: 10 mg (round) and 25 mg (caplet), white to off-white in color, for oral use. Inactive ingredients are lactose monohydrate, partly pre-gelantinized starch, hydroxypropyl cellulose, stearic acid, magnesium stearate, triacetin, hydroxypropyl methylcellulose, polyethylene glycol and titanium oxide. VIC-1911 is manufactured by PCI, Pharma Services, Tredegar, Gwent, UK.

8.1.2. Study Drug Packaging and Labeling

The tablets are packaged in 50 mL High Density Polyethylene (HDPE) bottles. The bottles are sealed with a solid medicinal safe cap. Each bottle contains 60 tablets. The study drug bottles are labeled with the product name, dose strength and other information as per local regulatory requirements.

8.1.3. Study Drug Storage

VIC-1911 is demonstrated to be stable when stored in the defined container closure system. VIC-1911 should be stored at room temperature (15 - 25°C), protected from light.

8.1.4. Administration

VIC-1911 will be provided to the clinical site pharmacy directly from the drug distribution center designated by the Sponsor. Subjects should be scheduled to begin study therapy following completion of Enrollment process.

VIC-1911 will be administered orally twice daily at the dose level prescribed per cohort (approximately every 12 hours).

A sufficient supply of VIC-1911 will be dispensed to the subject by the investigator or trained designee for the subject to take on an outpatient basis between visits.

The following instructions should be reviewed with the subject, and a written copy of the instructions should be provided to the subject:

- Take the prescribed dose of VIC-1911 tablets (either 10 mg or 25 mg, or both) by mouth twice each day as prescribed. Take the second dose about 12 hours after the first dose.
- Take the tablets with a full glass of water (approximately 8 ounces). Swallow the tablets whole.
- Doses will be taken in the fasted state, approximately 1 hour before or 2 hours after a meal. Instructions will be given to take your morning dose 1 hour before or 2 hours after finishing breakfast and, approximately 12 hours later, your evening dose 1 hour before or 2 hours after finishing dinner.

- The dose may be reduced if side effects occur. If a dose reduction is required, the investigator or trained designee will provide instructions to you. Do not reduce the dose unless instructed by the investigator or trained designee.
- If a scheduled dose of study drug is missed and less than 6 hours have passed since the scheduled dosing time, immediately take the missed dose. If more than 6 hours have passed since the scheduled dosing time, do not take the missed dose. Wait and take the next regularly scheduled dose.
- If the dose is vomited after taking, do not retake the dose. Wait for the next scheduled dose. Record the vomiting episode on the Dosing Diary and how long after dosing the vomiting occurred.
- Each day record the number and dosage of tablets taken on the Dosing Diary. If a dose is missed, include the reason the dose was not taken.
- Return the Dosing Diary to the study doctor at each visit.
- Return opened and unopened bottles in which the tablets were dispensed.
- Adherence with the study treatment regimen must be assessed at each visit by checking the returned drug supply and reviewing the Dosing Diary. Study drug therapy must be reported accurately by the clinic staff on the appropriate eCRF.

8.2. Sotorasib

8.2.1. Description

Sotorasib (LUMAKRAS) is an inhibitor of the RAS GTPase family and a specific inhibitor of KRAS G12C, a tumor-restricted, mutant-oncogenic form of the KRAS GTPase.

Sotorasib is supplied as film-coated tablets for oral use containing 120 mg of sotorasib.

See the sotorasib (LUMAKRAS) U.S. Product Label for additional information on study drug description.[23]

8.2.2. Packaging and Labeling

See the sotorasib (LUMAKRAS) U.S. Product Label.[23]

8.2.3. Storage

See the sotorasib (LUMAKRAS) U.S. Product Label.[23]

8.2.4. Administration

Subjects should be instructed to take sotorasib once daily at about the same time each day, at least 1 hour before or at least 2 hours after finishing breakfast.

Acid-reducing agents PPIs and histamine H2 receptor antagonists decrease the concentration of sotorasib. If an acid-reducing agent cannot be avoided, administer sotorasib 4 hours before or 10 hours after a local antacid.

Sotorasib coadministration with strong CYP3A4 inducers may decrease the concentration of sotorasib and should be avoided.

Sotorasib coadministration with strong CYP3A4 substrates for which minimal concentration changes may lead to therapeutic failures of the substrate should be avoided. If coadministration cannot be avoided, adjust the substrate dosage in accordance with its Prescribing Information.

Sotorasib coadministration with P-gp substrates for which minimal concentration changes may lead to serious toxicities should be avoided. If coadministration cannot be avoided, decrease the substrate dosage in accordance with its Prescribing Information.

See Section 7.2.2 on avoidance of coadministration of sotorasib with acid-reducing agents, strong CYP3A4 inducers, CYP3A4 substrates and P-gp substrates.

The subject may be advised to read the FDA-approved Patient Information found in the LUMAKRAS U.S. Product Label. See LUMAKRAS prescribing information for additional information.[23]

The following instructions should be reviewed with the subject, and a written copy of the instructions should be provided to the subject:

- Take the prescribed dose of sotorasib tablets by mouth once each day as prescribed.
- Take the tablets with a full glass of water (approximately 8 ounces). Swallow the tablets whole.
- Doses will be taken in the fasted state, approximately 1 hour before or 2 hours after a meal. Instructions will be given to take your morning dose 1 hour before or 2 hours after finishing breakfast.
- The dose may be reduced if side effects occur. If a dose reduction is required, the investigator or trained designee will provide instructions to you. Do not reduce the dose unless instructed by the investigator or trained designee.
- If a scheduled dose of study drug is missed and less than 6 hours have passed since the scheduled dosing time, immediately take the missed dose. If more than 6 hours have passed since the scheduled dosing time, do not take the missed dose. Wait and take the next regularly scheduled dose.
- If the dose is vomited after taking, do not retake the dose. Wait for the next scheduled dose. Record the vomiting episode on the Dosing Diary and how long after dosing the vomiting occurred.
- Each day record the number and dosage of tablets taken on the Dosing Diary. If a dose is missed, include the reason the dose was not taken.
- Return the Dosing Diary to the study doctor at each visit.
- Return opened and unopened bottles in which the tablets were dispensed.
- Adherence with the study treatment regimen must be assessed at each visit by checking the returned drug supply and reviewing the Dosing Diary. Study drug therapy must be reported accurately by the clinic staff on the appropriate eCRF.

8.3. Study Drug Accountability

The investigator must maintain accurate records of receipt of VIC-1911 study drug, dispensing information, and the prompt return or destruction of unused supplies. Drug accountability logs will be supplied to each clinical site for purposes of recording VIC-1911 study drug dispensation and will be monitored by Sponsor personnel. If the site has an electronic study drug accountability form that is in keeping with institutional practice and the form collects the same information as the forms supplied by the Sponsor, this form may be substituted for the Sponsor's drug accountability forms.

Sotorasib will be dispensed via on-label prescription. Study staff must verify that subjects were prescribed and received sotorasib at the correct dose on Day 1 of each cycle, assess compliance at each visit and perform a tablet count at the end of each cycle.

8.4. Study Drug Handling and Disposal

Unused or expired VIC-1911 will be destroyed per institutional policy. Unused sotorasib will be handled according to institutional policy.

9. STUDY PROCEDURES

See Schedule of Study Procedures in Appendix D.

9.1. Screening Procedures

The following evaluations are to be performed within 28 days of study treatment to determine subject eligibility:

- Administration of informed consent
- Medical history, physical examination and vital signs
- ECOG Performance Status
- Height and weight
- The following laboratory tests:
  - Hematology
  - Coagulation
  - Serum Chemistry
  - Urinalysis
- Beta HCG pregnancy test for WCBP
- 12-lead ECG
- Ophthalmologic examination
- Review of concomitant medications
- Baseline computed tomography (CT) or magnetic resonance imaging (MRI) of systemic and intracranial disease
- Archived tumor tissue for pharmacodynamic assessment, or fresh biopsy, if clinically feasible

9.2. Requirements During Treatment Cycle 1

9.2.1. Cycle 1, Day 1

- Abbreviated physical examination *(may be performed within the previous 24 hours)*
- Vital signs *(may be performed within the previous 24 hours)*
- ECOG Performance Status *(may be performed within the previous 24 hours)*
- Weight *(may be performed within the previous 24 hours)*
- The following lab tests
  - Hematology *(if not performed within the previous 72 hours)*

  - Coagulation *(if not performed within the previous 72 hours)*
  - Serum chemistry *(if not performed within the previous 72 hours)*
  - Urinalysis *(if not performed within the previous 72 hours)*
- 12-lead ECG, pre-dose and at approximately 2 hours post-dose (following first daily dose only) *(pre-dose ECG may be performed within the previous 24 hours)*
- Review of concomitant medications
- Begin VIC-1911 or VIC-1911 plus sotorasib treatment
- Provide subject with VIC-1911 and sotorasib *(if applicable)* Dosing Diary to record study treatments
- Peripheral blood collection in EDTA for PK assessments pre-dose, 15 and 30 minutes (± 5 minutes), 1 hour (± 15 minutes), 2 and 4 hours (± 30 minutes), 8 hours (± 1 hour) and 24 hours (± 2 hours) following the first daily dose. Withhold the evening dose of VIC-1911. On Cycle 1 Day 2, the morning doses of sotorasib and/or VIC-1911 will be delayed until completion of the Cycle 1 Day 1 24-hour post-first-dose blood draw. *(Dose Escalation Phase only)*
- Peripheral blood collection in EDTA for pharmacodynamic assessments pre-dose *(Expansion Phase Cohorts 2b and 2c only)*
- Assessment of AEs
- Assessment for survival

9.2.2. Cycle 1, Day 15 (± 1 day)

- Vital signs
- ECOG Performance Status
- The following lab tests
  - Hematology
  - Coagulation
  - Serum chemistry
- 12-lead ECG, pre-dose and at approximately 2 hours post-dose (following first daily dose only)
- Review of concomitant medications
- Assessment of AEs
- Continue VIC-1911 or VIC-1911 plus sotorasib treatment. Withhold the evening dose of VIC-1911. On Cycle 1 Day 16, the morning doses of sotorasib and/or VIC-1911 will be delayed until completion of the Cycle 1 Day 15 24-hour post-first-dose blood draw (*Dose Escalation Phase only*).

- Review VIC-1911 and sotorasib *(if applicable)* Dosing Diary with subject
- Peripheral blood collection in EDTA for PK assessments, pre-dose, 15 and 30 minutes (± 5 minutes), 1 hour (± 15 minutes), 2 and 4 hours (± 30 minutes), 8 hours (± 1 hour) and 24 hours (± 2 hours) following the first daily dose *(Dose Escalation Phase only)*
- Assessment for survival

9.3. Cycles 2 and 3 (to be performed within 3 days prior to Day 1 of each cycle, unless otherwise specified)

- Abbreviated physical examination
- Vital signs
- ECOG Performance Status
- Weight
- The following lab tests
  - Hematology *(also on Day 15)*
  - Coagulation *(also on Day 15)*
  - Serum chemistry *(also on Day 15)*
  - Urinalysis
- Review of concomitant medications
- Assessment of AEs
- Continue VIC-1911 or VIC-1911 plus sotorasib treatment
- Review VIC-1911 and sotorasib *(if applicable)* Dosing Diaries with subject
- Peripheral blood collection in EDTA for PK assessments pre-dose *(Day 1, Cycle 2, Dose Escalation Phase only)*
- Tumor sample for pharmacodynamic assessment pre-dose, if clinically feasible *(Day 1, Cycle 3, Expansion Phase only)*
- Assessment for survival
- CT or MRI for disease re-staging *(every 8 weeks, ± 7 days)*

9.4. Cycle 4 and Beyond (To be performed within 3 days prior to Day 1 of each cycle, unless otherwise stated)

- Abbreviated physical examination
- Vital signs
- ECOG Performance Status

- Weight
- The following lab tests
  - Hematology
  - Coagulation
  - Serum chemistry
  - Urinalysis
- Review of concomitant medications
- Assessment of AEs
- Continue VIC-1911 or VIC-1911 plus sotorasib treatment
- Review VIC-1911 and sotorasib *(if applicable)* Dosing Diary with subject
- Peripheral blood collection in EDTA for PK assessments pre-dose *(Day 1, Cycles 4 and 6 only) (Dose Escalation Phase only)*
- Assessment for survival
- CT or MRI for disease re-staging *(every 8 weeks, ± 7 days)*

9.5. At Relapse or Progression of Disease

- Disease assessment for response
- Review of concomitant medications
- Assessment of AEs
- Peripheral blood collection in EDTA for pharmacodynamic assessment *(Expansion Phase Cohorts 2b and 2c only)*
- Tumor biopsy for pharmacodynamic assessment, if clinically feasible *(Expansion Phase only*)
- Assessment for survival

9.6. End of Treatment (28 Days After Last Dose of VIC-1911 or VIC-1911 Plus Sotorasib Study Medication ± 5 days)

- Physical examination
- Vital signs
- ECOG Performance Status
- Weight
- The following lab tests
  - Hematology

  - Coagulation
  - Serum chemistry
  - Urinalysis
- 12-lead ECG
- Ophthalmologic examination
- Review of concomitant medications
- Assessment of AEs
- Review VIC-1911 and sotorasib *(if applicable)* Dosing Diary with subject
- Assessment for survival

9.7. Long-Term Follow-Up

Long-term follow-up will consist of a clinic visit or telephone call to assess survival every 3 months for up to 6 months.

10. DESCRIPTION OF ASSESSMENTS

10.1. Safety Assessments

Safety will be assessed through the monitoring of AEs, clinical laboratory parameters (hematology, coagulation parameters, serum chemistry, urinalysis), vital sign measurements, ECGs, ophthalmologic examinations and physical examinations. AEs will be classified according to the Medical Dictionary for Regulatory Affairs (MedDRA) and graded according to the NCI CTCAE version 5.0 or higher.

10.2. Safety Parameters

10.2.1. Vital Signs

Vital sign measurements include temperature, blood pressure and pulse rate. Additional measurements may be obtained if clinically indicated. Any value considered clinically significant by the investigator will be recorded as an AE on the eCRF. Clinically significant changes compared to baseline values should be followed until clinical resolution.

10.2.2. Weight and Height

Weight will be measured at Screening, Day 1 of each treatment cycle, and the End of Treatment Visit. Height will be measured at screening.

10.2.3. Physical Examination

Complete physical examinations include the following body system evaluations: General Appearance, Skin, Musculoskeletal, Eyes, Ears, Nose, Throat, Cardiovascular, Chest, Abdomen, Lymph Nodes, and Neurological. Symptom-oriented (abbreviated) evaluations will be performed at study visits where indicated, and otherwise when clinically indicated.

10.2.4. Electrocardiogram (ECG)

ECGs will be performed within 28 days prior to Cycle 1 Day 1, C1D1 and C1D15 and at the End of Treatment visit.

10.2.5. Ophthalmologic Tests

A complete eye examination, to include evaluation of the cornea, anterior chamber, lens, posterior chamber and retina, will be conducted on each eye independently within 28 days prior to Cycle 1 Day 1, and at the End of Treatment visit. At each of these visits, a full ophthalmologic examination will be conducted, to include slit lamp examination, visual acuity testing, visual field testing, color vision test, tonometry (intraocular pressure [IOP]), optical coherence tomography (OCT), dilated indirect fundoscopy and color fundus photography with attention to retinal abnormalities. Additional ophthalmic evaluations, to include the full ophthalmologic examination described above, may be conducted during the study, if clinically indicated.

10.2.6. Laboratory Assessments

Clinical laboratory tests include hematology, coagulation parameters, serum chemistry and urinalysis (Table 12).

Table 12: Clinical Laboratory Parameters

Hematology	Coagulation Parameters	Serum Chemistry	Urinalysis
Red blood cell count	APTT	Serum creatinine	pH
Hemoglobin	PT (INR)	BUN	Blood
Hematocrit		Glucose (non-fasting)	Nitrites
White blood cell count		Albumin	Glucose
Differential:		AST	Ketones
Neutrophils		ALT	Leucocytes
ANC		LDH	Protein
Lymphocytes		Total bilirubin	Microscopic exam
Monocytes		Total protein	
Eosinophils		Alkaline phosphatase	
Basophils		Amylase	
Platelets		Lipase	
		Calcium	
		Phosphorus	
		Magnesium	
		Sodium	
		Potassium	
		Chloride	
		Bicarbonate	

10.3. Adverse Events and Serious Adverse Events

10.3.1. Definition of Adverse Events

10.3.1.1. Adverse Event

An AE includes any noxious, pathological, or unintended change in anatomical, physiological, or metabolic functions as indicated by physical signs, symptoms, and/or laboratory changes occurring whether or not temporally associated with study drug administration and whether or not considered related to study drug. This definition includes an exacerbation of pre-existing medical conditions or events, intercurrent illnesses, hypersensitivity reactions, drug interactions, or clinically significant laboratory findings.

An AE does not include the following:

- Medical or surgical procedures, e.g., tooth extraction, transfusion, surgery (The medical condition that leads to the procedure is to be recorded as an AE.)
- Pre-existing conditions or procedures present or detected at the start of the study that do not worsen
- Hospitalization for elective surgeries or for other situations in which an untoward medical event has not occurred
- Abnormal laboratory value, unless it is clinically significant
- Overdose of study drug or concomitant medication unaccompanied by signs/symptoms (If sign/symptoms occur, the final diagnosis should be recorded as an AE.)
- Pregnancy by itself, unless a complication occurs during pregnancy leading to hospitalization; in this case (The medical condition that leads to the hospitalization is to be recorded as the AE.)
- A significant worsening of the disease under investigation which is captured as an efficacy parameter in this study and, thus, is not to be recorded as an AE.

10.3.1.2. Serious Adverse Event

An SAE is defined as an AE that results in any of the following outcomes:

- Death
- Life-threatening, i.e., immediate risk of death from the event as it occurred. (This does not include an AE that, had it occurred in a more serious form, might have caused death.)
- Persistent or substantial disability/incapacitation
- Results in or prolongs an existing inpatient hospitalization
- Congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based on medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.3.1.3. Unexpected Adverse Event

An AE or suspected adverse reaction is considered "unexpected" if it is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, is not consistent with the risk information described in the protocol or elsewhere. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator's Brochure listed only cerebral vascular accidents.

"Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from

the pharmacological properties of the investigational therapy but are not specifically mentioned as occurring with the investigational therapy.

10.3.1.4. Adverse Event Reporting Period

The AE reporting period begins from the date of the first dose of study drug(s) to 28 days following the last dose of study drug(s).

10.3.1.5. Recording of Adverse Events

Each AE should be recorded in standard medical terminology on the AE eCRF. Whenever possible, the AE should be evaluated and reported as a diagnosis rather than as individual signs or symptoms. For example, cough, runny nose, sneezing, sore throat, and head congestion should be reported as 'upper respiratory infection'. If a definitive diagnosis is not possible, the individual signs and symptoms should be recorded. Dates of start (onset) and stop (recovery), action taken, and outcome will be recorded on the AE eCRF.

All clinically significant abnormal changes in laboratory parameters will be recorded as an AE on the AE module, with the following exceptions: clinically significant abnormal laboratory changes determined to be related to the study condition and concomitant conditions, e.g., diabetes, of which the investigator was previously aware and that have not worsened.

The investigator will evaluate all AEs with regard to maximum intensity and relationship to study drug, as follows.

10.3.1.5.1. Maximum Intensity

Maximum intensity should be assigned using one of the severity grades as outlined in the NCI CTCAE, version 5.0 or higher; if the AE is not specifically listed in the CTCAE, use the following grades:

- Grade 1: mild
- Grade 2: moderate
- Grade 3: severe
- Grade 4: life-threatening or disabling
- Grade 5: death

10.3.1.5.2. Relationship to Study Drug

The degree of certainty with which an AE is attributed to study drug (or alternative causes, e.g., natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of known pharmacology of the study drug and/or reactions of similar nature previously observed with study drug. Each AE will be assigned one of the following five categories:

- *Not related:* There is not a temporal relationship to the study drug (e.g., too early, too late), or there is a reasonable causal relationship to another drug, concurrent illness, or circumstance.

- *Unlikely related*: There is a temporal relationship to study drug, but there is not a reasonable causal relationship between the time of study drug administration and the AE (i.e., it is doubtful the AE is related to the study drug); could be reasonably explained by other factors, including underlying disease, complications, concomitant drugs, or concurrent treatment.
- *Possibly related*: There is a reasonable temporal sequence from time of study drug administration (e.g., occurred in a time frame relevant to study drug dose); or for which the possibility of the study drug being the causative factor (e.g., existence of similar reports attributed to the study drug; reactions attributable to the pharmacological effect) could not be excluded, although other factors such as underlying disease, complications, concomitant drugs, or concurrent treatment are presumable.
- *Probably related*: There is a reasonable temporal sequence from time of study drug administration; and for which the possibility of factors other than the study drug administration, such as underlying disease, complications, concomitant drugs, or concurrent treatment, could not be excluded as the cause.
- *Definitely related*: Follows a clear temporal sequence from time of study drug administration; could not be possibly explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; follows a response pattern known to be associated with study drug administration.

10.3.1.6. Adverse Event Reporting

Each AE is to be reported by the investigator as serious or non-serious according to the definitions above. This classification determines the regulatory reporting procedures to be followed as described in Table 13.

Table 13: Reporting Guidelines for Adverse Events

Gravity of AE	Reporting Time to Sponsor	Type of Report
Serious	Within 24 hours after the site becomes aware of the event	Initial SAE Report/ Completed AE eCRF
Non-Serious	Per AE eCRF	Completed AE eCRF

Any SAE, regardless of relationship to investigational therapy that occurs within 28 days following the last dose of study drug must be reported to the Sponsor within 24 hours after the site becomes aware of the event. The investigator is encouraged to discuss with the Medical Monitor any adverse experiences for which the issue of reportability is unclear or questioned. If some information is not available at the time of awareness of the event, the initial report should be followed by submission of a more detailed SAE Report when follow-up information is available.

If the SAE occurs more than 28 days after the last dose of study drug, SAEs should be reported only if considered related to VIC-1911 or sotorasib. In the event of subject death, the reason for death should be recorded as the SAE, with 'death' recorded as the outcome on the SAE Report.

The SAE also will be recorded as an AE on the AE eCRF. Note: the SAE Report is different from the AE CRF. In areas of both forms where the same data are reported, the forms will be completed in a consistent manner. For example, the same term should be used for the AE on both forms, with the same start and stop dates, action taken, outcome, etc. A checkbox on the AE eCRF for whether the AE resulted in an SAE, will link the two types of reports for a given event.

An SAE Report should be prepared with as much available information concerning the event as possible so that a written report can be filed with the appropriate regulatory authorities. If causality cannot be determined definitively at the time of the SAE occurrence, it is important to notify the Sponsor within the timeline stated above, and to attribute the relationship as 'Not Assessable' (only applicable for the initial SAE Report). When new significant information is obtained, and the outcome and attribution of the event is known, the investigator will communicate this in a follow-up SAE Report. This relevant information will be provided in a timely manner to allow reporting to regulatory authorities within the required reporting period. Any SAE follow-up information requested by the Sponsor should be provided in a timely manner.

As necessary, the SAE Report should be accompanied by relevant pages from the eCRFs, e.g., medical history, AEs, concomitant medications. Additional information may be requested by the Sponsor in an expedited manner to ensure that the initial reporting of the SAE made to the regulatory authorities complies with the required time frame. The Sponsor may be required to collect and report additional information to the regulatory authorities in a follow-up report, containing a final evaluation of the event, including copies of hospital reports, autopsy reports, or other relevant information.

10.3.1.7. Adverse Event and Serious Adverse Event Follow-Up

All AEs and SAEs should be followed until resolution, return to baseline, or until the point it is deemed that further recovery is unlikely. All measures required for AE management and the ultimate outcome of the AE will be recorded in the source document and AE eCRF.

10.3.1.8. Ongoing Safety Evaluation

A study safety evaluation will be conducted on a regular (monthly) basis by teleconference. Dose exposure, dose-limiting toxicity, AE/SAE profiles and clinical laboratory abnormalities, and other safety measures will be reviewed during each convened meeting. Subject accrual will not be interrupted during the regular scheduled safety evaluations. These discussions will be led by the Sponsor Medical Monitor and Principal Investigator.

10.4. Efficacy Assessments

Efficacy assessments will be determined on the basis of MRI and/or CT scans with best treatment response of CR, PR, SD or PD at any protocol-specified time point. TTR, DoR, DCR, PFS and OS will be evaluated.

10.4.1. Efficacy Endpoints

10.4.1.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with objective response (OR) following VIC-1911 and VIC-1911 plus sotorasib treatment in the Expansion Phase of the study (Cohorts 2a, 2b and 2c). OR includes a best response of CR or PR, as defined by RECIST v.1.1[33] (Appendix E).

10.4.1.2. Secondary Efficacy Endpoints

Secondary efficacy endpoints include:

- Duration of Response (DoR): length of time from the first evidence of objective response (CR, PR) to the first objective evidence of progression
- Time to Response (TTR): length of time from date of first administration of study drug to first evidence of OR
- Disease Control Rate (DCR): Proportion of subjects with best response of CR, PR or SD
- Progression-Free Survival (PFS): length of time from the date of first administration of study drug to the first objective evidence of disease progression or death, whichever is earlier
- Overall Survival (OS): length of time from the date of first administration of study drug to the date of death from any cause.
- In subjects refractory to or relapsed on prior KRAS G12C inhibitor therapy, the effect of prior KRAS G12C *de novo* resistance versus KRAS G12C acquired resistance on clinical outcome

10.4.2. Timing of Assessments to Determine Objective Response

Disease assessments will be made every 8 weeks (± 7 days). Disease assessments may be made at other time points at the discretion of the Investigator.

10.4.3. Timing of ctDNA and Tumor Pharmacodynamic Assessments

Blood for assessment of ctDNA will be collected in the Expansion Phase Cohorts 2b and 2c pre-dose Cycle 1 Day 1 and at progression of disease for biomarker assessment.

If clinically feasible, tumor biopsies will be collected on all subjects (Dose Escalation and Expansion phases) at Screening (archived or fresh) and on subjects in the Expansion Phase only at Cycle 3 Day 1 and at time of progression for biomarker assessment.

Results of ctDNA and tumor biomarker assessment also will be correlated with disease assessments made every 8 weeks.

10.5. Pharmacokinetic Assessment

Because plasma concentrations will be determined at a limited number of time points during the study, a complete pharmacokinetic profile of VIC-1911 at each dose level may not be possible.

Limited pharmacokinetic analyses will be performed, as VIC-1911 monotherapy and when given in combination with sotorasib. Additionally, any identified DDIs between VIC-1911 and sotorasib will be characterized.

10.6. Pharmacodynamic Assessment

Assessment of ctDNA will be made in blood collected during the study, summarized and results correlated with clinical outcome (e.g., objective response, disease progression, resistance development).

Tumor biomarkers will be analyzed for patterns of *de novo* and acquired resistance to AurA kinase and KRAS G12C inhibitor therapy on pre-study and on-study samples. See Appendix F for tumor correlative analysis plan.

11. STATISTICAL METHODOLOGY

11.1. Determination of Sample Size

Phase 1a (Dose Escalation): A total of up to 36 subjects are planned in a 3+3 dose escalation schema (3 to 6 subjects in each of 6 dose levels).

Cohort 1a: Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will receive VIC-1911 monotherapy. A total of up to 24 subjects are planned (3 to 6 subjects in each of 4 dose levels). A total of 6 subjects will be treated at the MTD before initiating Phase 1b (Expansion Phase), Cohort 2a.

Cohort 1b: Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy or are naïve to KRAS G12C inhibitor therapy will receive VIC-1911 plus sotorasib combination therapy. A total of up to 12 subjects are anticipated to establish an MTD of VIC-1911 plus sotorasib (3 to 6 subjects in each of 2 dose levels). A total of 6 subjects will be treated at the MTD before initiating the Expansion Phase, Cohorts 2b and 2c.

Phase 1b (Expansion Phase): The statistical objective is the evaluation of the ORR, defined as CR or PR. The sample sizes are based on Simon's 2-stage optimal design.[30]

Cohort 2a: Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will receive VIC-1911 monotherapy. The null hypothesis that the true OR rate (p_0) ≤ 5% will be tested against a one-sided alternative true OR rate (p_1) ≥ 20%. In the first stage, 10 subjects will be accrued. If there are 0 ORs in these 10 subjects, the cohort will be terminated due to futility. If there is at least 1 OR in these 10 subjects, 19 additional subjects will be accrued for a total of n = 29 evaluable subjects. The null hypothesis will be rejected if 4 or more responses are observed in a total of 29 evaluable subjects. The design yields a type 1 error rate of 0.05% and power of 80% when the true response rate is at least 20% and provides evidence of clinical utility to move forward with continued clinical development in this patient population.

Cohort 2b: Subjects who are refractory to or relapsed on prior KRAS G12C inhibitor therapy will receive VIC-1911 plus sotorasib combination therapy. The null hypothesis that the true OR rate (p_0) ≤ 5% will be tested against a one-sided alternative true OR rate (p_1) ≥ 20%. In the first stage, 10 subjects will be accrued. If there are 0 ORs in these 10 subjects, the cohort will be terminated due to futility. If there is at least 1 OR in these 10 subjects, 19 additional subjects will be accrued for a total of n = 29 evaluable subjects. The null hypothesis will be rejected if 4 or more responses are observed in a total of 29 evaluable subjects. The design yields a type 1 error rate of 0.05% and power of 80% when the true response rate is at least 20% and provides evidence of clinical utility to move forward with continued clinical development in this patient population.

Cohort 2c: Subjects who are naïve to KRAS G12C inhibitor therapy will receive VIC-1911 plus sotorasib combination therapy. The null hypothesis that the true OR rate (p_0) ≤ 30% will be tested against a one-sided alternative true OR rate (p_1) ≥ 50%. In the first stage, 15 subjects will be accrued. If there are 5 or fewer ORs in these 15 subjects, the cohort will be terminated due to futility. If there is at least 6 ORs in these 15 subjects, 31 additional subjects will be accrued for a total of n = 46 evaluable subjects. The null hypothesis will be rejected if 19 or more responses are observed in a total of 46 evaluable subjects. The design yields a type 1 error rate of 0.05% and

power of 80% when the true response rate is at least 50% and provides evidence of clinical utility to move forward with continued clinical development in this patient population.

A sample size of n = 46 evaluable subjects also yields a type 1 error rate of 0.05% and power of 79% when the median PFS is 10 months (from 6 months historical) based on a one-sample log-rank test.

11.2. Monitoring Guidelines (Early Stopping Rules for Excess Toxicity)

In the Dose Escalation Phase, DLT criteria dictate stopping rules. If 2 of 6 subjects experience DLT, no further dose escalation will be made, and the next lower dose will be declared the MTD. A minimum of 6 subjects will be enrolled in Phase 1a (Dose Escalation Phase) in each the VIC-1911 monotherapy and VIC-1911 plus sotorasib combination cohorts, with no observed DLT during the DLT evaluation period, before opening the Expansion Phase.

During the Expansion Phase, we will use continuous monitoring for excess toxicity using a Popcock-type boundary,[32] with the following assumptions: DLT event probability = 0.30 (30%) with 0.05 (5%) desired probability of stopping early.

The maximum planned sample sizes for the Expansion Phase Cohorts 2a and 2b are n = 29 each. In each of these cohorts, sequential boundaries will be used to monitor the rates of DLTs. The accrual will be halted if excessive numbers of DLTs are seen, that is, if the number of DLTs is equal to or exceeds $\mathbf{b_n}$ out of **n** subjects with full follow-up through C1D28. This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most (probability of early stopping) when the rate of dose-limiting toxicity is equal to the acceptable rate (event probability θ). For the maximum planned samples sizes of n = 29 for each Cohorts 2a and 2b, the boundary is equivalent to testing the null hypothesis, after each subject, that the event rate is equal to 0.3, using a one-sided test level of 0.017846.

The maximum planned sample size for the Expansion Phase Cohort 2c is n = 46. In this cohort, sequential boundaries will be used to monitor the rates of DLTs. The accrual will be halted if excessive DLTs are seen, that is, if the number of subjects with a DLT is equal to or exceeds $\mathbf{b_n}$ out of **n** subjects with full follow-up through C1D28. This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most (probability of early stopping) when the rate of dose-limiting toxicity is equal to the acceptable rate (event probability θ). For the maximum planned samples size of n = 46 for Cohort 2c, the boundary is equivalent to testing the null hypothesis, after each subject, that the event rate is equal to 0.3, using a one-sided test level of 0.011900.

Each cohort in the Expansion Phase will be stopped if the number of subjects with a DLT is equal to or exceeds $\mathbf{b_n}$ out of **n** subjects with completed follow up through C1D28.

Cohorts 2a and 2b	
n	**b_n**
1	-
2	-
3	-
4	4
5	5
6	5
7	6
8	6
9	7
10	7
11	8
12	8
13	9
14	9
15	9
16	10
17	10
18	11
19	11
20	11
21	12
22	12
23	13
24	13
25	13
26	14
27	14
28	15
29	15

Cohort 2c	
n	**b_n**
1	-
2	-
3	-
4	4
5	5
6	5
7	6
8	6
9	7
10	7
11	8
12	8
13	9
14	9
15	10
16	10
17	11
18	11
19	11
20	12
21	12
22	13
23	13
24	13
25	14
26	14
27	15
28	15
29	15
30	16
31	16
32	17
33	17
34	17
35	18
36	18
37	19
38	19
39	19
40	20
41	20
42	21
43	21
44	21
45	22
46	22

11.3. Analysis Populations

The full analysis set (FAS) includes all subjects who are administered any fraction of a dose of VIC-1911 or VIC-1911 plus sotorasib study medication. For a particular measure, the per-protocol set (PPS) includes those subjects in the FAS who have a valid baseline and one or more post-treatment assessments for that measure of interest.

The PK population consists of all subjects in the FAS who complete a baseline and at least one follow-up PK assessment.

The pharmacodynamic population consists of all subjects in the FAS who complete a baseline and at least one follow-up pharmacodynamic assessment.

Efficacy analyses will be conducted separately by cohort for both Dose Escalation and Expansion phases of the study.

11.4. Statistical Analysis Methods

All data will be analyzed using SAS Version 9.4 or higher for Windows (SAS Institute, Cary, NC). Continuous variables will be summarized using number, mean, standard deviation, median, minimum, and maximum. Categorical variables will be summarized using number and frequencies.

11.4.1. Safety Analysis

11.4.1.1. Adverse Events

All safety endpoints will be summarized using descriptive statistics and will be based on the FAS dataset.

All AEs will be coded based on the Medical Dictionary for Regulatory Affairs (MedDRA; version 24.0 or higher). An AE will be considered a TEAE if the onset is after the first dose of study drug or if the condition was present at baseline but worsened after the first dose.

All AEs for each subject will be listed, including intensity grading, relationship to study drug, action taken and outcome. Subject listings of deaths, SAEs, and AEs leading to treatment discontinuation will be provided. Subject narratives will be provided for deaths, SAEs and other significant AEs. Summary tables will be prepared to examine TEAE severity and relationship to study treatment.

AE summaries will be produced separately for each dose cohort and overall, each disease cohort by dose and overall, and by monotherapy and combination phases of the study. All summaries will show, by subject group, dose cohort and overall, the number and percentage of subjects experiencing at least 1 TEAE of each preferred term, arranged by system organ class, and the number of occurrences of the event. Separate summaries will be produced by relationship to study medication, by severity, and for those events with an incidence rate of at least 2% in any group or overall.

SAEs will be summarized in a similar manner; overall, by relationship to study medication, and by severity.

In addition to the above, summaries of the number and percentage of subjects discontinuing the study due to AEs and, due to death, will be presented.

11.4.1.2. Laboratory Data

Laboratory data will be listed by subject. Values above and below normal ranges will be indicated, and whether clinically significant. All laboratory values will be graded according to the NCI-CTCAE criteria, version 5.0 or higher. Laboratory data will be summarized by actual value and change from baseline using number of non-missing observations, mean standard deviation, median, minimum and maximum. In addition, shift tables and the incidence of Grade 3 or 4 laboratory values will be presented.

11.4.1.3. Vital Signs

Vital signs will be listed by subject. Values above and below normal ranges will be indicated as will clinical significance. Vital sign data will be summarized by actual value and change from baseline using number of non-missing observations, mean, standard deviation, median, minimum and maximum.

11.4.1.4. Other Safety Data

Data collected for physical examinations, ECGs, ophthalmologic examinations and related measures will be listed.

11.4.2. Efficacy Analysis

11.4.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the proportion of subjects with objective response (OR) following VIC-1911 or VIC-1911 plus sotorasib treated at the MTDs/RP2Ds in the Expansion Phase of the study (Cohorts 2a, 2b and 2c). OR will be summarized using number and percentage of subjects in each cohort with a best response of CR, PR, SD or PD assessed by RECIST v. 1.1,[33] and 95% confidence intervals will be estimated.

11.4.2.2. Secondary Efficacy Endpoints

For the Dose Escalation Phase (Cohorts 1a and 1b), OR will be determined, as above, and summarized using number and percentage of subjects, with estimation of 95% confidence intervals.

Other secondary endpoints will be summarized for all subjects in the Dose Escalation and Expansion phases of the study by cohort as follows:

- The proportion of subjects with disease control (CR, PR or SD) will be summarized using the number and percentage of subjects with a best response rate of CR, PR, SD or PD assessed by RECIST v. 1.1.
- DoR, TTR, PFS and overall survival will be summarized using the Kaplan-Meier product-limit method to estimate the median survival. Subjects who do not have disease progression will be censored at the last follow-up time.

DoR will be calculated from the date of first evidence of response to the date of progression or death.

TTR will be calculated from the date of first treatment to the date of first evidence of response.

PFS will be calculated from the date of first treatment to the date of first evidence of progression or death.

OS will be calculated from the date of first treatment to the date of death from any cause; subjects who do not experience death will be censored at the last follow-up time.

In subjects refractory to or relapsed on prior KRAS G12C inhibitor therapy, the effect of prior KRAS G12C de novo resistance versus KRAS G12C acquired resistance on clinical outcome (e.g., OR, PFS, OS.

11.4.3. Pharmacokinetic Endpoint Analysis

Because plasma concentrations will be determined at a limited number of time points during the study, a complete pharmacokinetic profile of VIC-1911 at each dose level may not be possible. Limited pharmacokinetic analyses will be performed, as VIC-1911 monotherapy and when given in combination with sotorasib. Additionally, any identified DDIs between VIC-1911 and sotorasib will be characterized.

11.4.4. Pharmacodynamic Endpoint Analysis

Assessment of ctDNA will be made in blood collected during the study, summarized and results correlated with clinical outcome (e.g., objective response, disease progression, resistance development).

Tumor biomarkers will be analyzed for patterns of *de novo* and acquired resistance to AurA kinase and KRAS G12C inhibitor therapy on pre-study and on-study samples. See Appendix F for tumor correlative analysis plan.

12. STUDY MANAGEMENT

12.1. Data Management

The investigator is responsible for completing and maintaining adequate and accurate source documentation. Source documentation constitutes original records, which may include progress notes, medication administration records, laboratory reports, ECG tracings, discharge summaries, eCRF worksheets, etc. Data for this study will be submitted electronically. Access to the database will be provided following a brief on-line training session. Each user will receive a unique username and password, which should not be shared. The investigator must sign the investigator's statement for each subject indicating that the data reported are accurate.

12.2. Monitoring

The Sponsor is responsible for ensuring the proper conduct of the study with regard to ethics, protocol adherence, site procedures, integrity of the data, and applicable laws and/or regulations. At regular intervals during the study and following completion of the study, the Sponsor's study monitors will contact the study site via visits to the site, telephone calls, and letters in order to review study progress, eCRF completion, and address any concerns or questions regarding the study conduct. During monitoring visits, the following aspects of study conduct will be carefully reviewed: informed consent of subjects, subject recruitment, subject compliance with the study procedures, source data verification, drug accountability, use of concomitant therapy by subjects, AE and SAE documentation and reporting, and quality of data. Records pertaining to these aspects are expected to be kept current.

12.3. Audits and Inspections

Authorized representatives of the Sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice (GCP) guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. The investigator should contact the Sponsor, or Sponsor's representatives, immediately if contacted by a regulatory agency about an inspection.

12.4. Amendments

Any amendments to the protocol will be written and approved by the Sponsor. All amendments must be submitted to the IRB for approval prior to implementing the changes. In some instances, an amendment requires changes to the informed consent document (ICD), which also must be submitted for IRB approval prior to administration to subjects. If any changes to the eCRFs are required, the Sponsor will issue supplemental or revised eCRFs on behalf of the Sponsor.

12.5. Institutional Review Board

The Principal Investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the subject consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

13. QUALITY CONTROL AND QUALITY ASSURANCE

To ensure compliance with GCP and all applicable regulatory requirements, the Sponsor may conduct a quality assurance audit. See Section 12.3 for more details regarding the audit process.

14. ETHICS

14.1. Ethics Review

The final study protocol, including the final version of the ICD, must be approved or given a favorable opinion in writing by an IRB or Independent Ethics Committee (IEC) as appropriate. The investigator must submit written approval to the Sponsor, or the Sponsor's representatives, before he or she can enroll any subject into the study.

The Principal Investigator is responsible for informing the IRB or IEC of any amendment to the protocol in accordance with local requirements. In addition, the IRB or IEC must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB or IEC upon receipt of amendments and annually, as local regulations require.

The Principal Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the investigational product. The Sponsor will provide this information to the Principal Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or IEC according to local regulations and guidelines.

14.2. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, applicable regulatory requirements and corporate policy on Ethical Standards (Appendix G).

14.3. Written Informed Consent

The Principal Investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures.

The Principal Investigator(s) must maintain the original, signed ICD. A copy of the signed ICD must be given to the subject.

15. DATA HANDLING AND RECORDKEEPING

15.1. Health Insurance Portability Accountability Act of 1996

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR. Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

15.2. Financial Disclosure

The investigator shall provide to the Sponsor sufficient accurate financial information to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the FDA. The investigator shall promptly update this information yearly and for one year following completion of the study.

15.3. Inspection of Records

The Sponsor, or Sponsor' representatives, will be allowed to conduct site visits to the investigation facilities for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

15.4. Access to Original Records

It is an expectation of regulatory authorities that monitors, auditors, and representatives of national and international government regulatory agency bodies have access to original source documentation to ensure data integrity. "Original" in this context is defined as the first documentation of an observation and does not differentiate between hard copy and electronic records.

15.5. Retention of Records

Study-related records must be retained for 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 at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by applicable regulatory requirements or by an agreement with the Sponsor.

The investigator must not destroy any study-related records without receiving approval from the Sponsor. The investigator must notify the Sponsor in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the Sponsor must be contacted to arrange alternative record storage options.

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APPENDIX A. EASTERN COOPERATIVE GROUP (ECOG) PERFORMANCE STATUS SCALE

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

* From ECOG, Robert Comis, MD, Group Chair

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

APPENDIX B. COCKCROFT-GAULT FORMULA FOR CALCULATION OF CREATININE CLEARANCE

Creatinine clearance must either be measured or estimated using the Cockroft-Gault formula, as outlined below.

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age [years]}) \times \text{weight [kg]}}{\text{serum creatinine [µmol/L]}} \quad \text{(Females)}$$

$$\frac{(140 - \text{age [years]}) \times \text{weight [kg]} \times 1.2}{\text{serum creatinine [µmol /L]}} \quad \text{(Males)}$$

* Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

APPENDIX C. NEW YORK HEART ASSOCIATION (NYCA) CLASSIFICATION FOR HEART FAILURE – THE STAGES OF HEART FAILURE

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX D. SCHEDULE OF STUDY PROCEDURES

Study Activity	Screening[a]	Treatment Cycle 1		Treatment Cycles 2 and 3			Treatment Cycles 4+		Progression or Relapse	End of Treatment[w]	Long-Term Follow-Up[x]
		Day 1[s]	Day 15[t]	Day 1[u]	Day 15[t]	End of Cycle 2[v]	Day 1[u]	End of Cycle 4[v]			
Signed ICD	X										
Medical History	X										
Physical Examination	X	X		X[b]			X[b]			X	
Vital Signs	X	X	X	X			X			X	
ECOG Performance Status	X	X	X	X			X			X	
Height	X										
Weight	X	X		X			X			X	
Hematology[c]	X	X	X	X	X		X			X	
Coagulation Parameters[d]	X	X	X	X	X		X			X	
Serum Chemistry[e]	X	X	X	X	X		X			X	
Urinalysis[f]	X	X		X			X			X	
Beta-hCG for WCBP	X										
12-lead ECG	X	X[g]	X[g]							X	
Ophthalmologic Examination[h]	X									X	
Concomitant Medications	X	Continuous									
AE Assessment		Continuous									
Tumor sample	X[i]			X[o]					X[o]		
Disease Assessment[j]	X					X		X	X		

Study Activity	Screening[a]	Treatment Cycle 1		Treatment Cycles 2 and 3			Treatment Cycles 4+		Progression or Relapse	End of Treatment[w]	Long-Term Follow-Up[x]
		Day 1[s]	Day 15[t]	Day 1[u]	Day 15[t]	End of Cycle 2[v]	Day 1[u]	End of Cycle 4[v]			
Peripheral Blood for PK Assessment[k]		X	X	X[l]			X[m]				
Peripheral Blood for Pharmacodynamic Assessment[n]		X							X		
VIC-1911 Dosing[p]		b.i.d. according to dose regimen									
Sotorasib Dosing[q]		q.d. according to dose regimen									
VIC-1911 and Sotorasib Dosing Diaries[r]		X	X	X	X		X			X	
Survival Assessment		Continuous									

[a] Screening to be performed within 28 days of Cycle 1, Day 1
[b] Abbreviated physical exam
[c] Hematology parameters collected at Screening, Cycle 1 Day 1 (only if not performed in the previous 72 hours), Day 15 *for the first 3 cycles*, Day 1 of each subsequent cycle (within 3 days prior to Day 1 of each subsequent cycle) and End of Treatment. See Table 12 for tests to be conducted at each time point.
[d] Coagulation parameters collected at Screening, Cycle 1 Day 1 (only if not performed within the previous 72 hours), Day 15 *for the first 3 cycles*, Day 1 of each subsequent cycle (within 3 days prior to Day 1 of each subsequent cycle) and End of Treatment. See Table 12 for tests to be conducted at each time point.
[e] Serum chemistry collected at Screening, Cycle 1 Day 1 (only if not performed within the previous 72 hours), Day 15 *for the first 3 cycles*, Day 1 of each subsequent cycle (within 3 days prior to Day 1 of each subsequent cycle) and End of Treatment. See Table 12 for tests to be conducted at each time point.
[f] Urinalysis performed at Screening, Cycle 1 Day 1 (only if not performed in the previous 72 hours), Day 1 of each subsequent cycle *(within 3 days prior to Day 1 of each subsequent cycle)* and End of Treatment. See Table 12 for tests to be conducted at each time point.
[g] ECGs performed pre-dose and approximately 2 hours post-dose (following first daily dose only), Cycle 1 Day 1 and Day 15
[h] Ophthalmologic tests performed within 28 days of Cycle 1 Day 1, End of Treatment and as clinically indicated throughout the study. See Section 10.2.5 for tests to be conducted at these visits.
[i] Archived, or if clinically feasible, fresh biopsy, for pharmacodynamic assessment at Screening
[j] Disease Assessment may include CT, MRI, and/or physical exam. Should be performed every 8 weeks (± 7 days)
[k] Peripheral blood collected in EDTA for PK assessment Cycle 1 Day 1 and Day 15 pre-dose, at 15 and 30 minutes *(± 5 minutes)*, 1 hour *(± 15 minutes*), 2 and 4 hours *(± 30 minutes)*, 8 hours *(± 1 hour)* and 24 hours *(± 2 hours)* following the first daily dose, and pre-first dose Cycle 2, 4, 6 *(Dose Escalation Phase only)*.
[l] Pre-first dose C2 only

[m] Pre-first dose C4 and C6 only
[n] Peripheral blood collected in EDTA for pharmacodynamic assessment pre-dose C1D1 and at progression of disease *(Expansion Phase Cohorts 2b and 2c only)*
[o] Fresh biopsy pre-first dose C3 only and relapse/progression, if clinically feasible *(Expansion Phase only)*
[p] VIC-1911 dose orally twice daily, per assigned dose regimen. Provide VIC-1911 Dosing Diary. Withhold the evening dose on C1D1 and C1D15. On C1D2 and C1D16, delay the morning dose until completion of the Cycle 1 Day 1 and Day 15 24-hour post-first-dose blood draw.
[q] Sotorasib dose orally once daily, continuously. Provide VIC-1911 Plus Sotorasib Dosing Diary. On C1D2 and C1D16, delay the morning dose until completion of the Cycle 1 Day 1 and Day 15 24-hour post-first-dose blood draw.
[r] Review VIC-1911 and VIC-1911 Plus Sotorasib Dosing Diaries with subject (each clinic visit + End of Treatment).
[s] Day 1 PE, vital signs, weight, ECOG performance status, pre-dose ECG may be completed within 24 hours prior to C1D1.
[t] Day 15 (±1 day)
[u] Day 1 (within 3 days prior to Day 1 of each cycle)
[v] Day 28 (±7 days)
[w] End of Treatment visit should be 28 days from last dose of study medication (±5 days)
[x] Long-term follow-up for 6 months consists of clinic visits or telephone calls every 3 months to assess survival status

APPENDIX E. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST 1.1)[33]

1. Measurability of Tumor at Baseline

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1. Measurable

Tumor 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:

- 10mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15mm in short axis when assessed by CT 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. See also notes below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

1.1.2. Non-measurable

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥ 10 to < 15mm 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.

1.1.3. 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 noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2. Specifications by methods of measurements

1.2.1. Measurement of lesions

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 4 weeks before the beginning of the treatment.

1.2.2. Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans). More

details concerning the use of both CT and MRI for assessment of objective tumour response evaluation are provided in Appendix II of the paper.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

2. Tumor response evaluation

2.1. Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion (as detailed above in Section 1). In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

2.2. Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded). For evidence to support the selection of only five target lesions, see analyses on a large prospective database in the article by Bogaerts J, et al, Eur Jour Cancer,2009;45:248-260.

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. As noted in Section 1, pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20mm· 30mm has a short axis of 20mm and qualifies as a malignant, measurable node. In this example, 20mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

2.3. Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

2.3.1. Evaluation of target lesions

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

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

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

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

2.3.2. Special notes on the assessment of target lesions

Lymph nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure'. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report themas being 'too small to measure'. When this occurs, it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate,

however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5mm.

Lesions that split or coalesce on treatment. As noted in Appendix II of the paper, when non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

2.3.3. Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only *qualitatively* at the time points specified in the protocol.

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

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

Progressive Disease (PD): Unequivocal progression (see comments below) of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

2.3.4. Special notes on assessment of progression of nontarget disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease. In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality 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 PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a

measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

2.3.5. New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET (=FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image) at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow- up:

   - If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

   - If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

   - If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.4. Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement (See Section 1.6). Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

2.4.1. Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1: Criteria for Overall Response for Target (+/- Non-target) Disease

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
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, PR= partial response, SD=stable disease, PD= progressive disease, NE=inevaluable			

Table 2: Criteria for Overall Response for Non-target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD
CR = complete response, PR= partial response, SD=stable disease, PD= progressive disease, NE=inevaluable		

2.4.2. Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3. Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (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). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

Table 3: Best Overall Response When Confirmation of CR and PR is Required

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR= partial response, SD=stable disease, PD= progressive disease, NE=inevaluable

[a]If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and, in fact, the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR, and the best response is PR.

2.4.4. Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in **Tables 1–3.**

Conditions that define 'early progression, early death and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/ sensitivity.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

2.5. Frequency of tumor re-evaluation

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances, certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy,

drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

2.6. Confirmatory measurement/duration of response

2.6.1. Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials (see Bogaerts J, et al, Eur Jour Cancer,2009;45:248-260). However, in all other circumstances, i.e., in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

2.6.2. Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/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 on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.6.3. Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD).

The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made.

2.7. Progression-free survival/proportion progression-free

2.7.1. Phase II trials

This guideline is focused primarily on the use of objective response endpoints for phase II trials. In some circumstances, 'response rate' may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases 'progression-free survival' (PFS) or the 'proportion progression-free' at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as patient selection and not the impact of the intervention. Thus, phase II screening trials utilizing these endpoints are best designed with a randomized control. Exceptions may exist where the behavior patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomized trial is justifiable. However, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion progression-free in the absence of a treatment effect.

2.7.2. Phase III trials

Phase III trials in advanced cancers are increasingly designed to evaluate progression-free survival or time to progression as the primary outcome of interest. Assessment of progression is relatively straightforward if the protocol requires all patients to have measurable disease. However, restricting entry to this subset of patients is subject to criticism: it may result in a trial where the results are less likely to be generalizable if, in the disease under study, a substantial proportion of patients would be excluded. Moreover, the restriction to entry will slow recruitment to the study. Increasingly, therefore, trials allow entry of both patients with measurable disease as well as those with non-measurable disease only. In this circumstance, care must be taken to explicitly describe the findings which would qualify for progressive disease for those patients without measurable lesions. Furthermore, in this setting, protocols must indicate if the maximum number of recorded target lesions for those patients with measurable disease may be relaxed from five to three. As found in the 'special notes on assessment of progression', these guidelines offer recommendations for assessment of progression in this setting. Furthermore, if available, validated tumor marker measures of progression (as has been proposed for ovarian cancer) may be useful to integrate into the definition of progression. Centralized blinded review of imaging studies or of source imaging reports to verify 'unequivocal progression' may be needed if important drug development or drug approval decisions are to be based on the study outcome. Finally, as noted earlier, because the date of progression is subject to ascertainment bias, timing of investigations in study arms should be the same.

APPENDIX F. VIC-1911-01 TUMOR CORRELATIVE ANALYSIS PLAN

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Mutant *KRAS* was long considered an undruggable target due to absence of binding pockets for small-molecule inhibitors. Recently, covalent direct KRAS inhibitors which bind to cysteine 12 of the GDP-bound form of the KRAS G12C protein have been developed, and rapidly entered the clinic. While these represent a genuine breakthrough in management of *KRAS*-mutated NSCLC, the response rates of 37 to 45% indicate that not all *KRAS G12C*-mutated NSCLCs respond to these agents, and acquired resistance is common, with median PFS of under 7 months.

Intrinsic resistance may be related to additional abnormalities in the MEK signaling pathway, while both adaptive and mutational mechanisms may underlie acquired resistance. Zhao et. al. describes acquired (treatment-emergent) alterations in 63% of sotorasib-treated, predominantly NSCLC, patients (DOI: 10.1038/s41586-021-04065-2). Secondary mutations were identified in *KRAS, NRAS, BRAF, EGFR, FGFR2, MYC* and other genes. Patient-derived xenograft and cell line models exhibited resistance to KRAS(G12C) inhibition when low allele frequency hotspot mutations in *KRAS (G12V or G13D)*, *NRAS (Q61K or G13R)*, *MRAS (Q71R)* and/or *BRAF (G596R)* were observed. Co-mutation of *TP53* and *KRAS*, often described in NSCLC, was present in a subset of the patients in this study.

Awad et. al. (DOI: 10.1056/NEJMoa2105281) conducted genomic analysis of NSCLC and colorectal cancer patients with acquired resistance to adagrasib, and found putative mechanisms of resistance in 45%, including 18% with multiple coincident mechanisms. Most commonly observed were secondary *KRAS* alterations: *G12D/R/V/W, G13D, Q61H, R68S, H95D/Q/R, Y96C,* and high-level amplification of the KRASG12C allele. Acquired bypass mechanisms of resistance included MET amplification; activating mutations in NRAS, BRAF, MAP2K1, and RET; oncogenic fusions involving ALK, RET, BRAF, RAF1, and FGFR3; and loss-of-function mutations in *NF1* and *PTEN*. Histologic transformation to squamous-cell carcinoma was also observed. Separately, acquired HER2 copy number gain has been observed in a patient with sotorasib resistance (DOI: 10.1016/j.ejca.2021.10.003). Single cell analyses in models of resistance *in vitro* have demonstrated adaptive resistance mediated by Aurora A and MEK signaling (Nature. 2020 Jan;577(7790):421-425. DOI: 10.1038/s41586-019-1884-x.)

Baseline levels of Aurora A expression and protein stability may vary in NSCLC patients due to abnormalities in expression of Aurora interacting proteins. *TP53* negatively regulates transcription of AURA kinase, and loss of *TP53* typically increases the transcription of AURA kinase mRNA, contributing to higher cellular levels of AURA kinase protein. Further, direct physical interaction of AURA kinase with partner proteins regulates AURA kinase stability and expression levels. Prominent among these is NEDD9, a scaffolding protein that binds AURA kinase to stimulate its activity in mitosis and cytokinesis. Overexpression of NEDD9 promotes resistance to AURA kinase inhibition, based on triggering conformational changes in the AURA kianse protein, and induces ERK1/2, AKT, and EMT signaling. Another AURA kinase-binding protein that increases both AURA kinase expression and may relate to resistance to AURA kinase inhibition is TPX2. A recent study of therapeutic resistance in lung cancer models determined that post-translational

activation of AURA kinase by its upregulated coactivator TPX2 contributes to adaptive (non-genomic) resistance to EGFR inhibitors, reducing EGFR inhibitor-induced apoptosis.

In this correlative biomarker plan, we will characterize tumor samples from patients enrolled in VIC-1911-01 for baseline and acquired resistance mutations, as well as differences in transcription and expression of Aurora A and its interacting partners, and histologic evidence of tumor transformation to other histological subtypes including squamous cell histology.

Pre-treatment tumor biopsies will be obtained from all patients in whom it is safe and feasible to do so. Archived tissue may be substituted for fresh biopsies if not clinically feasible to obtain a fresh biopsy at Screening. This material will be examined by H&E. Tissue will be submitted to the Yale Center for Genome Analysis for WES and RNA sequencing. Immunohistochemistry for expression of Aurora A, phosphoAurora A, phosphoERK, TPX2 and NEDD9 will be performed on pre-treatment biopsies on all cases. Non-Yale sites will submit FFPE to the Burtness Lab at Yale for analysis.

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Post-treatment tumor biopsies will be obtained in Phase 1b (Expansion Phase) at the beginning of Cycle 3 and at disease progression.

Organoid +/- PDX development will be conducted under the existing Yale Advanced Lung Cancer Tissue protocol (HIC #1603017333, Scott Gettinger, PI) under the direction of Dr. Katerina Politi. Material from pre- and post-treatment specimens from patients in the Phase 1b [Expansion Phase) who are treated at Yale will be approached to provide consent for these samples.

APPENDIX G. ETHICAL STANDARDS

Ethics and Regulatory Considerations

This study will be conducted according to Good Clinical Practice (GCP), US 21 Code of Federal Regulations (CFR) Part 50, (Protection of Human Subjects), US 21 CFR Part 56 (Institutional Review Boards), International Conference on Harmonisation Guidance for Industry, E6 Good Clinical Practice: Consolidated Guidance, the Nuremberg Code, and the Declaration of Helsinki.

General Instructions

The U.S. Food and Drug Administration (FDA) regulates studies of drugs, biologics, and medical devices. Consequently, these studies are subject to GCP and FDA regulations and guidance issued by the FDA and are included in, but not limited to, the following parts of the CFR and guideline document:

- 21 CFR Part 11 – Electronic Records; electronic signatures
- 21 CFR Part 50 – Protection of Human Subjects
- 21 CFR Part 54 – Financial Disclosure
- 21 CFR Part 56 – Institutional Review Boards
- 21 CFR Part 312 – Investigational New Drug Application
- FDA Guidance for Industry: Oversight of Clinical Investigations – A Risk-Based Approach to Monitoring, August 2013
- FDA Guidance for IRBs, Clinical Investigators, and Sponsors, June 2010
- FDA Guidance for Industry: Investigator Responsibilities – Protecting the Rights, Safety, and Welfare of Study Subjects, October 2009
- FDA Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE studies, December 2012
- Guidance for Industry E6 Good Clinical Practice: Consolidated Guidance, 1996

Copies of these materials are available from the Sponsor upon request. The purpose of these regulations and legal obligations is to define the standards and principles for the proper conduct of clinical trials that have been developed by the medical, scientific, and regulatory communities. They are not intended to impede or restrict clinical research.

The ethical standards defined within GCP are intended to ensure that:

- Human subjects are provided with an adequate understanding of the possible risks of their participation in the study, and that they have a free choice to participate or not;
- The study is conducted with diligence and in conformance with the protocol in such a way as to insure the integrity of the findings;
- The potential benefits of the research justify the risks.

- VITRAC Therapeutics, LLC is the Sponsor of the IND. The Sponsor is responsible for the following:
- Selecting qualified investigators,
- Providing investigators with the information they need to properly conduct an investigation,
- Ensuring proper monitoring of the investigation,
- Ensuring that the study is conducted according to the general investigational plan and protocols contained in the IND,
- Maintaining the IND, and
- Ensuring that FDA and all participating investigators are properly informed of significant new information regarding adverse effects or risks associated with the drug being studied.