PROTOCOL SYNOPSIS

Study Number	EP0031-101
Title	A Modular, Open-label, Phase I/II Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of EP0031 in Patients with Advanced *RET*-altered Malignancies
Sponsor	**Ellipses Pharma Limited** 10 Stratton Street London W1J 8LG United Kingdom
Clinical Phase	Phase I/II
Study Centres	Approximately 30 study centres globally in the USA and Europe
Investigational Agent	EP0031 is an orally available, potent second-generation selective RET inhibitor (SRI)
Study Type	This is a modular, interventional Phase I/II dose escalation and expansion study to investigate the optimal dose of EP0031
Population Studied	Adult patients with advanced *RET*-altered malignancies
Study Purpose and Rationale	There are currently no RET-targeted treatment options for patients who progress on first-generation SRIs (Solomon et al, 2020, Subbiah et al, 2021). It is proposed that EP0031 can overcome resistance mechanisms to first-generation SRIs. The available preclinical evidence indicates that EP0031 has an activity profile that is differentiated from first-generation SRIs (selpercatinib and pralsetinib) (EP0031 Investigator's Brochure): ▪ EP0031 is a potent and selective RET inhibitor with broad activity against common RET fusions and mutations (KIF5B–RET, CCDC6–RET, RET^{M918T}) ▪ EP0031 inhibits tumour growth in a dose-dependent manner in a number of relevant in vivo xenograft models, comparing favourably with first-generation SRIs ▪ EP0031 is active against $RET^{V804\ E/M/L}$ gatekeeper mutations and $RET^{G810\ C/S/R}$ solvent front mutations ▪ Non-clinically, EP0031 was shown to penetrate the brain and was found to extend the survival time with a numerical, but not statistical, benefit compared with both pralsetinib and selpercatinib in a mouse brain orthotopic PDX model of CR2518 (CCDC6-RET) colon cancer. Therefore, EP0031 has the potential to have activity in brain metastases

	▪ In addition, EP0031 has good selectivity for RET over VEGFR
OBJECTIVES	
Module A Monotherapy—dose escalation	**Primary** ▪ To investigate the safety and tolerability of EP0031 given as monotherapy **Secondary** ▪ To characterize the PK of EP0031 given as monotherapy, after a single dose and at steady state after multiple dosing **Exploratory** ▪ To assess the efficacy of EP0031 given as monotherapy in patients with *RET*-altered tumours who have progressed following first-generation SRI therapy and in patients with RET-altered tumours with no prior SRI therapy (by RECIST v1.1)
Modules B and C Monotherapy—dose expansion	**Primary** ▪ To assess the efficacy of EP0031 given as monotherapy in patients with *RET*-altered tumours who have progressed following first-generation SRI therapy and in patients with *RET*-altered tumours with no prior SRI therapy (by RECIST v1.1) **Secondary** ▪ To investigate the safety and tolerability of EP0031 given as monotherapy ▪ To characterize the PK of EP0031 given as monotherapy
Modules A, B, and C	**Exploratory biomarker objectives** ▪ To assess the PD responses and mode of action of EP0031 ▪ To explore the relationship between EP0031 PK exposure and PD biomarkers ▪ To investigate biomarkers that might predict response or resistance to EP0031
ENDPOINTS	
Module A Monotherapy—dose escalation	**Primary** ▪ Incidence of DLTs, AEs, SAEs, and changes in laboratory parameters, physical examination, vital signs, and ECG **Secondary** ▪ Plasma PK parameters (AUC_{0-48}, AUC_{last}, AUC_{inf}, C_{max} and/or C_{min}, t_{max}, $t_{½}$, CL/F, V/F, and/or Vz/F) after single and multiple doses

	Exploratory ▪ Objective response rate (ORR) ▪ Best overall response (BOR) ▪ Duration of response (DOR) ▪ Change in tumour size ▪ Progression free survival (PFS) ▪ Overall survival (OS)
Modules B and C Monotherapy—dose expansion	**Primary** ▪ ORR ▪ BOR ▪ DoR ▪ Change in tumour size ▪ PFS ▪ OS **Secondary** ▪ Incidence of DLTs, AEs, SAEs, and changes in laboratory parameters, physical examination, vital signs, and ECG ▪ Plasma PK parameters (eg, AUC_{0-48}, AUC_{last}, AUC_{inf}, C_{max} and/or C_{min}, t_{max}, $t_{½}$, CL/F, V/F, and/or Vz/F)
Modules A, B, and C	**Exploratory biomarker endpoints** ▪ Biomarkers in blood (eg, growth factors, gene expression, and circulating tumour DNA [ctDNA]) will be examined for correlations with dose and efficacy endpoints ▪ Tumour biopsy and ctDNA will be used to determine *RET* gene fusions and mutations ▪ Tumour biopsy tissue may be examined for evidence of downregulation of RET pathway activation and potential mechanisms of resistance to EP0031 ▪ Response to EP0031 may be assessed through determination of tumour-related biomarkers such as calcitonin, CA 19.9, CEA, CYFRA 21-1, thyroglobulin, and TG Abs, depending on tumour type ▪ ctDNA may be used to monitor response through determination of levels of ctDNA during and post-progression on EP0031, and by monitoring the emergence of new RET alterations and other tumour-specific mutations
STUDY DESIGN	
Core Study Design	The design consists of a core study protocol and individual Modules. The modular study design is one recognized and accepted by key regulatory authorities to allow investigation of patients with various advanced malignancies. This study will consist of 3 modules: ▪ **Module A:** Monotherapy dose escalation in *RET*-altered solid tumours (including a paired biopsy cohort)

	The EP0031 starting dose and schedule of EP0031 in Module A has been selected using non-clinical data, available clinical data from the Kelun Biotech first-in-human trial (KL400-I/II-01), and the FDA and ICH S9 Guideline on Non-Clinical Evaluation for Anti-Cancer Pharmaceuticals for selection of a starting dose in cancer patients. The frequency of dosing may change based upon emerging data, as reviewed and agreed by the Safety Monitoring Committee (SMC), without the requirement to submit a substantial amendment to the protocol. ▪ **Module B:** Dose expansion in patients who have progressed following first-generation selective RET inhibitor (SRI) therapy (pralsetinib or selpercatinib) (Cohorts 1–3) and in patients who have had no prior SRI therapy (Cohorts 4–6), with the following *RET*-altered tumours: – Cohort 1: RET fusion positive non-small cell lung cancer (NSCLC) – Cohort 2: RET mutation positive medullary thyroid cancer (MTC) – Cohort 3: other RET-altered solid tumours – Cohort 4: RET fusion positive NSCLC (no prior SRI) – Cohort 5: RET mutation positive MTC (no prior SRI) – Cohort 6: other RET-altered solid tumours (no prior SRI) ▪ **Module C:** Further dose expansion in patients who have progressed following first-generation SRI therapy, in patients with *RET*-altered tumours: – Cohort 1: RET fusion positive NSCLC – Cohort 2: RET mutation positive MTC – Cohort 3: other RET-altered solid tumours Module C, Cohorts 1–3 are continuations of Module B, Cohorts 1–3.
Module A Monotherapy—dose escalation and RP2D optimisation	Phase I dose escalation to investigate safety, tolerability, PK, and PD and to define the maximum tolerated dose (MTD) and/or recommended phase II dose (RP2D), using a rolling 6 design. Within Module A dose escalation, a paired biopsy cohort will be included (for patients who have progressed after a first-generation SRI and at a biologically active dose). In this cohort, approximately 12 patients will be enrolled to deliver up to 7 evaluable paired biopsies. Patients within the paired biopsy cohort may receive different doses of EP0031 (see **Section 7.5.10** and **Table 17** for further details). Following identification of the MTD, and review of the PK, safety and efficacy data, additional patients will be recruited to further characterize the optimal clinical dose and facilitate selection of an optimum RP2D for Modules B and C: 1) Further expansion of the preceding dose level (MTD-1) to a total of 10 patients

	2) Exploration of an additional dose level which is intermediate between MTD-1 and MTD, or lower than the MTD-1, with expansion to a total of 10 patients following satisfactory completion of an initial 3 or 6 patients All doses will be selected by the SMC (see **Section 6.4.4**).
Module B Monotherapy—dose expansion and initial efficacy	Once an RP2D is established from Module A, expansion cohorts of approximately 25 evaluable patients will be opened to further explore the safety and tolerability of EP0031 and provide preliminary efficacy data in selected patients populations with *RET*-altered tumours. Cohorts will include the following tumour types: ▪ Four cohorts will be in selected tumour types (NSCLC and MTC in patients who have progressed following first-generation SRI therapy (immediate prior therapy) and in patients with no prior SRI therapy) ▪ Two cohorts will include patients with other solid tumours (in patients who have progressed following first-generation SRI therapy (immediate prior therapy), and in patients with no prior SRI therapy) If fewer than 7 evaluable paired biopsies were collected during Module A, further patients may be consented to provide paired biopsies during Module B (Cohorts 1–3) (see **Section 7.5.10** and **Table 17** for further details).
Module C Monotherapy—further dose expansion and efficacy assessment	Following determination of an RP2D and when safety and tolerability are better established, further assessment of efficacy will be conducted in cohorts of approximately 25 patients who have progressed following treatment with first-generation SRIs (continuation of Module B, Cohorts 1–3). Two cohorts will be in selected tumour types (NSCLC and MTC), and the third cohort will include patients with other *RET*-altered malignancies. Populations for Cohorts 1–3 may be further defined, dependent on data and PD biomarker findings from Modules A and B. Dependent on the data from SRI-naïve patients dosed during Module B, Cohorts 4–6 may be further expanded in Module C. This will be defined in a protocol amendment.
Number of Patients (planned)	▪ **Module A:** The number of patients to be enrolled is dependent on the number of dose escalations required in the dose escalation part of the study. Dose escalation will be based on a rolling 6 design and is expected to recruit approximately 40 patients. Two of these cohorts will be expanded to 10 patients to facilitate selection of an optimum RP2D for Modules B and C. ▪ **Module B:** For each of the 6 planned cohorts in the dose expansion part of the study, approximately 25 evaluable patients will be enrolled

	▪ **Module C:** For each of Cohorts 1–3, an additional 25 evaluable patients will be enrolled (a total of approximately 50 patients per cohort in Modules B and C) Therefore, a total of approximately 265 patients will be enrolled.
CORE ELIGIBILITY CRITERIA	
Inclusion criteria For the complete list of inclusion criteria, see **Section 5.3**.	1. Male or female patients ≥ 18 years of age, at the time of informed consent, with a diagnosis of advanced solid tumour (locally advanced or metastatic which is not amenable to treatment with curative intent) 2. Documented *RET*-altered malignancy as determined by a DNA- or RNA-based assay of tumour tissue and/or a liquid biopsy based on local testing 3. Patients with *RET*-altered cancers that may be eligible for the study, who have not received a prior SRI should be well informed and consented about alternative treatment options including approved RET-targeted therapies 4. Patients with *RET*-altered cancers that may be eligible for the study having progressed on a prior SRI should be well informed and consented about alternative approved therapies, as applicable 5. Tissue or liquid biopsy at screening for retrospective confirmation of RET aberration status, after progression on first-generation SRI (when specified for cohort): a. Archival tissue (if available, should not be older than 6 months) b. Or a fresh tissue biopsy, if feasible from a safely accessible site, per Investigator's determination, provided the patient has more than one measurable target lesion and the patient has given consent for a fresh biopsy c. Or liquid biopsy (if archival or fresh is not available/feasible) 6. Patients in the paired biopsy cohort must have a tumour that is accessible (providing that the Investigator judges the biopsy technically feasible with minimal risk to the patient and with patient consent, see **Section 7.5.10**) 7. Module A: Measurable or non-measurable disease as per RECIST v1.1 8. Modules B and C: At least one lesion (not previously irradiated and not chosen for biopsy during the study screening period) that is measurable as defined by RECIST v1.1 9. ECOG performance status of 0 or 1 10. Ability to swallow and retain oral medication

	11. Ability to understand and provide written informed consent before any study-specific procedures, sampling, or analyses, including access to archival tumour tissue
Exclusion criteria For the complete list of exclusion criteria, see **Section 5.4**.	1. Any other known major driver gene alterations except RET 2. Any other invasive malignancy which has been active or treated within the past 3 years, with the exception of cervical intraepithelial neoplasia and non-melanoma skin cancer 3. Any unresolved toxicities from prior systemic therapy greater than CTCAE Grade 1 at the time of starting study drug, with the exception of alopecia and Grade 2 chemotherapy-induced neuropathy 4. Spinal cord compression or unstable brain metastases. Patients with stable brain metastases who have completed definitive therapy, are not on steroids, and have a stable neurological status for at least 4 weeks after completion of definitive therapy and steroids can be enrolled. Patients with asymptomatic brain metastases may be eligible for inclusion, if, in the opinion of the Investigator, immediate definitive treatment is not indicated 5. Active infection requiring systemic antibiotic, antifungal, or antiviral medication within 7 days prior to first dose of EP0031 6. Severe or uncontrolled medical condition (eg, severe Parkinson's disease, active inflammatory bowel disease, severe chronic obstructive pulmonary disease, or interstitial lung disease/pneumonitis - patients with a history of interstitial lung disease/pneumonitis that has recovered to ≤ Grade 1 can be enrolled after discussion with the Medical Monitor) or psychiatric condition 7. Active bleeding diatheses 8. Chronic glomerulonephritis or renal transplant 9. Known active hepatitis B, or active hepatitis C 10. Patients with active HIV infection. Patients living with HIV will be eligible if they have CD4+ T-cell count ≥ 350 cells/µL, no history of AIDS-defining opportunistic infections in the past 12 months, and can be managed on a regimen consistent with this protocol's permitted concomitant medications 11. Active infection with SARS-Cov-2 12. Breastfeeding or pregnancy 13. Receipt of any immunotherapy or antibody therapy within 28 days before the first dose of EP0031 14. Receipt of any systemic anticancer therapy (with the exception of immunotherapy or antibody therapy) and all forms of radiotherapy within 14 days or < 5 half-lives, whichever is shorter, before the first dose of EP0031

15. Receipt of any strong inhibitor or inducer of CYP3A4 within 14 days or < 5 half-lives, whichever is shorter, before the first dose of EP0031
16. Receipt of systemic corticosteroids (at a dose > 10 mg prednisone/day or equivalent) within 14 days before the first dose of EP0031
17. Known hypersensitivity to other SRIs or to the excipients of EP0031
18. Impaired hepatic or renal function as demonstrated by any of the following laboratory values:
    - AST or ALT > 3 × ULN
    - Total bilirubin > 1.5 × ULN
    - Estimated GFR ≤ 60 mL/min (based on Cockcroft Gault)
19. Serum calcium, magnesium, or potassium below institutional LLN (can be corrected prior to enrolment)
20. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values:
    - ANC < 1.5 × 10^9/L
    - Platelet count < 100 × 10^9/L
    - Haemoglobin < 90 g/L
21. Any clinically important abnormalities in rhythm, conduction, or morphology on resting ECG (eg, complete left bundle branch block, third-degree heart block, confirmed QTcF > 470 msec on screening ECG). Controlled atrial fibrillation (AF) is permitted (eg, managed with beta blockers)
22. Any factor that increases the risk of QTc prolongation or of arrhythmic events (eg, heart failure, electrolyte abnormalities as per exclusion criterion no. 18, congenital long QT syndrome, immediate family history of long QT syndrome, or unexplained sudden death under 40 years of age or requirement for concomitant medications that are known to prolong the QTc interval and cause Torsade de Pointes within < 5 half-lives before the first dose of EP0031; see **Appendix 6**)
23. Congestive heart failure Grade II–IV according to the New York Heart Association, myocardial infarction or unstable angina within the previous 6 months
24. Uncontrolled hypertension (ie, sustained systolic BP >150 mmHg or diastolic BP >90 mmHg; based on the mean of 3 readings)
25. Corneal ulceration at the screening ophthalmic assessment
26. For MTC patients: involvement of the trachea or oesophagus, or complete encasement of great vessels (eg, aorta or pulmonary artery) which, in the opinion of the Investigator, could result in life-threatening complications due to rapid tumour regression

	27. Any major (in the Investigator's judgement) surgical procedure within 4 weeks of the first dose of study treatment or planned or anticipated during study treatment (minimally invasive procedures such as bronchoscopy, tumour biopsy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery and are not exclusionary) 28. In the opinion of the Investigator, unlikely to comply with study procedures, restrictions, or requirements 29. Has received a live-virus vaccination within 28 days or less of planned treatment start
Contraception Criteria	1. Female patients should either be of non-childbearing potential or must agree to use a highly effective method of contraception from Screening until 3 months following administration of the last dose of study drug 2. Male patients must agree not to father a child or donate sperm from enrolment through treatment and for 6 months following administration of the last dose of study drug (if their partner is of childbearing potential this may be by the male using a condom or by their partner using highly effective contraception)

Study Drug	The study drug EP0031 will be supplied by the Sponsor, Ellipses Pharma Ltd. EP0031 will be supplied as capsules containing a white to light-yellow powder and will be administered at doses from 20 to 200 mg QD. For the first dose of EP0031, a physician must be present at the site, or be immediately available to respond to emergencies. In the event of toxicities, the dose of EP0031 may be modified and a revised dose/schedule selected (see **Section 6.13**).
Duration of Treatment	Patients may continue to receive EP0031 until they have progressive disease (by RECIST v1.1) or are clinically unstable, have unacceptable toxicity, withdraw from treatment for any reason, or the Investigator believes they are no longer receiving benefit from treatment. If a patient has disease progression based on RECIST v1.1 but the patient is well and the Investigator considers that they are still achieving clinical benefit and there are no toxicities, the patient may continue to receive EP0031 (see **Section 6.10**).
Efficacy Assessments	Treatment response will be assessed by the Investigator in accordance with RECIST v1.1. Baseline imaging will be obtained within 28 days before the first dose and the same imaging modality will be used to assess response in 8-week intervals, beginning 8 weeks after the first dose of study drug for 48 weeks (12 treatment cycles), and thereafter every 12 weeks (± 2 weeks) until disease progression. Confirmatory imaging will be performed at least 4 weeks after the initial response, which may be the next scheduled scan, in accordance with RECIST v1.1 requirements, for confirmation of complete response (CR) or partial response (PR). Disease progression in this study is defined by RECIST v1.1.
Safety Assessments	▪ AEs grading using NCI CTCAE (v5.0) ▪ Laboratory: haematology, biochemistry, and urinalysis ▪ Vital signs, physical examination, ECG, ECOG performance status ▪ Safety assessed by the nature, frequency, severity, and drug-relatedness of AEs ▪ Patients to be assessed for safety at screening, during the treatment period, and during the follow-up period The Investigator must notify the Sponsor immediately (within 24 hours) of any SAE or adverse event of special interest (AESI).

STATISTICAL METHODS	
Module A Monotherapy—dose escalation	The precise sample size cannot be determined as it is dependent on the number of cohorts. The escalation will be based on a rolling 6 design for MTD determination in up to 6 dose cohorts. Patients will be enrolled to ensure a minimum of 3 and a maximum of 6 evaluable patients per dose cohort. Two of these cohorts will be expanded to 10 patients to facilitate selection of an optimum RP2D for Modules B and C.
Modules B and C Monotherapy—dose expansion	In the expansion cohorts, 25 evaluable patients are deemed sufficient to explore an initial efficacy signal using Simon's two-stage design (Simon, 1989) to guide go/no go decision making. In Cohorts 1–3, the target ORR is 45%. The null hypothesis that the true response rate is 25% will be tested against a one-sided alternative. In the first stage (Module B), approximately 25 patients will be accrued. If there are 7 or fewer responses in these 25 patients, the cohort will not progress to Module C. Otherwise, approximately 25 additional patients will be accrued in Module C for a total of 50 patients. The null hypothesis will be rejected if 17 or more responses are observed in 50 patients. This design yields a type I error rate of 5% one-sided and power of 90% when the true response rate is 45%. Before making a decision to stop any cohort based on ORR after Module B, the tumour response data (including the impact of acquired resistance mutations and biomarkers) will be reviewed in detail including duration of response and assessment of change in tumour size over time to determine if responses are likely with further follow-up, or if there is a consistent reduction in tumour size that is likely to translate to a benefit in PFS. No formal statistical analysis will be carried out. Descriptive statistics (including means, standard deviations and medians for continuous variables and proportions and confidence intervals [CIs] for discrete variables) will be used to summarize data as appropriate. A comprehensive statistical analysis plan will be prepared and signed off before database lock.
Safety Analysis	▪ Safety analyses will be performed in each study module using the Safety Analysis Set ▪ Safety data, AEs, and treatment-emergent AEs (TEAEs) from all cycles of treatment will be presented graphically, as is deemed appropriate for each module. These will be summarised by MedDRA SOC, MedDRA PT, and CTCAE grade ▪ SAEs will be analysed and reported separately ▪ Details of any deaths will be listed

	▪ All laboratory results, ECOG performance status, ECG parameters, weight, and vital signs will be listed individually by patient and summarized descriptively for each module. Qualitative urinalysis assessments will be summarized using the number of patients with results of negative, trace, or positive
PK Analysis	▪ PK analyses will be performed using the PK Analysis Set. PK parameters will be derived using standard non-compartmental methods ▪ EP0031 plasma concentrations and derived PK parameters will be summarised by dose level ▪ PK parameters following single and multiple dosing will be summarized separately. Appropriate statistics will be used to summarize plasma concentrations and PK parameters
Efficacy Analysis	The key efficacy variable is ORR, defined as the proportion of patients with BOR of a confirmed CR or PR based on local Investigator assessment, as defined per RECIST v1.1. This will be summarized for each expansion cohort, with corresponding 90% CIs.