



**A Phase 3, Randomized, Double-blind, Placebo-Controlled, Multicenter
Study of ABSK021 to Assess the Efficacy and Safety in Patients with
Tenosynovial Giant Cell Tumor**

Protocol Number:	ABSK021-301
Trial Phase:	Phase 3
Sponsor:	Abbisko Therapeutics Co., Ltd. Building 3, Lane 898, Halei Road, Pudong, Shanghai, 201203, China Tel: + 86-021-68912098
US IND Number:	143665
EU CT Number:	2023-503245-58-00
Universal Trial Number (UTN):	U1111-1286-9453
Version No.:	2.2
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This study will be conducted according to the protocol and in compliance with Good Clinical Practice, the ethical principles stated in the Declaration of Helsinki, and other applicable regulatory requirements.

Confidential Information

The information in this document is confidential and is not to be disclosed without the written consent of Abbisko Therapeutics except to the extent that disclosure would be required by law **and** for the purpose of evaluating and/or conducting a clinical study for Abbisko Therapeutics. You are allowed to disclose the contents of this document only to your Institutional Review Board and study personnel directly involved with conducting this protocol. Persons to whom the information is disclosed must be informed that the information is confidential and proprietary to Abbisko and that it may not be further disclosed to third parties.

SPONSOR SIGNATURE PAGE

I have read and agreed on the contents of this protocol in detail, and I will perform the responsibilities of the sponsor in strict accordance with Good Clinical Practice and other relevant laws and regulations.



Chief Medical Officer

Date

INVESTIGATOR SIGNATURE PAGE

I understand that all documentation provided to me by Abbisko Therapeutics or its designated representative(s) concerning this study that has not been published previously will be kept in the strictest confidence. This documentation includes the study protocol, Investigator brochure, case report forms, and other scientific data.

This study will not commence without the prior written approval of a properly constituted Institutional Review Board (IRB)/Independent Ethics Committee (IEC). No changes will be made to the study protocol without the prior written approval of Abbisko Therapeutics and IRB/IEC, except where necessary to eliminate an immediate hazard to the patient.

I have read, understood, and agree to abide by all the conditions and instructions contained in this protocol.

Investigator Signature

Date

Name of Investigator site

PROTOCOL SYNOPSIS

Study Title	A Phase 3, Randomized, Double-blind, Placebo-Controlled, Multicenter Study of ABSK021 to Assess the Efficacy and Safety in Patients with Tenosynovial Giant Cell Tumor
Protocol No.	ABSK021-301
Study Phase	Phase 3
Planned Patient No.	Approximately 90 patients with Tenosynovial Giant Cell Tumor (TGCT) are planned to be enrolled, including 60 patients in the ABSK021 group and 30 patients in the placebo group.
Study Objectives	<p><u>Primary Objective</u></p> <ul style="list-style-type: none"> To compare the Objective Response Rate (ORR) within 25 weeks after treatment with ABSK021 or placebo in TGCT patients based on RECIST v1.1. <p><u>Secondary Objective</u></p> <ul style="list-style-type: none"> To compare the Objective Response Rate (ORR) within 25 weeks after treatment with ABSK021 or placebo in TGCT patients based on Tumor Volume Score (TVS); To compare the effects of ABSK021 and placebo on the Range of Motion (ROM) in TGCT patients at Week 25; To compare the effects of ABSK021 and placebo on Patient-Reported Outcome (PRO) in TGCT patients at Week 25; To compare the Duration of Response (DOR) after treatment with ABSK021 or placebo in TGCT patients based on RECIST v1.1 and TVS, respectively; To compare the safety of ABSK021 and placebo in TGCT patients; To evaluate the pharmacokinetic (PK) profile of oral ABSK021.
Study	<u>Primary Study Endpoints</u>

<p>Endpoints</p>	<ul style="list-style-type: none"> • 25-Week ORR by Blinded Independent Review Committee (BIRC) based on RECIST v1.1: the proportion of patients who achieve the Best Overall Response (BOR) of either Complete Response (CR) or Partial Response (PR) as assessed by BIRC within 25 weeks according to RECIST v1.1. <p><u>Key Secondary Study Endpoints</u></p> <ul style="list-style-type: none"> • 25-Week ORR by BIRC based on TVS: the proportion of patients who achieve the BOR of either CR or PR as assessed by BIRC within 25 weeks according to TVS criteria; • Mean change from baseline in Range of Motion (presented as relative ROM) of the affected joint at Week 25, according to the reference criteria for the same joint; • Mean change from baseline in the Worst Stiffness Numeric Rating Scale (NRS) score at Week 25; • Mean change from baseline in the BPI Worst Pain Numeric Rating Scale (NRS) score at Week 25; • Mean change from baseline in the Patient-reported Outcomes Measurement Information System (PROMIS) Physical Functioning score at Week 25. <p><u>Other Secondary Study Endpoints</u></p> <ul style="list-style-type: none"> • DOR by BIRC based on RECIST v1.1: the time (months) from the first documentation of objective response (CR or PR as assessed by BIRC per RECIST v1.1 criteria) to the first documentation of radiographic disease progression (PD) or death due to any cause, whichever occurs first; • DOR by BIRC based on TVS: the time (months) from the first documentation of objective response (CR or PR as assessed by BIRC per TVS criteria) to the first documentation of radiographic PD or death due to any cause, whichever occurs first; • 25-week ORR by Investigator per RECIST v1.1: proportion of patients with a BOR of CR or PR assessed by the Investigator within 25 weeks according to RECIST v1.1;
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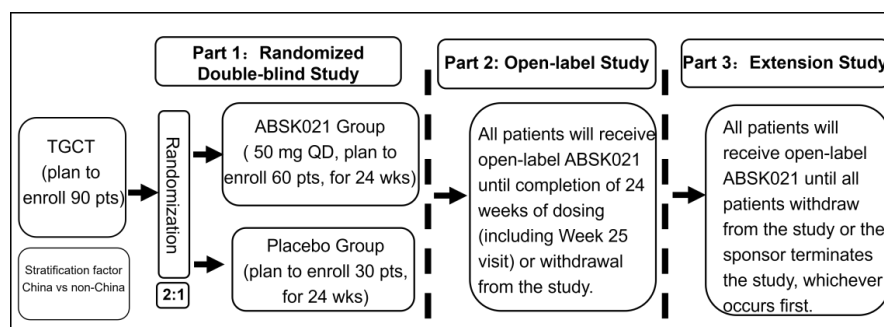
	<ul style="list-style-type: none"> • DOR by Investigator per RECIST v1.1: the time (months) from the first documentation of objective response (CR or PR as assessed by the Investigator per RECIST v1.1 criteria) to the first documentation of radiographic PD or death due to any cause, whichever occurs first; • Mean change from baseline in EuroQol 5-dimension, 5-level questionnaire (EQ-5D-5L) visual analogue scale (VAS) score at Week 25; • Safety endpoints, including but not limited to treatment emergent adverse events (TEAEs), dose modifications, laboratory tests, vital signs, electrocardiograms (ECGs), echocardiography, and related items in NCI-PRO-CTCAE; • PK profile of ABSK021.
Study Design	<p>This is a randomized, double-blind, placebo-controlled Phase 3 clinical study to evaluate the efficacy and safety of ABSK021 at the dose of 50 mg QD in patients with Tenosynovial Giant Cell Tumor. This study consists of Part 1, Part 2, and a long-term extension treatment phase (i.e., Part 3). Part 1 is a double-blind phase, eligible patients will be randomized in a 2:1 ratio to ABSK021 treatment group or matching placebo group and will receive 50 mg QD of ABSK021 or matching placebo (28 days/cycle) until completion of treatment and follow-up in Part 1 (i.e., completion of ABSK021 administration at Week 24 and completion of Week 25 follow-up visit including MRI) or withdraw from the study. Randomization will be stratified by China and non-China sites. All patients who complete Part 1 treatment and meet eligibility criteria will be eligible to continue in Part 2 of the study.</p> <p>Part 2 is an open-label treatment phase, and all patients entering this phase will receive 50 mg QD of open-label ABSK021 until completion of 24 weeks of dosing or withdrawal from the study (If a patient has dose modification in Part 1, the patient will continue to be administered at the modified dose in Part 2). Patients must continue to meet eligibility criteria to continue on to Part 2. After the patient has achieved a sustained tumor response (defined as</p>

continuous radiological PR or CR for more than 6 months by BIRC or Investigator based on RECIST v1.1), the Investigator and the sponsor will discuss and decide whether the current recommended starting dose can be reduced to 25 mg QD during the subsequent maintenance treatment. If the Investigator assesses that the patient will not benefit from subsequent treatment, the patient may be discontinued from the study treatment. Part 2 will end after all patients have completed 24 weeks of dosing (including follow-up at Week 25) or have withdrawn from the study.

Patients who complete Part 1 will be invited by the site investigator or staff to take part in an optional qualitative interview, to explore the disease experience during the clinical trial. See appendix 12.9 and 12.10 for more details.

All patients who complete 24 weeks of dosing in Part 2 and continue to meet eligibility criteria will enter the open-label extension treatment phase (i.e., Part 3) for a longer period treatment and safety follow-up. Part 3 will end when all patients withdraw from the study, or the sponsor decides to terminate the study, whichever occurs first.

The study design is specified in the following figure:



An independent Data Monitoring Committee (IDMC) will be established in Part 1 and Part 2 of this study to continuously monitor the safety profile and oversee the overall conduct of the study. In order to improve the integrity of the study, the IDMC may also make recommendations on patient selection, recruitment, and management in order to improve patient compliance and improve data management and quality control procedures. A separate IDMC charter will define

	IDMC members, roles, and responsibilities, as well as the process of providing advice to the sponsor.
Inclusion and Exclusion Criteria	<p>Inclusion criteria:</p> <ol style="list-style-type: none"> 1. Patients should understand the study procedures and sign the informed consent form prior to screening. 2. Age \geq 18 years. 3. A diagnosis of TGCT, and meet the following 2 requirements prior to randomization: (i) that has been histologically confirmed either by local or central laboratory; (ii) unresectable, defined as confirmed by assessment by at least two clinical experts (including at least one independent expert who is not part of the trial conduct), meeting one of the following 2 requirements: ① located in a complex anatomical site, is extensively invasive, and cannot be completely resected; or ② surgical operation may cause dysfunction or serious complications. 4. Measurable disease as defined by RECIST v1.1 and with at least one lesion of \geq 2 cm (assessed by MRI scans in local site) prior to randomization. 5. For patients with an analgesic need, a stable prescription of analgesic regimen assessed by the Investigator during the 2 weeks prior to randomization. 6. During the 2 weeks prior to randomization, at least 4 of 7 consecutive days of BPI Worst Pain NRS items and Worst Stiffness NRS items completed correctly. 7. Symptomatic disease because of active TGCT, defined as one or more of the following: (i) a worst pain of at least 4 within 2 weeks prior to randomization (based on scale of 0 to 10, with 10 representing “pain as bad as you can imagine”), (ii) a worst stiffness of at least 4 within 2 weeks prior to randomization (based on a scale of 0 to 10, with 10 representing “stiffness as bad as you can imagine”).

8. Willingness and ability to complete the patient-reported outcome (PRO) assessments throughout the study, including BPI-Worst-Pain-NRS, Worst-Stiffness-NRS, PROMIS Physical Functioning Scale, NCI-PRO-CTCAE and EQ-5D-5L Health Scale.
9. ECOG PS (Eastern Cooperative Oncology Group Performance Status) of 0 or 1.
10. Adequate organ function and bone marrow function as indicated by the following screening assessments performed within 14 days prior to randomization:
 - a) Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/\text{L}$;
 - b) Platelet count (PLT) $\geq 90 \times 10^9/\text{L}$;
 - c) Hemoglobin (Hb) $\geq 90 \text{ g/L}$ (or $\geq 9 \text{ g/dL}$);
 - d) Total bilirubin (TBIL) $\leq 1.5 \times \text{ULN}$;
 - e) Aspartate transaminase (AST) and Alanine transaminase (ALT) $\leq 1.5 \times \text{ULN}$;
 - f) Alkaline phosphatase (ALP) $\leq 1.5 \times \text{ULN}$;
 - g) Creatinine clearance (Crcl) $\geq 50 \text{ mL/min}$ (Cockcroft-Gault formula).

Note: if the results of screening laboratory test do not meet the above criteria, re-examination will be allowed for only once during the screening period at Investigator's discretion.

Exclusion criteria:

1. Known allergy or hypersensitivity to any components of the investigational drug product.
2. Previous treatment with highly selective inhibitors targeting CSF-1/CSF-1R prior to randomization. However, patients who have received prior treatment with multi-kinase inhibitors that include the CSF-1/CSF-1R pathway are allowed, such as Imatinib and Nilotinib.
3. Known additional malignancy that required active treatment and may affect the patient's participation in the study or affect the

	<p>outcome of the study as assessed by the Investigator. Exceptions include cured basal cell carcinoma of skin, squamous cell carcinoma of skin, and other carcinoma in situ.</p> <ol style="list-style-type: none">4. Known metastatic TGCT.5. Significant concomitant arthropathy in the affected joint, serious disease, uncontrolled infection.6. Known MRI contraindications.7. Has factors that significantly affected the absorption of oral drug, such as inability to take oral medication or significant nausea and vomiting, malabsorption, external bile duct drainage, massive small bowel resection, etc.8. Major surgery or previous anti-tumor therapy for TGCT within 4 weeks prior to randomization, or unhealed, infected, or dehiscence of previous surgical wounds, or adverse events from prior therapies did not recover to \leq Grade 1 (CTCAE 5.0). <i>Patients with Grade ≤ 2 adverse events during Part 1 are allowed to continue on to Part 2, based on the Investigator's overall risk-benefit assessment. Patients with Grade ≤ 2 adverse events during Part 2 are allowed to continue on to Part 3, based on the Investigator's overall risk-benefit assessment.</i>9. Concomitant use of strong inhibitors or inducers of CYP3A4 within 14 days prior to randomization. Grapefruit juice, grapefruit hybrids, pomegranates, carambola, grapefruit, Seville oranges and juice or other processed product consumption within 3 days prior to randomization.10. Impaired cardiac function or clinically significant cardiac disease, including any one of the following:<ol style="list-style-type: none">a) New York Heart Association (NYHA) class III or IV heart disease, active ischemia or any other uncontrolled cardiac condition such as angina pectoris, clinically significant cardiac arrhythmia requiring therapy, uncontrolled hypertension or congestive heart failure;
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	<p>b) Prolongation of the rate-corrected QT interval based on repeated demonstration of QTcF > 480 ms (QTc interval corrected by Fridericia's formula), or history of long QT interval corrected (QTc) syndrome;</p> <p>c) Left ventricular ejection fraction (LVEF) < 50% or below the lower limit of normal, whichever is higher.</p> <p>11. Known active human immunodeficiency virus (HIV antibody test positive), active hepatitis B (HBsAg positive and HBV-DNA > upper limit of reference range), active hepatitis C (HCV-Ab positive and HCV-RNA > upper limit of reference range), or known active tuberculosis prior to randomization.</p> <p>12. Known active liver or biliary disease, or other diseases that may lead to abnormal liver function test results during the study, including but not limited to Gilbert's Syndrome, Nonalcoholic Steatohepatitis (NASH) and cirrhosis.</p> <p>13. Pregnant or lactating women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test within 7 days prior to randomization.</p> <p>14. Childbearing potential males or non-surgically sterilized female patients must agree to use effective methods of contraception from at least 14 days prior to randomization until 6 months after the last dose of study drug. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.</p> <p>15. Any other clinically significant comorbidities, such as uncontrollable pulmonary disease, active infection, or any other condition, which in the judgment of the Investigator, could compromise compliance with the protocol, interfere with the interpretation of study results, or predispose the patient to safety risks.</p>
Investigational Product and Dosing	In Part 1, patients in ABSK021 group will receive ABSK021 (25 mg/capsule), 2 capsules once daily, with a total daily dose of 50 mg; patients in the placebo group will receive ABSK021-matching placebo

Regimen	<p>2 capsules once daily. All patients will receive repeated oral doses with each treatment cycle of 28 days until the completion of 24 weeks of dosing or withdrawal from the study. Patients who complete treatment and follow-up in Part 1 (i.e., completion of 24 weeks of dosing and follow-up at Week 25 including MRI) and meet eligibility criteria will be eligible to continue in Part 2 or end of treatment.</p> <p>In Part 2, all patients will receive open-label ABSK021 (25 mg/capsule), 2 capsules once daily, with a total daily dose of 50 mg (If a patient have dose modification in Part 1, the patient will continue to be administered at the modified dose in Part 2). All patients will receive treatment with ABSK021 until completion of 24 weeks of dosing or withdrawal from the study.</p> <p>In Part 3, all patients will continue to receive open-label ABSK021 once daily until any of the following events occurs: disease progression, experiencing unacceptable toxicity, withdrawal of inform consent form, commercialization of the study drug for the treatment of TGCT approved by the local regulatory authorities, decision by the sponsor to terminate the study, or until 2 years after the last patient enters Part 3, whichever occurs first. The starting dose in Part 3 for an individual patient will be determined by the dose he/she received at the end of Part 2.</p>
Dose Selection Rationale	<p>In the dose escalation part of a Phase 1 study, data from 32 tumor patients who have been treated with ABSK021 (from 25 mg QD to 100 mg QD, 26 DLT-evaluable patients) has been accumulated as of December 2021. Results showed that ABSK021 was safe and well tolerated, no DLTs were observed in the 25 mg QD group (a total of 6 DLT-evaluable patients), no DLT was observed in the 50 mg QD group (a total of 12 DLT-evaluable patients), and 1 patient in the 75 mg QD group (a total of 6 DLT-evaluable patients) had a DLT, and 2 patients in the 100 mg QD group (a total of 2 DLT-evaluable patients) had DLTs. The current MTD is 75 mg QD and the mean $t_{1/2}$ of ABSK021 ranged from 39 to 60 hours in dose range of 25 mg to 100 mg. These results support further exploration of QD dose regimen. Therefore, 50 mg QD was used as the first RDE dose in the Phase 1 expansion part and 25 mg QD was used as the second RDE dose for TGCT patients in the Phase 1 expansion part.</p>

	<p>As of 1st June 2022, a total of 27 patients with unresectable TGCT have been treated with ABSK021 at 50 mg QD in the expansion part, and more than 20 patients have been on treatment for ≥ 3 months. The majority of TEAEs reported were Grade 1 or 2, and no drug-related TEAEs \geq Grade 3 have been reported. Dose reduction due to AEs was not reported. Favorable antitumor activity was observed in TGCT patients, as tumor regression was observed in almost all evaluated patients. Preliminary PK-PD analysis also supported the dose selection of 50 mg QD. The effect of ABSK021 exposure on non-classical monocytes was almost saturated at doses ≥ 25 mg QD. There was a positive correlation between changes in CSF-1 levels and ABSK021 concentration in vivo, considering higher PK exposure at 50 mg QD than 25 mg QD (preliminary results showed C_{\max} was 325 ng/mL and 191 ng/mL, AUC_{last} was 3204 hr * ng/mL and 2043 hr * ng/mL, under 50 mg and 25 mg QD dosing, respectively) and good safety data, this selected dose may lead to better efficacy in TGCT patients.</p> <p>The effect of high-fat food on the PK of a 25 mg single oral dose ABSK021 was evaluated in study ABSK021-102, and the results suggested that, after oral administration with high-fat food, the overall exposure AUC_{inf} of ABSK021 showed no difference with that of ABSK021 administrated under a fasting state. Therefore, impact on efficacy is not expected in TGCT patients whether ABSK021 is taken with or without food. Meanwhile, high-fat food will delay the time to peak of ABSK021 from 1 hour to 4 hours, and reduce the peak concentration by approximately 45%, as a result, co-administration with food is not expected to pose an additional risk of AEs such as CK and AST increased, which are more common in patients.</p> <p>Based on the above safety, efficacy, preliminary PK-PD and food effect study data, oral administration of ABSK021 at 50 mg QD is selected as the recommended dose in this study and co-administration with food is not restricted.</p>
Treatment Duration	<p>The Part 1 study consists of a screening period (within 28 days prior to randomization) and a treatment period of 6 cycles (28 days/cycle, 24 weeks in total). The primary endpoint analysis will be performed after the last patient has completed Week 25 follow-up and tumor</p>

	<p>assessments (including Investigator assessment and BIRC assessment).</p> <p>The Part 2 study consists of a treatment period of 6 cycles (28 days/cycle, 24 weeks in total). Patients who complete treatment in Part 2 will be eligible to enter Part 3 to continue a longer period of treatment and safety follow-up.</p> <p>Part 3 is an extension treatment phase. All patients will continue to receive open-label ABSK021 continuously (28 days per cycle) until any of the following events occur: disease progression, experiencing unacceptable toxicity, withdrawal of informed consent form, commercialization of the study drug for the treatment of TGCT approved by the local regulatory authorities, decision by the sponsor to terminate the study, or until 2 years after the last patient enters Part 3, whichever occurs first.</p>
<p>Statistical</p> <p>Method</p>	<p>Sample Size Determination</p> <p>Patients will be randomized in a 2:1 ratio to ABSK021 treatment group or placebo group. Assuming a 25-week ORR of 6% (P_0) in the placebo group and 40% (P_1) in ABSK021 group, by using Fisher's exact test with a two-sided significance level α of 0.05, a sample size of 75 evaluable patients provides a 90% power to detect the difference in the ORR between the two groups ($H_0: P_1 = P_0$ vs. $H_a: P_1 \neq P_0$). The power is calculated using the binomial distribution enumeration method. Considering a dropout rate of about 15%, approximately 90 TGCT patients need to be enrolled, including 60 patients in the ABSK021 treatment group and 30 patients in the placebo group.</p> <p>Statistical Analysis</p> <p>This study includes three planned analyses. The first analysis is the primary analysis of this study and will be performed after all randomized patients have either completed Part 1 of treatments for 24 weeks and a follow-up MRI scan at Week 25 visit or have withdrawn from informed consent or died. The effect of ABSK021 on ORR will be primarily evaluated in this analysis. All data up to the data cut-off date for the primary analysis (including all data from Part 1 and available data from Part 2) will be cleaned before treatment codes are unblinded for the analysis, but this unblinding will only apply to the</p>

sponsor and contract research organization (CRO). The second analysis (i.e., the final analysis) will be performed after the completion of study Part 2 to supplement a long-term efficacy, safety, and tolerability profile (including all data from Part 1, Part 2, and available data from Part 3). After the study is completed, the accumulated results, such as safety data and other clinical data, will be analyzed.

Data will be summarized descriptively according to the data type as appropriate. The primary analysis sets include the Intent-to-treat Analysis Set (ITT), the Safety Analysis Set (SST), the Per Protocol Set (PPS), and the PK Analysis Set (PKS). The PPS is a subset of ITT that includes all patients who have received at least one dose of study drug and have no major protocol deviations which may affect efficacy assessment.

Primary and Secondary Efficacy Analyses

ITT will be used as the primary analysis set for the primary and secondary efficacy analyses. The PPS will be used for the supportive analysis of the primary efficacy analysis.

The primary efficacy endpoint, 25-Week ORR by BIRC (RECIST v1.1), will be summarized by treatment group and its exact two-sided 95% CI will be calculated using the Clopper-Pearson method. The primary efficacy endpoint will be compared at a two-sided significance level of 0.05 using Fisher's exact test. The 95% CI in ORR difference (ABSK021 - placebo) will be calculated using the Wilson method. In addition, considering the effect of stratification factors (China vs. non-China), the ORR difference will be tested using the Cochran-Mantel-Haenszel (CMH) method as a sensitivity analysis, in which the ORR difference between ABSK021 and placebo group will be calculated, with its two-sided 95% CI calculated using the CMH weighting method. Fisher's exact test will be considered more appropriate if the expected response event is less than 5 in any stratified group.

Key secondary efficacy endpoints to be tested (in the following order) include: 1) 25-week ORR by BIRC based on TVS (TVS-ORR); 2) Mean change from baseline in ROM (presented as relative to ROM) of the affected joint at Week 25; 3) Mean change from baseline in

Worst-Stiffness-NRS score at Week 25; 4) Mean change from baseline in the BPI Worst Pain Numeric Rating Scale (NRS) score at Week 25; 5) Mean change from baseline in PROMIS Physical Function scale score at Week 25. A hierarchical gatekeeping testing procedure will be applied to test the treatment effect on these secondary endpoints. Therefore, the treatment effect on the second endpoint #1 can only be evaluated if the statistically significant treatment effect on the 25-Week ORR by BIRC has been established at the 2-sided significance level of 0.05 ($P < 0.05$); and the treatment effect on the second endpoint #2 will be evaluated only if the statistically significant treatment effect on the second endpoint #1 has been established at the 2-sided significance level of 0.05. Similarly, all remaining secondary endpoints can be sequentially tested at a two-sided significance level of 0.05 in the pre-specified order. A statistical test for any subsequent secondary endpoint(s) will not be performed if the treatment effect on any preceding secondary endpoint is not statistically significant.

TVS-ORR will be analyzed using the same analysis method as the primary efficacy endpoint ORR; continuous endpoints, including change from baseline in relative ROM, Worst-Stiffness-NRS, BPI Worst-Pain-NRS, and PROMIS will be analyzed using mixed models for repeated measures (MMRM). The model will include change from baseline as the dependent variable, and treatment, baseline, visit, stratification-factor of China vs. non-China, and treatment-by-visit interaction, and the baseline-by-visit interaction as fixed effects. In addition, for the endpoint of relative ROM, additional fixed terms of joint type category will be added to the MMRM. An unstructured variance-covariance matrix will be used. Formal statistical comparisons between groups will be made at Week 25.

The distribution characteristics of time-to-event variables including DOR will be estimated using the Kaplan-Meier method, where data allows.

Safety Analyses

Safety and tolerability will be assessed by adverse events, dose modifications, laboratory tests, vital signs, electrocardiograms, and echocardiography. Data from both scheduled and unscheduled visits will be included in the safety analysis. All safety data will be

	summarized descriptively based on the Safety Analysis Set. Any adverse events, treatment-related adverse events, adverse events leading to discontinuation of study drug, and adverse events leading to dose modification will be summarized by system organ class, preferred term, and CTCAE grade. Additional safety data will be summarized by treatment group, as appropriate.
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Table 1: Schedule of Events - Part 1

<div> <div>Cycle/Day</div> <div>Study Procedure</div> </div>	Screening ¹		Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7 ²	End of Treatment Visit (EOT) ³	Safety Follow-up ⁴	Progression Follow-up ⁵
	Within 28 Days Prior To Randomization	Within 14 Days Prior To Randomization	C1D1 (-1 day)	C1D15 (± 1 day)	C2D1 (± 2 days)	C2D15 (± 2 days)	C3D1 (± 7 days)	C4D1 (± 7 days)	C5D1 (± 7 days)	C6D1 (± 7 days)	C7D1 (± 7 days)			
			Week 1	Week 3	Week 5	Week 7	Week 9	Week 13	Week 17	Week 21	Week 25			
Informed Consent	X													
Eligibility Criteria	X													
Demographics ⁶	X													
Prior and current Medical History ⁶	X													
Physical examination/ECOG score ⁷		X		X	X		X	X	X	X	X	X		
Vital Signs ⁸		X	X	X	X	X	X	X	X	X	X	X		
Clinical laboratory tests														
Pregnancy test ⁹		X ⁹			X		X	X	X	X	X	X		
Hematology ¹⁰		X	X	X	X		X	X	X	X	X	X		
Blood chemistry ¹¹		X	X	X	X	X	X	X	X	X	X	X		
Myocardial Enzyme Test ¹²		X	X	X	X	X	X	X	X	X	X	X		
Coagulation ¹³		X						X			X	X		

<div> <div>Cycle/Day</div> <div>Study Procedure</div> </div>	Screening ¹		Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7 ²	End of Treatment Visit (EOT) ³	Safety Follow-up ⁴	Progression Follow-up ⁵
	Within 28 Days Prior To Randomization	Within 14 Days Prior To Randomization	C1D1 (-1 day)	C1D15 (± 1 day)	C2D1 (± 2 days)	C2D15 (± 2 days)	C3D1 (± 7 days)	C4D1 (± 7 days)	C5D1 (± 7 days)	C6D1 (± 7 days)	C7D1 (± 7 days)			
			Week 1	Week 3	Week 5	Week 7	Week 9	Week 13	Week 17	Week 21	Week 25			
Urinalysis ¹⁴		X	X	X	X		X	X	X	X	X	X		
Thyroid function tests ¹⁵		X						X			X	X		
Virology ¹⁶	X													
12-lead ECG ¹⁷		X	X	X	X	X	X	X	X	X	X	X		
Echocardiography/MUGA ¹⁸	X							X			X	X		
Adverse Event Reporting ¹⁹	X		X	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications and Concomitant Therapies ²⁰	X		X	X	X	X	X	X	X	X	X	X	X	
Randomization ²¹			X ²¹											
Dispensing of ABSK021 or placebo ²²			X		X		X	X	X	X				
PK Sample Collection ²³			X	X				X			X	X		
Tissue Specimen Collection ²⁴	X													
Tumor Imaging Assessment ²⁵	X							X			X	X		X
Range of motion (ROM) of affected joints ²⁶		X						X			X	X		

<div> <div>Cycle/Day</div> <div>Study Procedure</div> </div>	Screening ¹		Cycle 1		Cycle 2		Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7 ²	End of Treatment Visit (EOT) ³	Safety Follow-up ⁴	Progression Follow-up ⁵
	Within 28 Days Prior To Randomization	Within 14 Days Prior To Randomization	C1D1 (-1 day)	C1D15 (± 1 day)	C2D1 (± 2 days)	C2D15 (± 2 days)	C3D1 (± 7 days)	C4D1 (± 7 days)	C5D1 (± 7 days)	C6D1 (± 7 days)	C7D1 (± 7 days)			
			Week 1	Week 3	Week 5	Week 7	Week 9	Week 13	Week 17	Week 21	Week 25			
Worst Stiffness NRS and BPI Worst Pain NRS ²⁷		X	X		X		X	X	X	X	X	X		
PROMIS Physical Functioning Scale ²⁸		X	X		X		X	X	X	X	X	X		
EQ-5D-5L Health Scale ²⁸		X	X		X		X	X	X	X	X	X		
NCI-PRO-CTCAE ²⁹		X	X	X	X	X	X	X	X	X	X	X		
Pre-Part 2 Evaluation ³⁰											X			
New anti-tumor therapy after discontinuation of study drug													X	X

Abbreviations: ALT= Alanine transaminase; AST= Aspartate transaminase; APTT= activated partial thromboplastin time; BUN= Blood urea nitrogen; CK= creatine phosphokinase; CK-MB= phosphocreatine kinase isoenzyme; ECG= electrocardiogram; ECOG= Eastern Cooperative Oncology Group; EOT= End-of-Treatment; Fbg=fibrinogen; HBV= Hepatitis B virus; HCV= Hepatitis C virus; HIV-Ab=Human Immunodeficiency Virus – Antibody; LDH= lactate dehydrogenase; MRI= magnetic resonance imaging; MUGA= multigated acquisition scans; PK= Pharmacokinetic; PS= Performance status; TSH= Thyroid stimulating hormone; FT3= Free triiodothyronine; FT4= Free Thyroxine; WBC= white blood cells.

Footnotes:

Additional unscheduled safety or efficacy assessments may be performed as clinically indicated to determine the relationship between events and/or the duration of the event. All time windows in the table are for visits and not for drug administration.

- Screening: screening should be completed within 28 days prior to randomization. If screening cannot be completed within 28 days prior to randomization, the sponsor should be contacted to determine if the screening process performed prior to 28 days should be repeated prior to randomization. Clinical laboratory tests (pregnancy test, hematology, blood chemistry, myocardial enzymes, coagulation, thyroid function tests, urinalysis, etc.) and ECG, physical examinations/ECOG scoring, and vital signs

must be performed within 14 days prior to randomization. If the screening examination overlaps with the one conducted on C1D1 visit and the visit interval does not exceed 3 days, it is not necessary to repeat the examination on C1D1. For patients with screening failure, if the Investigator assesses that the original factors leading to screening failure have been excluded, the informed consent can be re-signed for re-screening.

2. All patients who complete Cycle 7 Visit (including MRI) and meet eligibility criteria will be eligible to enter Part 2 and receive treatment with open-label ABSK021, or end treatment. For patients who end treatment, an end-of-treatment (EOT) visit and a safety follow-up visit will be performed.
3. The End of Treatment Visit (EOT Visit) is required to be performed within 7 days after the patient permanently terminates the study drug treatment (if any test in EOT visit has been performed in the previous visit and the interval between two visits does not exceed 7 days, no need to repeat the tests in the EOT Visit). Patients who complete Part 1 and enter Part 2 do not need to have an EOT visit in Part 1.
4. Safety Follow-up Visit will occur 30 days \pm 7 days after the end of treatment (i.e., after the last dose of study drug) and patients will be contacted to collect new information (telephone follow-up, etc.) on adverse events and concomitant medications. Patients who complete Part 1 and enter Part 2 do not need to have a safety follow-up visit in Part 1.
5. Patients who discontinue treatment prematurely for reasons other than disease progression will be followed up for disease progression until disease progression, death, lost to follow-up, or the patient receives alternative anti-tumor therapy (including surgery), whichever occurs first. Disease progression follow-up will be conducted every 12 weeks (\pm 7 days). In principle, the maximum follow-up time will not exceed 12 months.
6. Demographic information (including sex, year of birth, age, ethnicity, race, etc.), prior medical history, current medical history, and detailed tumor history, including prior anti-tumor therapy information, will be collected at screening.
7. A complete physical examination is required during the screening period. Physical examination may be performed by a qualified physician, physician assistant, or registered nurse (if delegated by the PI). The examination includes general condition, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, blood vessels, and nervous system. Additional rectal, external genital, breast, and pelvic examinations are required if indicated by medical history or clinical symptoms. Physical examination is recommended to focus on primary tumor sites, areas of known abnormalities, or informed by clinical findings and/or subjects. Weight information will be collected at each physical examination and height will only be collected at screening. A general physical examination will be performed at subsequent visits. Investigators may perform more frequent physical examinations if clinically indicated. The ECOG score will be assessed concurrently with the physical examination.
8. Vital signs measurements include sitting blood pressure, pulse, respiratory rate, and pre-dose body temperature. When PK sampling is performed, vital signs are recommended to be measured after ECG and before PK sampling.
9. For women of childbearing potential, a pregnancy test is required during screening, C2D1 (\pm 2 days), C3D1 (\pm 7 days), C4D1 (\pm 7 days), C5D1 (\pm 7 days), C6D1 (\pm 7 days), C7D1 (\pm 7 days) and EOT visit. Serum pregnancy tests are required during screening, C7D1 and EOT visits, either serum or urine pregnancy test is acceptable at other visits. Pregnancy tests at screening should be completed within 7 days prior to randomization.
10. Hematology includes red blood cell count, hemoglobin concentration, hematocrit, white blood cell count, differential and absolute value of white blood cells (including

neutrophils count, lymphocytes count, monocytes count, eosinophils count, and basophils count), and platelet count.

11. Blood chemistry includes sodium, potassium, chloride, bicarbonate/ $\text{CO}_2/\text{CO}_2\text{CP}$, BUN/Urea, glucose, creatinine, AST, ALT, LDH, gamma-glutamyl transferase, alkaline phosphatase, total and direct bilirubin, total protein, albumin, calcium, magnesium, phosphorus, cholesterol, triglycerides, lipase, and amylase (if lipase and amylase cannot be tested simultaneously, one of which can be selected according to local site conditions). In the event of \geq Grade 2 transaminase elevations, more frequent liver function tests (e.g., twice weekly transaminase tests, etc.) are recommended until recovery.
12. Myocardial Enzyme tests include creatine kinase (CK) and creatine kinase isoenzyme (CK-MB). Cardiac troponin-T or cardiac troponin-I will be measured at baseline and further evaluation is recommended during the study if ECG morphology suggests the possibility of myocardial ischemia or infarction, or if CK increases \geq Grade 3.
13. Coagulation will be performed at screening, on C4D1 (± 7 days), and C7D1 (± 7 days). Tests included prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen (Fbg), and thrombin time (TT).
14. Urinalysis includes specific gravity, glucose, total protein, ketones, and red blood cells. If urine protein is $\geq 2+$ at any visit time point, further evaluation is recommended, such as 24-hour urine protein quantification, at the Investigator's discretion.
15. Thyroid function tests include TSH, FT3, and FT4. This will be performed at screening, on C4D1 (± 7 days), and C7D1 (± 7 days).
16. Virological testing includes testing for HIV, HBV, and HCV infection. HIV infection will be tested by HIV-Ab. HBV infection will be tested by hepatitis B virus surface antigen (HBsAg). If the test result of hepatitis B expressed antigen is positive, HBV-DNA test is required. HCV infection will be detected by hepatitis C virus antibody (confirmed by Western Blot or ELISA). If the test result is positive, hepatitis C RNA testing should be supplemented. Virological testing will be performed at screening.
17. The 12-lead ECG will be performed at screening, all on-study visits, and at the EOT visit. ECGs will be performed pre-dose (within 1 hour pre-dose) and post-dose (3 ± 0.5 hours post-dose) on Cycle 1 Day 1 (C1D1) and Cycle 1 Day 15 (C1D15), and ECGs at the remaining time points will be performed at any time on the day of the visit. Additional ECG tests may be performed as clinically indicated. Blood draws for vital signs, PK, and safety are recommended to be performed after the ECG, if applicable. Patients are advised to remain supine or semi-recumbent for at least 5 minutes prior to ECG testing.
18. Echocardiography or MUGA will be performed during screening period, on C4D1 (± 7 days), and C7D1 (± 7 days). The same examination (echocardiography or MUGA) should be used throughout the study.
19. Adverse events will be collected from the time the patient signs the informed consent form until 30 days (including Day 30) after the last dose of study drug.
20. All concomitant medications and concomitant treatments should be collected from randomization until 30 days after the last dose of study drug (or before the start of Part 2). Medications taken within 28 days prior to randomization are considered prior medications and will also be collected. Analgesic use will be collected (including but not limited to the name and dosage of analgesics) for assessment of patient pain relief.
21. Randomization should be performed within 3 days prior to the first dose.
22. The first day of continuous dosing of the study drug will be Day 1 Cycle 1. From Day 1 Cycle 1 until EOT, the study drug should be taken daily in accordance with the

requirements of this clinical study. On the visit with PK sampling, the study drug should be administered after the pre-dose PK sampling.

23. The PK sampling time window is shown in [Table 4](#) PK sampling table.
24. All patients are required to provide a tumor tissue specimen or a photograph of previous pathological diagnosis (not the diagnostic reports) for central pathological diagnosis. For patients who have no prior tumor tissue specimen and cannot provide photograph of previous pathological diagnosis, tumor biopsies should be performed during the screening period to collect fresh tumor tissue specimen.
25. Tumor imaging (MRI) will be performed at screening, on C4D1 (± 7 days), and C7D1 (± 7 days). MRI results within 28 days prior to dosing will be used as baseline, and the first tumor response evaluation will be performed on Day 4 Cycle Day 1 (C4D1 ± 7 days). At EOT visit, a corresponding tumor imaging assessment should be performed. A central review of resectability will be conducted at screening by at least one independent expert who is not part of the trial conduct.
26. The range of motion (ROM) of the affected joint or tumor site will be assessed using a goniometer according to local standard measurement methods. Measurements will be recorded in degrees. Assessments will be performed during the screening period, on C4D1 (± 7 days), and C7D1 (± 7 days). At EOT visit, a corresponding range of motion measurement of the joint should be performed.
27. For the BPI-Worst-Pain-NRS assessment, patients will be asked to recall their worst pain at the tumor site over the past 24 hours. Stiffness will be assessed using the Worst-Stiffness-NRS. Similar to the BPI-Worst-Pain-NRS, the Worst-Stiffness Numerical Rating Scale also uses a 24-hour recall cycle, and patients will be asked to recall their worst stiffness at the tumor site over the past 24 hours. Patients should complete the evaluation of BPI-Worst-Pain-NRS and Worst-Stiffness-NRS on 7 consecutive days (at least 4 days) during the 2 weeks prior to randomization, and on C1D1 (-1 day), C2D1 (at least 4 of 7 consecutive days from -7 days to +7 day), C3D1 (at least 4 of 7 consecutive days from -7 days to +7 day), C4D1 (at least 4 of 7 consecutive days from -7 days to +7 day), C5D1 (at least 4 of 7 consecutive days from -7 days to +7 day), C6D1 (at least 4 of 7 consecutive days from -7 days to +7 day) and C7D1 (at least 4 of 7 consecutive days from -7 days to +7 day). C1D1 assessments should be completed prior to dosing. The mean score of evaluations completed during the 2 weeks prior to randomization (at least 4 of 7 consecutive days) and on C1D1 will be used as the baseline. If there are multiple consecutive 7-day assessments, the baseline will be calculated from the most recent 7-day assessments as well as C1D1. In addition, mean score (at least 4 of 7 consecutive days) of BPI-Worst-Pain-NRS ≥ 4 or mean score (at least 4 of 7 consecutive days) of Worst-Stiffness-NRS ≥ 4 within 2 weeks prior to randomization (not include C1D1) is required for eligibility confirmation. On the day of all visits where a Numerical Rating Scale is required, including the screening period, it is recommended to be completed prior to any invasive clinical procedure. Even if a patient experiences disease progression or discontinues treatment, BPI-Worst-Pain-NRS and Worst-Stiffness-NRS are recommended to be completed from baseline up to week 25.
28. The PROMIS Physical Functioning Scale and the EQ-5D-5L Health Scale will be assessed during the screening period (within 14 days prior to randomization), on C1D1 (-1 day), C2D1 (± 7 days), C3D1 (± 7 days), C4D1 (± 7 days), C5D1 (± 7 days), C6D1 (± 7 days) and C7D1 (± 7 days), respectively. C1D1 assessments should be completed prior to dosing. The mean score of evaluations during the screening period (within 14 days prior to randomization) and on C1D1 will be used as baseline. The PROMIS Physical Functioning Scale includes two different sets of topics for the upper and lower extremities. Items assessing lower extremity function will be used for patients with lower extremity tumors, and the items for assessing upper extremity function will be used for patients with upper extremity tumors. On visit days when scales are required, including the screening period, it is recommended to be completed before any invasive clinical procedure is performed. Even if a patient experiences disease progression or discontinues treatment, PROMIS Physical Functioning Scale and the EQ-5D-5L Health Scale are recommended to be completed from baseline up to week 25.

29. NCI-PRO-CTCAE will be assessed during the screening period (within 14 days prior to randomization), on C1D1 (-1 day), C1D8(± 1 days), C1D15 (± 1 days), C1D22 (± 1 days), C2D1 (± 2 days), C2D8(± 2 days), C2D15 (± 2 days), and C2D22 (± 2 days), C3D1 (± 7 days), C4D1 (± 7 days), C5D1 (± 7 days), C6D1 (± 7 days), C7D1 (± 7 days), and EOT visit respectively.
30. Patient who completed the C7D1 visit of Part 1 will be further confirmed by the investigator whether to enter Part 2 and receive treatment with open-label ABSK021. Patients need to meet eligibility criteria to continue in Part 2. The investigator will comprehensively evaluate the benefits and risks of the patient entering Part 2, and make the final decision based on the principle of maximizing the patient's benefit-risk ratio. In principle, a maximum of 28 days is allowed from the end of C7D1 follow-up in Part 1 to entry into Part 2.

Table 2: Schedule of Events - Part 2

Study Procedure	Cycle 1 ¹	Cycle 2	Cycle 3	Cycle 4 ²	Cycle 7	End of Treatment Visit (EOT Visit) ³	Safety Follow-up ⁴	Progression Follow-up ⁵
	C1D1 (- 2 days)	C2D1 (± 7 days)	C3D1 (± 7 days)	C4D1 (± 7 days)	C7D1 (± 7 days)			
	Week 25	Week 29	Week 33	Week 37	Week 49			
Part 2 eligibility confirmation ¹	X							
Physical examination/ECOG score ⁶	X	X	X	X	X	X		
Vital Signs ⁷	X	X	X	X	X	X		
Clinical laboratory tests								
Pregnancy test ⁸	X			X	X	X		
Hematology ⁹	X	X	X	X	X	X		
Blood chemistry ¹⁰	X	X	X	X	X	X		
Myocardial Enzyme Test ¹¹	X	X	X	X	X	X		
Coagulation ¹²				X	X	X		
Urinalysis ¹³	X	X	X	X	X	X		
Thyroid function tests ¹⁴				X	X	X		
12-lead ECG ¹⁵	X	X	X	X	X	X		

Study Procedure	Cycle/Day	Cycle 1 ¹	Cycle 2	Cycle 3	Cycle 4 ²	Cycle 7	End of Treatment Visit (EOT Visit) ³	Safety Follow-up ⁴	Progression Follow-up ⁵
		C1D1 (- 2 days)	C2D1 (± 7 days)	C3D1 (± 7 days)	C4D1 (± 7 days)	C7D1 (± 7 days)			
		Week 25	Week 29	Week 33	Week 37	Week 49			
Echocardiography/MUGA ¹⁶		X			X	X	X		
Adverse Event Reporting ¹⁷		X	X	X	X	X	X	X	
Concomitant Medications and Concomitant Therapies ¹⁸		X	X	X	X	X	X	X	
Dispensing of ABSK021 ¹⁹		X	X	X	X				
PK Sample Collection ²⁰					X	X	X		
Tumor Imaging Assessment ²¹					X	X	X		X
ROM of affected joints ²²					X	X	X		
Worst Stiffness NRS and BPI Worst Pain NRS ²³		X	X	X	X	X	X		
PROMIS Physical Functioning Scale ²⁴		X	X	X	X	X	X		
EQ-5D-5L Health Scale ²⁴		X	X	X	X	X	X		
Pre-Part 3 Evaluation ²⁵						X			
New anti-tumor therapy after discontinuation of study drug								X	X

Abbreviations: ALT= Alanine transaminase; AST= Aspartate transaminase; APTT= activated partial thromboplastin time; BUN= Blood urea nitrogen; CK= creatine phosphokinase; CK-MB= phosphocreatine kinase isoenzyme; ECG= electrocardiogram; ECOG= Eastern Cooperative Oncology Group; EOT= End-of-Treatment; Fbg=fibrinogen; LDH= lactate dehydrogenase; MRI=

magnetic resonance imaging; MUGA= multigated acquisition scans; PK= Pharmacokinetic; PS= Performance status; TSH= Thyroid stimulating hormone; FT3= Free triiodothyronine; FT4= Free Thyroxine; WBC= white blood cells.

Footnote:

Additional unscheduled safety or efficacy assessments may be performed as clinically indicated to determine the relationship between events and/or the duration of the event. All time windows in the table are for visits and not for administration.

1. C1D1 of Part 2 (P2-C1D1) is defined as the day of Part 2 eligibility confirmation and the first dose of Part 2, and if any test to be performed at Part 2 C1D1 visit has been done at Part 1 C7D1 visit or the latest visit before Part 2 C1D1, with an interval no more than 7 days, repeated tests are not required on C1D1 of Part 2.
2. After completing the Cycle 4 (i.e., Week 37) visit of Part 2, patients will return to the study site for a visit every 12 weeks (± 7 days) with the next visit date of C7D1 ± 7 days.
3. The End of Treatment Visit (EOT Visit) is required to be performed within 7 days after the patient permanently terminates the study drug treatment (if any test in EOT visit has been performed in the previous visit and the interval between two visits does not exceed 7 days, no need to perform the tests in the EOT Visit).
4. Safety Follow-up Visit will occur 30 days ± 7 days after the end of treatment (i.e., after the last dose of study drug) and patients will be contacted to collect new information (telephone follow-up, etc.) on the outcome of adverse events and concomitant medications.
5. Patients who discontinue treatment for reasons other than disease progression will be followed up for disease progression until disease progression, death, lost to follow-up, or the patient receives alternative anti-tumor therapy (including surgery), whichever occurs first. Disease progression follow-up will be conducted every 12 weeks (± 7 days). In principle, the maximum follow-up time will not exceed 12 months.
6. Physical examination may be performed by a qualified physician, physician assistant, or registered nurse (if delegated by the PI). A complete physical examination will only be performed at screening in Part 1. In Part 2, only a general physical examination will be performed. The physical examination is recommended to focus on primary tumor sites, areas of known abnormalities, or informed by clinical findings and/or patients. Weight information will be collected at each physical examination and height will only be collected at screening in Part 1. Investigators may perform more frequent tests if clinically indicated. The ECOG score will be assessed concurrently with the physical examination.
7. Vital sign measurements include sitting blood pressure, pulse, respiratory rate, and pre-dose body temperature. When PK sampling is performed, vital signs are recommended to be measured after ECG and before PK sampling.
8. For women of childbearing potential, a pregnancy test is required on C1D1 (-2 days), C4D1 (± 7 days), C7D1 (± 7 days) and EOT visit. Serum pregnancy tests are required during screening, C7D1 and EOT visits. Serum or urine pregnancy tests are acceptable at other visits. If pregnancy test to be performed at Part 2 C1D1 visit has been done at Part 1 C7D1 visit or the latest visit before P2-C1D1, with an interval no more than 7 days, repeated tests are not required on C1D1 of Part 2.
9. Hematology includes red blood cell count, hemoglobin concentration, hematocrit, white blood cell count, differential and absolute value of white blood cells (including

neutrophils count, lymphocytes count, monocytes count, eosinophils count, and basophils count), and platelet count.

10. Blood chemistry includes sodium, potassium, chloride, bicarbonate/ $\text{CO}_2/\text{CO}_2\text{CP}$, BUN/Urea, glucose, creatinine, AST, ALT, LDH, gamma-glutamyl transferase, alkaline phosphatase, total and direct bilirubin, total protein, albumin, calcium, magnesium, phosphorus, cholesterol, triglycerides, lipase, and amylase (if lipase and amylase cannot be tested simultaneously, one of which can be selected according to local site conditions). In the event of \geq Grade 2 transaminase elevations, more frequent liver function tests (e.g., twice weekly transaminase tests, etc.) are recommended until recovery.
11. Myocardial Enzyme tests include creatine kinase (CK) and creatine kinase isoenzyme (CK-MB). Cardiac troponin-T or cardiac troponin-I will be measured at baseline and further evaluation is recommended during the study if ECG morphology shows the possibility of myocardial ischemia or infarction, or if CK increases \geq Grade 3.
12. Coagulation will be performed on C4D1 (± 7 days), and C7D1 (± 7 days). Tests included prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen (Fbg), and thrombin time (TT).
13. Urinalysis includes specific gravity, glucose, total protein, ketones, and red blood cells. If urine protein is $\geq 2+$ at any visit time point, further evaluation is recommended, such as 24-hour urine protein quantification, at the Investigator's discretion.
14. Thyroid function tests include TSH, FT3, and FT4. This will be performed on C4D1 (± 7 days), and C7D1 (± 7 days).
15. The 12-lead ECG will be performed all on-study visits, and at the EOT visit. Additional ECG tests may be performed as clinically indicated. Blood draws for vital signs, PK, and safety are recommended to be performed after the ECG, if applicable. Patients are advised to remain supine or semi-recumbent for at least 5 minutes prior to ECG testing.
16. Echocardiography or MUGA will be performed on C1D1 (-2 days), C4D1 (± 7 days), and C7D1 (± 7 days). The same examination (echocardiography or MUGA) should be used throughout the study. If the test to be performed at Part 2 C1D1 visit has been done at Part 1 C7D1 visit or the latest visit before P2-C1D1, with an interval of no more than 7 days, repeated tests are not required on C1D1 of Part 2.
17. Adverse events will be collected from the time the patient signs the informed consent form until 30 days (including Day 30) after the last dose of study drug.
18. All concomitant medications and concomitant treatments should be collected from the first dose of study drug in Part 2 until 30 days after the last dose of study drug (or before Part 3). Concomitant medications prior to the first dose of study drug in Part 2 will be collected in Part 1. Analgesic use will be collected (including but not limited name and dosage of analgesics) for assessment of patient pain relief.
19. From Cycle 1 Day 1 until EOT, the study drug should be taken daily in accordance with the requirements listed in the study protocol. Wherein, drug dispensation on C1D1 may be performed on the day of P1-C7D1 visit completion. The study drug will be dispensed every 3 months starting on C4D1. Study drug should be taken after pre-dose PK sampling on C4D1 and C7D1.
20. The PK sampling time window is shown in [Table 4](#) PK sampling table.

21. Tumor imaging (MRI) will be performed on C4D1 (± 7 days), and C7D1 (± 7 days). MRI results within 28 days prior to randomization in Part 1 will be used as baseline, and the first tumor response evaluation in Part 2 will be performed on Day 4 Cycle Day 1 (C4D1 ± 7 days). At EOT visit, a corresponding tumor imaging assessment should be performed.
22. The range of motion (ROM) of the affected joint or tumor site will be assessed using a goniometer according to local standard measurement methods. Measurements will be recorded in degrees. Assessments will be performed on C4D1 (± 7 days), and C7D1 (± 7 days). At EOT visit, a corresponding range of motion measurement of the joint should be performed.
23. Patients should complete BPI-Worst-Pain-NRS and Worst-Stiffness-NRS on C1D1 (at least 4 of 7 consecutive days within ± 7 days), C2D1 (at least 4 of 7 consecutive days within ± 7 days), C3D1 (at least 4 of 7 consecutive days within ± 7 days), C4D1 (at least 4 of 7 consecutive days within ± 7 days) and C7D1 (at least 4 of 7 consecutive days within ± 7 days). If the assessment to be performed at Part 2 C1D1 visit has been done at Part 1 C7D1 visit or the latest visit before P2-C1D1, with an interval of no more than 7 days, repeated assessments are not required on C1D1 of Part 2. On the days when a Numerical Rating Scale is required, it is recommended to be completed prior to any invasive clinical procedure.
24. The PROMIS Physical Functioning Scale and the EQ-5D-5L Health Scale will be assessed on C1D1 ($+ 7$ days), C2D1 (± 7 days), C3D1 (± 7 days), C4D1 (± 7 days), and C7D1 (± 7 days), respectively. The PROMIS Physical Functioning Scale includes two different sets of topics for the upper and lower extremities. Items assessing lower extremity function will be used for patients with lower extremity tumors, and the items for assessing upper extremity function will be used for patients with upper extremity tumors. If the assessment to be performed at Part 2 C1D1 visit has been done at Part 1 C7D1 visit or the latest visit before P2-C1D1, with an interval of no more than 7 days, repeated assessments are not required on C1D1 of Part 2. On visit days when scales are required, it is recommended to be completed before any invasive clinical procedure is performed.
25. Patient who completed the C7D1 visit of Part 2 will be further confirmed by the investigator whether to enter Part 3 and continue to receive treatment with open-label ABSK021. Patients need to meet eligibility criteria to continue in Part 3. The investigator will comprehensively evaluate the benefits and risks of the patient entering Part 3, and make the final decision based on the principle of maximizing the patient's benefit-risk ratio. In principle, a maximum of 28 days is allowed from the end of C7D1 follow-up in Part 2 to entry into Part 3.

Table 3: Schedule of Events - Part 3

Study Procedure	Cycle 1 ¹	Cycle 4	Cycle 7	Cycle 13 ²	≥ Cycle 19	End of Treatment Visit (EOT Visit) ³	Safety Follow-up ⁴	Progression Follow-up ⁵
	C1D1 (- 2 days)	C4D1 (± 7 days)	C7D1 (± 7 days)	C13D1 (± 14 days)	≥ C19D1 (± 14 days)			
	Week 49	Week 61	Week 73	Week 97	≥ Week 121			
Part 3 eligibility confirmation ¹	X							
Physical examination/ECOG score ⁶	X	X	X	X	X	X		
Vital Signs ⁷	X	X	X	X	X	X		
Clinical laboratory tests								
Pregnancy test ⁸	X	X	X	X	X	X		
Hematology ⁹	X	X	X	X	X	X		
Blood chemistry ¹⁰	X	X	X	X	X	X		
Myocardial Enzyme Test ¹¹	X	X	X	X	X	X		
Coagulation ¹²		X	X	X	X	X		
Urinalysis ¹³	X	X	X	X	X	X		
Thyroid function tests ¹⁴		X	X	X	X	X		
12-lead ECG ¹⁵	X	X	X	X	X	X		

Study Procedure	Cycle/Day	Cycle 1 ¹	Cycle 4	Cycle 7	Cycle 13 ²	≥ Cycle 19	End of Treatment Visit (EOT Visit) ³	Safety Follow-up ⁴	Progression Follow-up ⁵
		C1D1 (- 2 days)	C4D1 (± 7 days)	C7D1 (± 7 days)	C13D1 (± 14 days)	≥ C19D1 (± 14 days)			
		Week 49	Week 61	Week 73	Week 97	≥ Week 121			
Echocardiography/MUGA ¹⁶			X	X	X	X	X		
Adverse Event Reporting ¹⁷		X	X	X	X	X	X	X	
Concomitant Medications and Concomitant Therapies ¹⁸		X	X	X	X	X	X	X	
Dispensing of ABSK021 ¹⁹		X	X	X	X	X			
Tumor Imaging Assessment ²⁰			X	X	X	X	X		X
ROM of affected joints ²¹			X	X	X	X	X		
Worst Stiffness NRS and BPI Worst Pain NRS ²²		X	X	X	X	X	X		
PROMIS Physical Functioning Scale ²³		X	X	X	X	X	X		
EQ-5D-5L Health Scale ²³		X	X	X	X	X	X		
New anti-tumor therapy after discontinuation of study drug								X	X

Abbreviations: ALT= Alanine transaminase; AST= Aspartate transaminase; APTT= activated partial thromboplastin time; BUN= Blood urea nitrogen; CK= creatine phosphokinase; CK-MB= phosphocreatine kinase isoenzyme; ECG= electrocardiogram; ECOG= Eastern Cooperative Oncology Group; EOT= End-of-Treatment; Fbg=fibrinogen; LDH= lactate dehydrogenase; MRI= magnetic resonance imaging; MUGA= multigated acquisition scans; PS= Performance status; TSH= Thyroid stimulating hormone; FT3= Free triiodothyronine; FT4= Free Thyroxine; WBC= white blood cells.

Footnote:

Additional unscheduled safety or efficacy assessments may be performed as clinically indicated to determine the relationship between events and/or the duration of the event. All time windows in the table are for visits and not for administration.

1. C1D1 of Part 3 (P3-C1D1) is defined as the day of the first dose in Part 3, and if any test to be performed at Part 3 C1D1 visit has been done at Part 2 C7D1 visit or the latest visit before Part 3 C1D1, with an interval no more than 7 days, repeated tests are not required on C1D1 of Part 3.
2. After completing the Cycle 7 visit of Part 3, patients will return to the study site for a visit every 24 weeks (± 14 days) with the next visit date of C13D1 ± 14 days.
3. The End of Treatment Visit (EOT Visit) is required to be performed within 7 days after the patient permanently terminates the study drug treatment (if any test in EOT visit has been performed in the previous visit and the interval between two visits does not exceed 7 days, no need to perform these tests in the EOT Visit).
4. Safety Follow-up Visit will perform 30 days ± 7 days after the end of treatment (i.e., after the last dose of study drug) and patients will be contacted to collect new information (telephone follow-up, etc.) on the outcome of adverse events and concomitant medications.
5. Patients who discontinue treatment for reasons other than disease progression will be followed up for disease progression until disease progression, death, lost to follow-up, or the patient receives alternative anti-tumor therapy (including surgery), whichever occurs first. Disease progression follow-up will be conducted every 12 weeks (± 7 days). In principle, the maximum follow-up time will not exceed 12 months.
6. Physical examination may be performed by a qualified physician, physician assistant, or registered nurse (if delegated by the PI). The physical examination is recommended to focus on primary tumor sites, areas of known abnormalities, or informed by clinical findings and/or patients. Weight information will be collected at each physical examination and height will only be collected at screening in Part 1. Investigators may perform more frequent tests if clinically indicated. The ECOG score will be assessed concurrently with the physical examination.
7. Vital sign measurements include sitting blood pressure, pulse, respiratory rate, and pre-dose body temperature. Vital signs are recommended to be measured after ECG.
8. For women of childbearing potential, a pregnancy test is required at every visit during study and at EOT visit. Serum pregnancy tests are required on C1D1 and EOT visits. Serum or urine pregnancy tests are acceptable at other visits. If pregnancy test to be performed at Part 3 C1D1 visit has been done at Part 2 C7D1 visit or the latest visit before P3-C1D1, with an interval no more than 7 days, repeated tests are not required on C1D1 of Part 3.
9. Hematology includes red blood cell count, hemoglobin concentration, hematocrit, white blood cell count, differential and absolute value of white blood cells (including neutrophils count, lymphocytes count, monocytes count, eosinophils count, and basophils count), and platelet count.
10. Blood chemistry includes sodium, potassium, chloride, bicarbonate/ CO_2 / CO_2CP , BUN/Urea, glucose, creatinine, AST, ALT, LDH, gamma-glutamyl transferase, alkaline phosphatase, total and direct bilirubin, total protein, albumin, calcium, magnesium, phosphorus, cholesterol, triglycerides, lipase, and amylase (if lipase and amylase cannot be tested simultaneously, one of which can be selected according to local site conditions). In the event of \geq Grade 2 transaminase elevations, more frequent liver function tests (e.g., twice weekly transaminase tests, etc.) are recommended until recovery.
11. Myocardial Enzyme tests include creatine kinase (CK) and creatine kinase isoenzyme (CK-MB). Cardiac troponin-T or cardiac troponin-I will be measured at baseline

and further evaluation is recommended during the study if ECG morphology shows the possibility of myocardial ischemia or infarction, or if CK increases \geq Grade 3.

12. Coagulation will be performed on C4D1 (± 7 days), and subsequent visits. Tests included prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen (Fbg), and thrombin time (TT).
13. Urinalysis includes specific gravity, glucose, total protein, ketones, and red blood cells. If urine protein is $\geq 2+$ at any visit time point, further evaluation is recommended, such as 24-hour urine protein quantification, at the Investigator's discretion.
14. Thyroid function tests include TSH, FT3, and FT4. This will be performed on C4D1 (± 7 days), and subsequent visits.
15. The 12-lead ECG will be performed all on-study visits, and at the EOT visit. Additional ECG tests may be performed as clinically indicated. Blood draws for vital signs, and safety are recommended to be performed after the ECG, if applicable. Patients are advised to remain supine or semi-recumbent for at least 5 minutes prior to ECG testing.
16. Echocardiography or MUGA will be performed on C4D1 (± 7 days), C7D1 (± 7 days) and subsequent visits. The same examination (echocardiography or MUGA) should be used throughout the study.
17. Adverse events will be collected from the time the patient signs the informed consent form until 30 days (including Day 30) after the last dose of study drug.
18. All concomitant medications and concomitant treatments should be collected from the first dose of study drug in Part 3 until 30 days after the last dose of study drug. Concomitant medications prior to the first dose of study drug in Part 3 will be collected in Part 2. Analgesic use will be collected (including but not limited name and dosage of analgesics) for assessment of patient pain relief.
19. From Part 3 Cycle 1 Day 1 until EOT, the study drug should be taken daily in accordance with the requirements listed in the study protocol. Wherein, on C1D1 study drug should be dispensed after all the procedures required for Part 3 C1D1 are completed (If any test is repeated within 7 days, please refer to footnote 1). Study drug will still be dispensed every 12 weeks in the part 3 after Cycle 7.
20. Tumor imaging (MRI) will be performed on C4D1 (± 7 days), and C7D1 (± 7 days). After C7D1 visit, imaging examinations will be performed every 24 weeks (± 14 days), and the next imaging examination will be conducted on C13D1 (± 14 days). At EOT visit, a corresponding tumor imaging assessment should be performed.
21. The range of motion (ROM) of the affected joint or tumor site will be assessed using a goniometer. Measurements will be recorded in degrees. Assessments will be performed on C4D1 (± 7 days), and C7D1 (± 7 days). After C7D1 visit, ROM measurements will be performed every 24 weeks (± 14 days), and the next measurement will be conducted on C13D1 (± 14 days). At EOT visit, a corresponding range of motion measurement of the joint should be performed.
22. Patients should complete BPI-Worst-Pain-NRS and Worst-Stiffness-NRS on C1D1 (at least 4 of 7 consecutive days within ± 7 days), C4D1 (at least 4 of 7 consecutive days within ± 7 days) and C7D1 (at least 4 of 7 consecutive days within ± 7 days). After C7D1 visit, assessments will be performed every 24 weeks (at least 4 of 7 consecutive days within ± 14 days), and the next assessment will be conducted on C13D1 (± 14 days). If the assessment to be performed at Part 3 C1D1 visit has been done at Part 2 C7D1 visit or the latest visit before P3-C1D1, with an interval of no more than 7 days, repeated assessments are not required on C1D1 of Part 3. On the days when a

Numerical Rating Scale is required, it is recommended to be completed prior to any invasive clinical procedure.

23. The PROMIS Physical Functioning Scale and the EQ-5D-5L Health Scale will be assessed on C1D1 (- 7 days), C4D1 (\pm 7 days), and C7D1 (\pm 7 days), respectively. After C7D1 visit, assessments will be performed every 24 weeks (\pm 14 days), and the next assessment will be conducted on C13D1 (\pm 14 days). If the assessment to be performed at Part 3 C1D1 visit has been done at Part 2 C7D1 visit or the latest visit before P3-C1D1, with an interval of no more than 7 days, repeated assessments are not required on C1D1 of Part 3. The PROMIS Physical Functioning Scale includes two different sets of topics for the upper and lower extremities. Items assessing lower extremity function will be used for patients with lower extremity tumors, and the items for assessing upper extremity function will be used for patients with upper extremity tumors. On visit days when scales are required, it is recommended to be completed before any invasive clinical procedure is performed.

Table 4: PK Sampling Table**- Part 1**

Cycle/Day	PK sampling time (hours)	
	Pre-dose (- 60 min) ¹	3 hours post-dose (\pm 60 min)
C1D1	X	X
C1D15	X	X
C4D1	X	X
C7D1	X	X
EOT ^a	X	
NA	Unscheduled sampling (if required)	

^a Only for patients who ended treatment in Part 1.

- Part 2

Cycle/Day	PK sampling time (hours)	
	Pre-dose (- 60 min)	3 hours post-dose (\pm 60 min)
C4D1	X	X
C7D1	X	X
EOT ^b	X	
NA	Unscheduled sampling (if required)	

^b Only for patients who ended treatment in Part 2.

Note:

1. Pre-dose PK samples on Part 1 C1D1 can be collected within 2 hours prior to study drug administration.
2. When ECGs are required, the order of assessments is recommended to be ECG, vital sign monitoring, and PK sample collection; if ECGs are not required, it is recommended to perform vital sign examinations followed by PK sample collection.
3. If PK sampling cannot be performed at a pre-specified visit (e.g., schedule conflicts, adverse events, etc.), it may be performed on another study day as determined by the patient, Investigator and sponsor.
4. Additional PK blood samples may be collected at the latest study visit for suspected toxicity, disease progression, dose modification, unscheduled tumor assessment, or dose interruption due to scheduled study procedures or toxicity. For PK sampling after dose modification, the PK sample is recommended to be collected at 3 hours post-dose in the most recent visit after modification.

ABBREVIATIONS

Abbreviations	Definition
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
BIRC	Blinded Independent Review Committee
BOR	Best of response
BPI	Brief Pain Inventory
BUN	Blood urea nitrogen
CK	Creatine phosphokinase
CK-MB	Phosphocreatine kinase isoenzyme
C _{max}	Maximum observed concentration
CR	Complete response
Crcl	Creatinine clearance
CRF	Case report form
CRO	Contract research organization
CSF-1	Colony stimulating factor 1
CSF-1R	Colony stimulating factor 1 Receptor
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DCR	Disease control rate
DLT	Dose-limiting toxicity
IDMC	Independent Data Monitoring Committee
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
EOT	End-of-Treatment

Abbreviations	Definition
EQ-5D-5L	5-level EuroQoL-5 dimension questionnaire
Fbg	Fibrinogen
FDA	Food and Drug Administration
FT3	Free triiodothyronine
FT4	Free thyroxine
GCT-TS	Giant cell tumors of the tendon sheath
GI	Gastrointestinal
GLP	Good Laboratory Practice
Hb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HED	Human equivalent dose
HIV-Ab	Human immunodeficiency virus – antibody
HNSTD	Highest non-severely toxic dose
ICF	Informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ITT	Intent-to-treat Analysis Set
IWRS	Interactive Web Response System
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LVEF	Left ventricular ejection fraction
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
MUGA	Multigated acquisition scans
NRS	Numeric rating scale
NYHA	New York Heart Association
ORR	Objective response rate
PD	Progressive Disease

Abbreviations	Definition
PFS	Progression-free survival
PK	Pharmacokinetic
PKS	PK Analysis Set
PLT	Platelet count
PPS	Per Protocol Set
PR	Partial response
PRO	Patient-reported outcome
PROMIS	Patient-reported Outcomes Measurement Information System
PS	Performance status
PVNS	Pigmented villonodular synovitis
QD	Once a day
QTc	QT interval corrected
Rac	Accumulation rate
RDE	Recommended dose of expansion
RECIST	Response Evaluation Criteria in Solid Tumors
ROM	Range of motion
SAE	Serious adverse event
SD	Stable disease
SST	Safety Analysis Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Half-life
TBIL	Total bilirubin
TGCT	Tenosynovial giant cell tumour
t_{max}	Time to maximum observed concentration
TSH	Thyroid stimulating hormone
TVS	Tumor volume score
ULN	Upper limit of normal
VAS	Visual Analogue Scale
WBC	White blood cells

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1 Introduction

1.1 Overview of Disease and Treatment

1.1.1 Overview of Tenosynovial giant cell tumors (TGCT)

Tenosynovial giant cell tumors (TGCT) is a rare, locally invasive soft tissue tumor arising from the synovium of joints, bursa, and myosheaths, manifested by pain, swelling, stiffness, hemorrhagic joint effusion, periarticular erosion, cartilage degeneration, and secondary osteoarthritis in the affected joints. TGCT is generally not life-threatening, but some patients are not amenable to surgical excision and have a high risk of recurrence. Repeated surgeries are prone to lead to severe joint injury and surgical complications, and have a high risk of amputation, which has a serious impact on the quality of life of patients.¹ The World Health Organization (WHO) unified TGCT into diffuse and localized type² in 2013. Localized TGCT accounting for approximately 80-90% of all cases, mostly located in fingers and feet, is mainly treated with surgery, but still has a recurrence rate of up to 15%. Diffuse TGCT is a devastating and locally invasive tumor, usually involving larger joints, such as the knee, hip, and ankle. Although this subtype accounts for only 10-20% of all cases, surgical treatment is difficult and the tumor cannot be completely resected, resulting in a 5-year recurrence rate of approximately 45%.³

TGCT can occur in all age groups, including children, but is predominant in patients 20 to 50 years old, with a median age of approximately 40 years old at diagnosis.⁴ The incidence of TGCT is low and is considered a rare tumor with an incidence of approximately 5 cases per million in Europe^{5,6} and an estimated incidence of 11 cases per million in the United States, including 9.2 localized TGCT cases per million, and 1.8 diffuse TGCT cases per million.⁷ Although the disease is a locally invasive tumor, the clinical manifestations vary considerably between subtypes. Localized TGCT usually affects smaller joints and is characterized by growth of abnormal nodules or masses. This subtype is usually confined to specific areas of the joint, with slow initial tumor growth and painless swelling followed by a sensation of pain or stiffness in the affected joint. Diffuse TGCT mainly affected larger joints and tumors are widespread, with painless swelling as the initial symptom; some patients also experience joint pain and stiffness, as well as skin warmth and tenderness in affected joints. Disease progression includes joint damage, joint degeneration, and degeneration of surrounding cartilage and bone, which, if left untreated, may lead to other chronic diseases and dysfunction of affected joints, severely affecting the patient's quality of life. For patients who are amenable to surgical excision or have serious complications, the risk of limb amputation is extremely high.⁸

1.1.2 Potential Pathogenesis of TGCT

Genetic studies have shown that a small number of tumor cells constituting TGCT carry specific chromosomal translocations, which are considered to be possibly related to tumorigenesis. In

these tumor cells, the t (1; 2) (p13; q37) translocation is considered to be one of the leading causes, which results in the fusion of colony-stimulating factor 1 (CSF-1) on 1p13 to type VI alpha-3 collagen (COL6A3) located on 2q37 to form a CSF1-COL6A3 fusion gene, whereas the strong promoter of COL6A3 will result in overexpression of CSF-1.⁹ In addition to COL6A3, other partner genes fused to CSF-1 have also been found in recent years, these fusion genes will result in deletion of CSF-1 exon⁹ (which is a negative regulator of CSF-1 expression) and truncation of the 3'-UTR region, This may be a novel regulatory mechanism leading to upregulation of CSF-1 expression¹⁰ These tumor cells overexpressing CSF-1 will initiate tumor cell self-proliferation by means of an autocrine loop, while triggering the accumulation of inflammatory cells (e.g., monocytes and macrophages) that express CSF-1R in a paracrine manner. Thus, the majority of cells present in TGCT tumors express CSF-1R, whereas CSF-1 is present only in a low percentage of cells (2-16%). It is unclear what causes chromosomal translocations in tumor cells, and there are currently no clear environmental risk factors for the development of TGCT.

1.1.3 Existing Treatment Options for TGCT

TGCT is a form of local infiltrating soft tissue tumor. Based on the current treatment options, the main therapeutic methods of TGCT can be summarized as follows: 1) Surgical resection; 2) Systemic drug therapy.

Surgical resection has been a classic treatment for TGCT patients, with beneficial outcomes to many patients with TGCT. However, current treatment options pose the following challenges: 1) There are differences in the optimal surgical treatment. Arthroscopic or open surgery in combination with partial or extensive synovectomy are currently the two main surgical treatment modalities¹¹, however consensus has not been reached on the optimal surgical treatment¹¹⁻¹⁶ One study has shown that open surgery may be associated with higher local recurrence-free survival, but this association disappears after multivariate analyses¹⁷. 2) There is a high risk of surgical complications. In some cases, surgery may cause more damage to the patient than the disease itself, particularly in patients with diffuse tumors where large joints may be involved. Surgery in such patients usually involves synovectomy and may involve (partial) resection of the major tendon, resulting in high-intensity and long-term (6 to 9 months) postoperative physical therapy. Surgical resection may also involve critical neurovascular structures, such as elbows, wrists, or ankles, resulting in significant postoperative complications, such as hemarthrosis, joint instability, neurological injury, thromboembolic disease, and wound healing complications.⁴ At the same time, total joint replacement is often associated with tumors located deep in the hip joint, which will have a serious impact on the patient's subsequent life. 3) The probability of postoperative recurrence is high, particularly in patients with diffuse TGCT. For these patients, the tumor is extensive and diffusely growing, which results in a less likely complete surgical resection and a higher risk of postoperative recurrence. An international multicenter retrospective study found a 5-year relapse rate of 45% in patients with diffuse TGCT.³ Although the risk of postoperative

recurrence in patients with localized TGCT is lower than in patients with diffuse TGCT, the 10-year recurrence rate still exceeds 10%.¹⁸ These studies suggest that a high recurrence rate will limit the long-term benefit of surgical treatment in patients with TGCT. Repeated surgery can lead to serious joint damage and limb amputation risk.

Since aberrant expression of CSF-1 is an important genetic basis for the development of TGCT, preliminary progress has been made in targeted systemic therapies targeting the CSF-1/CSF-1R pathway. Imatinib and Nilotinib are two tyrosine kinase inhibitors that block multiple proteins, including CSF-1R, and may have limited antitumor activity in TGCT.^{19,20,21} The guidance issued by the National Comprehensive Cancer Network (NCCN) for soft tissue tumors (2022.v2) recommended Imatinib and Nilotinib as class 2 systemic therapy agents for the treatment of TGCT.²² Pexidartinib was approved by the US FDA in 2019 and it is recommended as the only one of class 1 systemic therapy agents for TGCT in the NCCN guideline. This is primarily based on the success of a Phase 3 randomized, double-blind, placebo-controlled study.²³ Pexidartinib treatment (n = 61) had a higher ORR at Week 25 compared with placebo (n = 59) (39% vs 0%; P < 0.0001).²³ However, the potential risk of fatal liver injury for this drug cannot be ignored, with a boxed warning of the risk of serious and potentially fatal liver injury in the package insert.²⁴

1.2 Introduction of Study Drug

ABSK021 is a highly selective and potent oral small molecule CSF-1R inhibitor. Preclinical in vitro pharmacology studies showed that ABSK021 significantly inhibited CSF-1R kinase activity with a mean IC₅₀ of 20.95 nM. Anti-proliferative efficacy assessment and kinase screening assays have demonstrated that ABSK021 is highly selective for CSF-1R. In the subcutaneous EMT-6 syngeneic breast cancer model in female BALB/c mice, ABSK021 showed significant antitumor efficacy either as a single agent or in combination with anti-PD-1, as did the subcutaneous A20 syngeneic B-cell lymphoma model and the subcutaneous CT26 syngeneic model.

Oral administration of ABSK021 has good drug metabolism and pharmacokinetics (DMPK) properties. Pharmacokinetic exposure increased proportionally with the oral dose in rat and monkey studies. Based on in vitro study data, the risk of DDI of ABSK021 is expected to be low.

Preclinical data from ABSK021 support the clinical development of this study drug. The toxicity profile of ABSK021 has been confirmed by preclinical safety assessments to support the conduct of the study drug in human clinical studies. Please refer to the Investigator's Brochure for more information on preclinical studies.

1.2.1 Preclinical Study Data

1.2.1.1 Preclinical Safety Pharmacology Studies

A series of safety pharmacology studies with ABSK021 have been completed in compliance with

FDA GLP regulations CFR 21 Part 58, including a study of the hERG potassium current in HEK293 cells, a study of cardiovascular and respiratory function in conscious cynomolgus monkeys, and a study of central nervous system function in Sprague-Dawley rats.

ABSK021 inhibited hERG current in HEK293 cells with IC₅₀ values exceeding 24.69 μ mol/L.

ABSK021 at oral gavage doses of 5, 15, and 30 mg/kg had no effect on cardiovascular function, respiratory function, and body temperature in conscious cynomolgus monkeys.

ABSK021 at oral gavage doses of 6, 20, and 60 mg/kg had no significant effect on central nervous system function in Sprague-Dawley rats.

1.2.1.2 Preclinical Pharmacokinetic Studies

Nonclinical IV data of ABSK021 evaluated after intravenous (IV) and intragastric (per os, PO) administration in Sprague-Dawley rats and cynomolgus monkeys showed clearance of 2.2 mL/min/kg and 7.68 mL/min/kg in rats and monkeys, respectively. V_{ss} was 1.38 L/kg in rats and 2.15 L/kg in monkeys and rats, respectively. Based on single-dose PO data, the t_{max} and t_{1/2} was 3-4 h and 9.4 h, respectively in rats, and 2 h and 5 h, respectively in monkeys. In rats and monkeys, C_{max} and AUC_{0-t} of ABSK021 were dose proportional when administered at doses ranging from 1.5 to 6 mg/kg and from 1 to 4 mg/kg, respectively. Multiple dose PO data in rats showed C_{max} and AUC_{0-t} after repeated doses were 1.42- and 1.38-fold higher as compared to single-dose results. Multiple-dose C_{max} and AUC_{0-t} were 1.13- and 1.12-fold higher in cynomolgus monkeys compared to single-dose administration, respectively.

No induction of CYP1A2, CYP2B6, and CYP3A4 by ABSK021 was found, and no inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2D6, and CYP3A4 by ABSK021 was found. The IC₅₀ for inhibition of CYP 2C9 and CYP 2C19 was 7.01 μ M and 48.87 μ M, indicating moderate and low inhibition, respectively. Although CYP2C9 and CYP2C19 are inhibited, ABSK021 has a low potential for drug interactions, which needs to be assessed based on ABSK021 human plasma concentrations.

ABSK021 showed no time-dependent inhibition of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4. CYP3A is the major CYP450 isoenzyme that catalyzes the oxidative metabolism of ABSK021.

1.2.1.3 Preclinical Pharmacodynamic Studies

ABSK021 significantly inhibited CSF-1R kinase activity in an ADP-Glo fluorometric assay with a mean IC₅₀ of 20.95 nM. The IC₅₀ values for the reference compounds PLX3397 and staurosporine (STSP) were 15.30 nM and 1.65 nM, respectively. Antiproliferative assays and kinase screening data demonstrate that ABSK021 has excellent selectivity for CSF-1R targets.

ABSK021 dose- and time-dependently inhibited c-fos mRNA expression in an MCSF-induced

in vivo PK/PD study in female DBA1 mice.

The following in vivo pharmacodynamic studies were conducted in female BALB/c mice: 1) subcutaneous allograft breast cancer model with EMT-6 cell line, 2) subcutaneous allograft B-cell lymphoma model with A20 cell line, and 3) subcutaneous allograft colon cancer model with CT26 cells. The above in vivo pharmacodynamic studies indicated that ABSK021 showed significant anti-tumor efficacy either as monotherapy or in combination with anti-PD-1 antibodies.

In addition, ABSK021 was tested in a series of different in vitro radioligand binding, enzymatic, and functional assays, including 37 molecular targets in the binding assay and 6 targets in the enzymatic and uptake assays. More than 50% inhibition or stimulation is considered to represent a significant effect of the test compound on this target. This significant effect was not observed on any of the receptors studied.

Please refer to the Investigator's Brochure for more information on preclinical pharmacodynamic studies.

1.2.2 Overview of Ongoing Clinical Studies

Two clinical studies are ongoing for ABSK021, ABSK021-101 and ABSK021-102. ABSK021-101 is an open-label, multi-center, global Phase I study to evaluate the safety, tolerability and pharmacokinetics of ABSK021 in advanced solid tumor patients, consisting of an escalation part and an expansion part. Safety and tolerability of ABSK021 is to be evaluated in the escalation part, in which patients with advanced solid tumor are given ABSK021 in repeated 28-day treatment cycles, and to determine the maximum tolerated dose (MTD) and recommended dose for expansion (RDE) of oral ABSK021. In the expansion part, ABSK021 at the Recommended Dose of Expansion (RDE) will be given to further evaluate the safety, tolerability and preliminary anti-tumor activity of ABSK021 in patients with selected tumor types, especially patients with tenosynovial giant cell tumor (TGCT). ABSK021-102 is a randomized, open-label, two-sequence, two-period, crossover study to evaluate the relative bioavailability of ABSK021 in healthy patients after single-dose administration at fasted state or after a high-fat meal and conducted in accordance with the approval of study ABSK021-101. The enrollment of escalation part of ABSK021-101 has been completed and a total of 32 patients with advanced solid tumors have been enrolled. At present, except for 1 patient who is still receiving ABSK021 at 25mg QD, all the other patients have completed the study treatment. A total of 4 doses (25mg QD, 50mg QD, 75mg QD and 100mg QD) were studied in the escalation part. The MTD is determined to be 75mg QD, and 50mg QD is selected as the first RDE in the expansion part (including patients with TGCT). 25 mg QD is selected as the second RDE for the TGCT cohort in the expansion part.

A total of 56 patients has been enrolled into the Expansion Part, including 33 patients with TGCT

and 23 patients with other solid tumors, by June 2022, and the enrollment is still ongoing. Two doses (25mg and 50mg) have been studied in patients with TGCT, including 32 enrolled patients. Six (6) patients have been included in the 25 mg dose group, and 27 patients in the 50 mg dose group. Efficacy data are not yet available for patients in the 25 mg dose group. Twenty-four patients in the 50 mg dose group have had at least 1 available post-treatment tumor assessment, and a total of 14 patients have achieved objective response (including 1 complete response [CR] and 13 partial responses [PR]) according to RECIST v1.1 by IRC. The overall objective response (ORR) rate was 58.3% (14/24; 95%CI: 36.64%-77.89%).

As of June 2022, overall compliance and tolerability were good in all TGCT patients (N = 32), with a mean treatment duration of 111 days (range: 30 days to 192 days), 97% (32/33) of patients with relative dose densities between 80% and 120% (data missing for the other patient), no patients had dose reductions or overdose, and 63.6% (21/33) of patients had never experienced dose interruption. In terms of safety, a total of 28 (28/33, 84.8%) patients experienced at least 1 TEAE, but most of them were Grade 1 or 2. Only 3 (3/33, 9.1%) patients reported TEAEs of CTCAE Grade ≥ 3 (1/33, 3.0% was regarded as drug-related), no drug-related serious TEAEs, no drug-related TEAEs leading to treatment discontinuation, and no TEAEs leading to death were reported.

The most common 10 TEAEs by preferred term were CK increased (23/33, 69.7%), LDH increased (23/33, 69.7%), α -hydroxybutyrate dehydrogenase increased (19/33, 57.6%), AST increased (16/33, 48.5%), amylase increased (9/33, 27.3%) ALT increased (8/33, 24.2%), rash (8/33, 24.2%), pruritus (8/33, 24.2%), somnolence (7/33, 21.2%), and dizziness (7/33, 21.2%), respectively. CK and transaminase elevations were asymptomatic and quickly recovered after drug interruptions. Based on the analysis of relevant literature²⁵ and clinical study results of other similar products, this may be related to the mechanism of action of the drug. Additionally, hair color changes or severe liver injury that may be related to off-target toxicity were not observed.

As of December 2022, a total of 49 TGCT patients were enrolled, including 37 patients in 50 mg dose group and 12 patients in 25 mg dose group. The updated data from 50 mg QD cohort as well as the preliminary data from 25 mg QD cohort had been read out. Tumor regression was observed across all evaluated patients, and median DOR was not reached in either cohort. The ORR was 77.4% (24/31, 95%CI: 58.90%-90.41%) in 50 mg QD cohort and 40% (4/10, 95%CI: 12.16%-73.76%) in 25 mg QD cohort by IRC based on RECIST v1.1 in response-evaluable analysis set. Average improvement of flexion range of knee at week 13 from baseline was 30.2 degrees (n=13, range: 2, 105) in 50 mg QD and 4.8 degrees (n=5, range: -12, 24) in 25 mg QD. These updated efficacy data showed significant anti-tumor effects of ABSK021 continuous dosing, especially in 50 mg QD cohort.

As of December 2022, the median treatment duration were 9.3 months and 6.2 months in 50mg and 25 mg QD cohort, respectively. Both 25mg QD and 50mg QD dosing of ABSK021 had

favorable safety and tolerability profile in TGCT patients. Most TEAEs were Grade 1 or 2 in both cohorts. No hair color changes or serious liver injuries were reported in either cohort. TEAE incidences were 91.7% (11/12) in 25 mg QD cohort and 94.6% (35/37) in 50 mg QD cohort. No drug-related serious TEAEs were reported in both cohorts. A total of 15 patients (15/49, 30.6%) have reported TEAEs leading to interruption of treatment, including 1 patient (1/12, 8.3%) in 25 mg QD cohort and 14 patients (14/37, 37.8%) in 50 mg QD cohort. But most of them were able to recover quickly and patients restarted the treatment of study drug within 1 month. Most common TEAEs ($\geq 20\%$) in both cohorts include LDH increase (37/49, 75.5%), CPK increase (33/49, 67.3%), α -HBDH increase (31/49, 63.3%), AST increase (21/49, 42.9%), amylase increase (13/49, 26.5%), ALT increase (12/49, 24.5%), pruritus (10/49, 20.4%) and rash (10/49, 20.4%). Due to the median duration of treatment in the 50 mg QD cohort is much longer than that in the 25 mg QD cohort, any comparison between these two dose levels should be interpreted with caution.

ABSK021-102 study has been completed and the clinical pharmacology data are detailed in 1.2.3 below. Efficacy data are not applicable in healthy subjects, and safety data are summarized as below:

A total of 16 healthy subjects were enrolled in this study, and a single-dose of ABSK021 was administered at fasted state or after a high-fat meal. All subjects demonstrated a favorable safety profile. All TEAEs were CTCAE Grade 1 or 2. Only 2 (2/16, 12.5%) drug-related TEAEs were reported, including Grade 1 of diarrhea and Grade 1 of myalgia, but both recovered by the end of the study. No TEAEs with CTCAE Grade ≥ 3 or serious TEAEs were reported. No TEAEs leading to withdrawal from the study or resulting in death were reported. No subjects reported drug-related clinically significant changes in laboratory tests (including hematology, urinalysis, liver function, myocardial enzyme test, etc.), vital signs or electrocardiograms.

The above results indicate that ABSK021 has potent anti-tumor activity in TGCT patients, and the overall safety and tolerability are favorable.

1.2.3 Summary of Clinical Pharmacology Data

As of 15 May 2022, all 32 patients in the Escalation Part have completed intensive PK sampling. The PK profile of ABSK021 after oral administration was similar between 25 mg and 100 mg, with a biexponential decreasing trend after peak concentrations. A non-compartmental analysis was performed based on the data from the escalation phase and the preliminary results suggest that:

After a single dose, in the 25 mg-100 mg dose groups, ABSK021 was rapidly absorbed after oral administration, with a median t_{\max} interval of 0.87 to 1.52 hours and an apparent volume of distribution (V_z/F) of ABSK021 of 469 to 849 L, suggesting extensive distribution in vivo. The apparent clearance (CL/F) of ABSK021 ranged from 5.12 to 11.9 L/h, and the mean terminal $t_{1/2}$

after oral administration of ABSK021 ranged from 43.6 to 63.5 hours.

After repeated dosing, the time to maximum concentration of ABSK021 was similar to that of a single dose (0.85 to 1.24 hours), and ABSK021 accumulated in vivo with an accumulation index of 2 to 3-fold at steady state (accumulation index of 1.6 to 2.2 based on C_{\max} , and 2.8 to 3.3 based on $AUC_{0-\tau}$) over the dose interval of 25 mg to 75 mg (intensive sampling after repeated dose failed to be collected at 100 mg).

Plasma exposure (C_{\max} and AUC_{last}) to ABSK021 increased slightly less than dose-proportionally between 25 mg and 75 mg after single and multiple doses. After administration at 100 mg, C_{\max} was 375 ng/mL slightly lower than the C_{\max} of 75 mg (508 ng/mL) and AUC_{last} was higher than the 75 mg dose (8402 h * ng/ml versus 4567 h * ng/ml), which requires cautious interpretation given that 100 mg dose group included only 2 patients.

The effect of a high-fat meal on the PK of a single dose of 25 mg ABSK021 was evaluated in Study ABSK021-102 and preliminary results suggested that high-fat food delayed the time to peak ABSK021 concentration, with the t_{\max} of 1 hour and 4 hours after dosing at fasted and fed state, respectively. In the meanwhile, high-fat food reduced the C_{\max} of ABSK021 by approximately 40% compared to fasted dosing, with C_{\max} of 165.4 ng/mL and 92.2 ng/mL under fasted and fed conditions, respectively. The AUC_{inf} after administration of ABSK021 was similar with 2156.8 h * ng/mL and 2446.6 h * ng/mL under high-fat food and fasted state, respectively.

1.3 Rationale of control arm selection

This study is a randomized, double-blind, placebo-controlled Phase 3 clinical study in subjects with TGCT not amenable to surgery and consists of Part 1, Part 2 and a long-term extension treatment phase (i.e., Part 3).

Placebo is selected as the control arm in Part 1 because there is no existing non-surgical treatment that is accepted as standard of care for TGCT outside of the U.S, such as Europe and China. Pexidartinib is the only systemic therapy approved by the FDA for adult patients with symptomatic TGCT associated with severe morbidity or functional limitations and not amenable to improvement with surgery. However, the potential risk of fatal liver injury for this drug cannot be ignored, with a boxed warning of the risk of serious and potentially fatal liver injury in the package insert. There are challenges of using pexidartinib as an active control, including the need for increased monitoring and lack of approval of pexidartinib outside of the U.S. Surgical treatment cannot be used as a control treatment because the patient population includes those for whom surgery is associated with potentially worsening function limitation or severe morbidity.

1.4 Risk-benefit analysis

In clinical evaluation to date, the most common TEAEs of all grades have been LDH increase, CPK increase, α -HBDH increase, AST increase, amylase increase, ALT increase, pruritus and

rash. CK and transaminase elevations were asymptomatic and quickly recovered after drug interruptions. Dosing modification guidance is included within the protocol in Section 5.5. Liver function (clinical chemistry), renal function (clinical chemistry), and heart electrophysiology (QTc evaluation) will be monitored during this study. More detailed and updated information regarding pre-clinical and clinical safety data can be found in the IB.

TGCT is a progressive disease with the standard of care is surgery. However, the guidelines and evidence-based data for the timing and extent of surgical intervention are lacking. Surgical outcomes may result in marked patient morbidity as reflected in post-operative pain, limitation in function, and cosmetic disfigurement. In extreme or recurrent cases, the tumor may be aggressive and require limb amputation. On the other hand, no systemic treatments have been approved for these diseases outside of the U.S. Pexidartinib is the only systemic therapy approved in the U.S, but the potential risk of fatal liver injury for this drug cannot be ignored. ABSK021, a highly selective CSF-1R inhibitor, displayed an acceptable safety profile and promising efficacy data at the selected dose in phase 1 study of TGCT patients, offers a promising new therapeutic option for patients with TGCT.

Placebo is selected as the control group due to there is no existing non-surgical treatment that is accepted as standard of care for TGCT outside of the U.S. It may not be helpful to the health problems of patients, which may remain the same or may worsen due to the natural progression of the disease. However, placebo is only used in Part 1 for 24 weeks, and the eligible patients will be randomized in a 2:1 ratio to receive ABSK021 or placebo. Patients who received the placebo still need to follow the same study procedures with the participants who will take the investigational drug. Given the slow-growing nature of TGCT, the safety risk for patients in placebo group is believed acceptable and manageable. More importantly, all patients who receive the placebo will have the opportunity to enter Part 2 study and receive the treatment of open-label ABSK021 after completed the study of Part 1.

In summary, given a favorable safety profile and significant antitumor activity of ABSK021 in subjects with TGCT from phase 1 study, the potential for a positive benefit/risk profile is assumed for the Phase 3 study.

2 Study Objectives and Study Endpoints

2.1 Study Objectives

2.1.1 Primary Study Objectives

- To compare the Objective Response Rate (ORR) within 25 weeks after treatment with ABSK021 or placebo in TGCT patients based on RECIST v1.1.

2.1.2 Secondary Study Objectives

- To compare the Objective Response Rate (ORR) within 25 weeks after treatment with ABSK021 or placebo in TGCT patients based on Tumor Volume Score (TVS);
- To compare the effects of ABSK021 and placebo on the Range of Motion (ROM) in TGCT patients at Week 25;
- To compare the effects of ABSK021 and placebo on Patient-Reported Outcome (PRO) in TGCT patients at Week 25;
- To compare the Duration of Response (DOR) after treatment with ABSK021 or placebo in TGCT patients based on RECIST v1.1 and TVS, respectively;
- To compare the safety of ABSK021 and placebo in TGCT patients;
- To evaluate the pharmacokinetic (PK) profile of oral ABSK021.

2.2 Study Endpoints

2.2.1 Primary Study Endpoints

- 25-Week ORR by Blinded Independent Review Committee (BIRC) based on RECIST v1.1: the proportion of patients who achieve the Best Overall Response (BOR) of either Complete Response (CR) or Partial Response (PR) as assessed by BIRC within 25 weeks according to RECIST v1.1.

2.2.2 Key Secondary Study Endpoints

- 25-Week ORR by BIRC based on TVS: the proportion of patients who achieve the BOR of either CR or PR as assessed by BIRC within 25 weeks according to TVS criteria;
- Mean change from baseline in Range of Motion (presented as relative ROM) of the affected joint at Week 25, according to the reference criteria for the same joint;
- Mean change from baseline in the Worst Stiffness Numeric Rating Scale (NRS) score at Week 25;
- Mean change from baseline in the BPI Worst Pain Numeric Rating Scale (NRS) score at Week 25;
- Mean change from baseline in the Patient-reported Outcomes Measurement Information System (PROMIS) Physical Functioning score at Week 25.

2.2.3 Other Secondary Study Endpoints

- DOR by BIRC based on RECIST v1.1: the time (months) from the first documentation of objective response (CR or PR as assessed by BIRC per RECIST v1.1 criteria) to the first documentation of radiographic disease progression (PD) or death due to any cause, whichever occurs first;
- DOR by BIRC based on TVS: the time (months) from the first documentation of objective response (CR or PR as assessed by BIRC per TVS criteria) to the first documentation of radiographic PD or death due to any cause, whichever occurs first;
- 25-week ORR by Investigator per RECIST v1.1: proportion of patients with a BOR of CR or PR assessed by the Investigator within 25 weeks according to RECIST v1.1;
- DOR by Investigator per RECIST v1.1: the time (months) from the first documentation of objective response (CR or PR as assessed by the Investigator per RECIST v1.1 criteria) to the first documentation of radiographic PD or death due to any cause, whichever occurs first;
- Mean change from baseline in EuroQol 5-dimension, 5-level questionnaire (EQ-5D-5L) visual analogue scale (VAS) score at Week 25;
- Safety endpoints, including but not limited to treatment emergent adverse events (TEAEs), dose modifications, laboratory tests, vital signs, electrocardiograms (ECGs), echocardiography, and related items in NCI-PRO-CTCAE;
- PK profile of ABSK021.

3 Study Design

3.1 Overall design

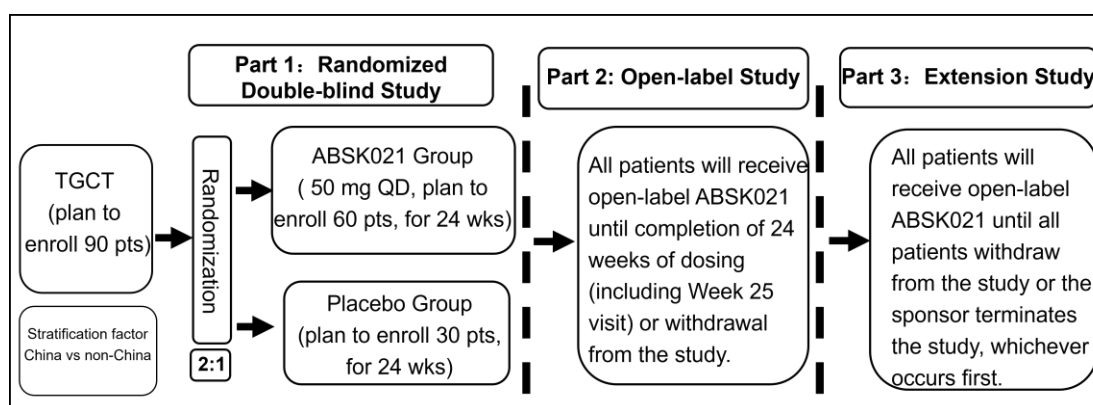
This is a randomized, double-blind, placebo-controlled Phase 3 clinical study to evaluate the efficacy and safety of ABSK021 at the dose of 50 mg QD in patients with TGCT. This study consists of Part 1, Part 2 and a long-term extension treatment phase (i.e., Part 3). Part 1 is a double-blind phase, eligible patients will be randomized in a 2:1 ratio to ABSK021 treatment group or matching placebo group and will receive 50 mg QD of ABSK021 or matching placebo (28 days/cycle) until completion of treatment and follow-up in Part 1 (i.e., completion of ABSK021 administration at Week 24 and completion of Week 25 follow-up visit including MRI) or withdraw from the study. Randomization will be stratified by China and non-China sites. All patients who complete Part 1 treatment and meet eligibility criteria will be eligible to continue in Part 2 of the study.

Part 2 is an open-label treatment phase, and all patients entering this phase will receive 50 mg QD of open-label ABSK021 until completion of 24 weeks of dosing or withdrawal from the study (If a patient has dose modification in Part 1, the patient will continue to be administered at the modified dose in Part 2). Patients must continue to meet eligibility criteria to continue on to Part 2. After the patient has achieved a sustained tumor response (defined as continuous radiological PR or CR for more than 6 months by BIRC or Investigator based on RECIST v1.1), the Investigator and the sponsor will discuss and decide whether the current recommended starting dose can be reduced to 25 mg QD during the subsequent maintenance treatment. If the Investigator assesses that the patient will not benefit from subsequent treatment, the patient may be discontinued from the study treatment. Part 2 will end after all patients have completed 24 weeks of dosing (including follow-up at Week 25) or have withdrawn from the study.

Patients who complete Part 1 will be invited by the site investigator or staff to take part in an optional qualitative interview, to explore the disease experience during the clinical trial. See appendix 12.9 and 12.10 for more details.

All patients who complete 24 weeks of dosing in Part 2 and continue to meet eligibility criteria will enter the open-label extension treatment phase (i.e., Part 3) for a longer period treatment and safety follow-up. Part 3 will end when all patients withdraw from the study, or the sponsor decides to terminate the study, whichever occurs first. The study design is specified in the following figure:

Figure 1 Study Overall Schema



An independent Data Monitoring Committee (IDMC) will be established in Part 1 and Part 2 of this study to continuously monitor the safety profile and oversee the overall conduct of the study. In order to improve the integrity of the study, the IDMC may also make recommendations on patient selection, recruitment, and management in order to improve patient compliance and improve data management and quality control procedures. A separate IDMC charter will define IDMC members, roles, and responsibilities, as well as the process of providing advice to the sponsor.

4 Study Population

4.1 Patient Sample Size

Approximately 90 patients with TGCT are planned to be enrolled, including 60 patients in the ABSK021 group and 30 patients in the placebo group.

4.2 Patient Selection Criteria

4.2.1 Inclusion Criteria

1. Patients should understand the study procedures and sign the informed consent form prior to screening.
2. Age \geq 18 years.
3. A diagnosis of TGCT, and meet the following 2 requirements prior to randomization: (i) that has been histologically confirmed either by local or central laboratory; (ii) unresectable, defined as confirmed by assessment by at least two clinical experts (including at least one independent expert who is not part of the trial conduct), meeting one of the following 2 requirements: ① located in a complex anatomical site, is extensively invasive, and cannot be completely resected; or ② surgical operation may cause dysfunction or serious complications.
4. Measurable disease as defined by RECIST v1.1, and with at least one lesion of \geq 2 cm (assessed by MRI scans in local site) prior to randomization.
5. For patients with an analgesic need, a stable prescription of analgesic regimen assessed by the Investigator during the 2 weeks prior to randomization.
6. During the 2 weeks prior to randomization, at least 4 of 7 consecutive days of BPI Worst Pain NRS items and Worst Stiffness NRS items completed correctly.
7. Symptomatic disease because of active TGCT, defined as one or more of the following: (i) a worst pain of at least 4 within 2 weeks prior to randomization (based on scale of 0 to 10, with 10 representing “pain as bad as you can imagine”), (ii) a worst stiffness of at least 4 within 2 weeks prior to randomization (based on a scale of 0 to 10, with 10 representing “stiffness as bad as you can imagine”).
8. Willingness and ability to complete the patient-reported outcome (PRO) assessments throughout the study, including BPI-Worst-Pain-NRS, Worst-Stiffness-NRS, PROMIS Physical Functioning Scale, NCI-PRO-CTCAE and EQ-5D-5L Health Scale.
9. ECOG PS (Eastern Cooperative Oncology Group Performance Status) of 0 or 1.

10. Adequate organ function and bone marrow function as indicated by the following screening assessments performed within 14 days prior to randomization:
 - a) Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/\text{L}$;
 - b) Platelet count (PLT) $\geq 90 \times 10^9/\text{L}$;
 - c) Hemoglobin (Hb) $\geq 90 \text{ g/L}$ (or $\geq 9 \text{ g/dL}$);
 - d) Total bilirubin (TBIL) $\leq 1.5 \times \text{ULN}$;
 - e) Aspartate transaminase (AST) and Alanine transaminase (ALT) $\leq 1.5 \times \text{ULN}$;
 - f) Alkaline phosphatase (ALP) $\leq 1.5 \times \text{ULN}$;
 - g) Creatinine clearance (Crcl) $\geq 50 \text{ mL/min}$ (Cockcroft-Gault formula, Appendix 12.3).

Note: if the results of screening laboratory test do not meet the above criteria, re-examination will be allowed for only once during the screening period at Investigator's discretion.

4.2.2 Exclusion Criteria

1. Known allergy or hypersensitivity to any components of the investigational drug product.
2. Previous treatment with highly selective inhibitors targeting CSF-1/CSF-1R prior to randomization. However, patients who have received prior treatment with multi-kinase inhibitors that include the CSF-1/CSF-1R pathway are allowed, such as Imatinib and Nilotinib.
3. Known additional malignancy that required active treatment and may affect the patient's participation in the study or affect the outcome of the study as assessed by the Investigator. Exceptions include cured basal cell carcinoma of skin, squamous cell carcinoma of skin, and other carcinoma in situ.
4. Known metastatic TGCT.
5. Significant concomitant arthropathy in the affected joint, serious disease, uncontrolled infection.
6. Known MRI contraindications.
7. Has factors that significantly affected the absorption of oral drug, such as inability to take oral medication or significant nausea and vomiting, malabsorption, external bile duct drainage, massive small bowel resection, etc.
8. Major surgery or previous anti-tumor therapy for TGCT within 4 weeks prior to

randomization, or unhealed, infected, or dehiscence of previous surgical wounds, or adverse events from prior therapies did not recover to \leq Grade 1 (CTCAE 5.0). *Patients with Grade \leq 2 adverse events during Part 1 are allowed to continue on to Part 2, based on the Investigator's overall risk-benefit assessment. Patients with Grade \leq 2 adverse events during Part 2 are allowed to continue on to Part 3, based on the Investigator's overall risk-benefit assessment.*

9. Concomitant use of strong inhibitors or inducers of CYP3A4 within 14 days prior to randomization. Grapefruit juice, grapefruit hybrids, pomegranates, carambola, grapefruit, Seville oranges and juice or other processed product consumption within 3 days prior to randomization.
10. Impaired cardiac function or clinically significant cardiac disease, including any one of the following:
 - a) New York Heart Association (NYHA) class III or IV heart disease, active ischemia or any other uncontrolled cardiac condition such as angina pectoris, clinically significant cardiac arrhythmia requiring therapy, uncontrolled hypertension or congestive heart failure;
 - b) Prolongation of the rate-corrected QT interval based on repeated demonstration of QTcF > 480 ms (QTc interval corrected by Fridericia's formula), or history of long QT interval corrected (QTc) syndrome;
 - c) Left ventricular ejection fraction (LVEF) $< 50\%$ or below the lower limit of normal, whichever is higher.
11. Known active human immunodeficiency virus (HIV antibody test positive), active hepatitis B (HBsAg positive and HBV-DNA $>$ upper limit of reference range), active hepatitis C (HCV-Ab positive and HCV-RNA $>$ upper limit of reference range), or known active tuberculosis prior to randomization.
12. Known active liver or biliary disease, or other diseases that may lead to abnormal liver function test results during the study, including but not limited to Gilbert's Syndrome, Nonalcoholic Steatohepatitis (NASH) and cirrhosis.
13. Pregnant or lactating women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive human chorionic gonadotropin (hCG) laboratory test within 7 days prior to randomization.
14. Childbearing potential males or non-surgically sterilized female patients must agree to use effective methods of contraception from at least 14 days prior to randomization until 6 months after the last dose of study drug. A condom is required to be used also

by vasectomized men in order to prevent delivery of the drug via seminal fluid.

15. Any other clinically significant comorbidities, such as uncontrollable pulmonary disease, active infection, or any other condition, which in the judgment of the Investigator, could compromise compliance with the protocol, interfere with the interpretation of study results, or predispose the patient to safety risks.

4.3 Withdrawal and Replacement of Patients

4.3.1 Patient Withdrawal from the Study

Patients may withdraw voluntarily from the study at any time. The Investigator may also request the patient to withdraw from the study based on the actual clinical situation of the patient. Reasons for discontinuation of treatment or withdrawal from study may include:

- Withdrawal by subject;
- Adverse event;
- Lost to follow-up;
- Non-compliance with drug therapy;
- Physician decision;
- Pregnancy;
- Death;
- Progression disease;
- Study terminated by sponsor;
- The Investigator considered that withdrawal from the study may bring greater benefit to the patient.

If a patient voluntarily withdraws from the study, an attempt should be made to contact the patient to determine the reason for withdrawal. When a patient is early withdrawn from the study, all study procedures and assessments required for the EOT Visit should be completed, regardless of the withdrawal reason.

For patients who develop radiographic disease progression in Part 1 (assessed by **BOTH** BIRC and the investigator based on RECIST v1.1, respectively), if the investigator, after full assessments, deems that the benefit of early entry into Part 2 to receive open-label ABSK021 treatment outweighs the risk, with the approval of the sponsor, patients may enter Part 2 in advance under blinded conditions. However, it is strongly recommended that patients complete all visits in Part 1 according to the protocol (including visits after disease progression) before

entering Part 2.

For patients who develop radiographic disease progression (assessed by BIRC **OR** the investigator based on RECIST v1.1) in Part 2 or Part 3, if the investigator deems that continued treatment may bring benefit to the patient based on the benefit-risk maximization principle, after communication and agreement with the sponsor, the patient can continue to receive the treatment with the consent of the him/her.

4.3.2 Patient Replacement

Replacement of patients is not allowed after randomization.

5 Study medication

5.1 ABSK021

5.1.1 Supply and storage of study drug

ABSK021 is supplied as oral capsules, each containing 25 mg of ABSK021.

Excipients include lactose monohydrate, microcrystalline cellulose, colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, and gelatin hard capsule shell. Lactose monohydrate and hard gelatin capsule shells are excipients of animal origin.

ABSK021 capsules are packaged in high-density polyethylene bottles with polypropylene child resistant (PPCR) closures lined with induction seals.

ABSK021 capsules should be stored according to drug label.

5.1.2 ABSK021 Administration

In Part 1, patients in the ABSK021 treatment group will receive 25 mg/capsule of ABSK021, 2 capsules once daily, with a total daily dose of 50 mg; the drug can be taken with or without food; patients will receive repeated oral doses in 28-day treatment cycles until completion of 24 weeks of dosing or withdrawal from the study. Patients who complete treatment and follow-up in Part 1 (i.e., complete 24 weeks of dosing and Week 25 follow-up including MRI) and meet eligibility criteria will be eligible to continue in Part 2 or end of treatment (For patients who have not completed dosing and follow-up due to imaging disease progression, please refer to Section 4.3.1).

In Part 2, all patients will receive open-label ABSK021 2 capsules once daily at a total daily dose of 50 mg. The drug can be taken with or without food (If a patient has dose modification in Part 1, the patient will continue to be administered at the modified dose in Part 2). All patients will receive treatment with ABSK021 until completion of 24 weeks of dosing or withdrawal from the study.

In Part 3, all patients will continue to receive open-label ABSK021 once daily until any of the following events occurs: disease progression, experiencing unacceptable toxicity, withdrawal of informed consent form, commercialization of the study drug for the treatment of TGCT approved by the local regulatory authorities, decision by the sponsor to terminate the study, or until 2 years after the last patient enters Part 3, whichever occurs first. The starting dose in Part 3 for an individual patient will be determined by the dose he/she received at the end of Part 2.

5.2 Placebo

5.2.1 Placebo Supply and Storage

ABSK021 matching placebo, to be provided as oral capsules, has the same appearance as ABSK021 and contains the similar excipients as ABSK021 but without the active pharmaceutical ingredient (API).

Colloidal silicon dioxide was used to improve the flowability of API, so there was no colloidal silicon dioxide in the placebo capsules.

The excipients of the placebo capsules include lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, and gelatin hard capsule shell.

Storage condition for placebo is the same as ABSK021.

5.2.2 Placebo Administration

In Part 1, patients in the placebo group will receive ABSK021-matching placebo 2 capsules once daily. Patients in the placebo group will receive repeated oral doses in 28-day treatment cycles. Part 2 will be an open-label study and all patients entering Part 2 will no longer receive placebo.

5.3 Rationale for Dose Selection

In the dose escalation phase of a Phase 1 study, data from 32 tumor patients who have been treated with ABSK021 (from 25 mg QD to 100 mg QD, 26 DLT-evaluable patients) have been accumulated as of December 2021. Results showed that ABSK021 was safe and tolerated, no DLTs were observed in the 25 mg QD group (a total of 6 DLT-evaluable patients), no DLTs were observed in the 50 mg QD group (a total of 12 DLT-evaluable patients), and 1 patient in the 75 mg QD group (a total of 6 DLT-evaluable patients) had a DLT, and 2 patients in the 100 mg QD group (a total of 2 DLT-evaluable patients) had DLT. The current MTD is 75 mg QD and the mean $t_{1/2}$ of ABSK021 ranged from 39 to 60 hours in dose range of 25 mg to 100 mg. These results support further exploration of QD dose regimen. Therefore, 50 mg QD was used as the first RDE dose in the Phase 1 expansion part and 25 mg QD was used as the second RDE dose for TGCT patients in the Phase 1 expansion part.

As of 1st June 2022, a total of 27 patients with unresectable TGCT have been treated with ABSK021 at 50 mg QD in the expansion part, and more than 20 patients have been on treatment for ≥ 3 months, and the majority of TEAEs reported were Grade 1 or 2, and no drug-related TEAEs \geq Grade 3 have been reported. Dose reductions due to AEs were not reported, and potent preliminary anti-tumor activity was found in patients treated, and tumor size reduction was observed in almost all evaluated patients. Preliminary PK-PD analysis also supported the dose selection of 50 mg QD. The effect of ABSK021 exposure on non-classical monocytes was almost saturated at doses ≥ 25 mg QD, and there was a positive correlation between changes in CSF-1 levels and ABSK021 concentration in vivo, considering higher PK exposure at 50 mg QD than 25 mg QD (preliminary results showed C_{\max} of 325 ng/mL and 191 ng/mL, AUC_{last} of 3204 hr * ng/mL and 2043 hr * ng/mL, after dosing at 50 mg and 25 mg QD, respectively) and good safety data, this dose may lead to better efficacy in TGCT patients.

The effect of high-fat food on the PK of a single oral dose of 25 mg ABSK021 was evaluated in Study ABSK021-102, and the results suggested that the overall exposure AUC_{inf} of ABSK021 after oral administration of ABSK021 with high-fat food showed no difference with the exposure after administration in fasting state. Therefore, it is not expected to affect the efficacy benefit in TGCT patients whether ABSK021 is taken with or without food. In the meanwhile, high-fat food will delay the time to peak ABSK021 concentration from 1 hour to 4 hours, and reduce the peak concentration by approximately 45%. As a result, co-administration with food is not expected to pose additional risks of AEs such as CK and AST increased, which are common in patients.

Based on the above safety, efficacy, preliminary PK-PD and food effect study data, oral administration of ABSK021 at 50 mg QD is selected as the recommended dose in this study for TGCT patients and co-administration with food is not restricted.

5.4 Treatment duration

The Part 1 study consists of a screening period (within 28 days prior to randomization) and a treatment period of 6 cycles (28 days/cycle, 24 weeks in total). The primary endpoint analysis will be performed after the last patient has completed Week 25 follow-up and tumor assessments (including Investigator assessment and BIRC assessment).

The Part 2 study consists of a treatment period of 6 cycles (28 days/cycle, 24 weeks in total). Patients who complete Part 2 treatment will be eligible to enter Part 3 to continue a longer period of treatment and safety follow-up.

Part 3 is an extension treatment phase. All patients will continue to receive open-label ABSK021 continuously (28 days per cycle) until any of the following events occur: disease progression, experiencing unacceptable toxicity, withdrawal of informed consent form, commercialization of the study drug for the treatment of TGCT approved by the local regulatory authorities, decision by the sponsor to terminate the study, or until 2 years after the last patient enters Part 3, whichever

occurs first.

5.5 Dose Modification

For patients who cannot tolerate the protocol-specified dosing schedule, dose modifications (dose interruption or dose reduction) are allowed to enable the patients to continue study treatment. All dose modifications should be based on the worst toxicity that occurred previously (CTCAE Version 5.0). A maximum reduction of one dose level to 25 mg QD is allowed. If any patient requires a therapeutic dose lower than 25 mg QD, the study drug must be discontinued and the patient must end the treatment (EOT) and accept safety follow-up visit. All dose interruptions or modifications must be documented in the eCRF.

5.5.1 Dose interruption due to unscheduled medical procedures

If a patient requires unscheduled surgery or other unscheduled medical procedures during the study, the Investigator should discuss with the sponsor to determine whether study drug interruption is required.

5.5.2 Dose interruption or modification due to intolerance or ADRs

The study drug administration may be interrupted or modified (i.e., dose reduction) at the discretion of the study personnel, e.g. in the event of an AE, or for other reasons after consultation with the sponsor. All dose modifications should be based on the worst toxicity that occurred previously. The dose modification guidelines described in Table 5 are recommended only and comprehensive judgement can be made by the Investigator based on the actual situation of the patient. Considering that some AEs may be related to the mechanism of action of the drug, the Investigator should have a prospective discussion with the sponsor whenever possible.

If the AE leading to dose modification recovers to Grade 1 or baseline within 14 days, the patient may continue to receive the same dose level at the time of the AE onset or restart the treatment at 1 dose level lower (to 25 mg QD).

If an AE leading to dose modification does not recover to Grade 1 or baseline within 14 days, discussion with the sponsor is required, and treatment may be restarted at one dose level lower (to 25 mg QD) if the Investigator considers the event to be clinically insignificant.

Dose interruptions due to non-AE causes (such as irresistible factors such as drug dispensing interruption due to epidemic quarantine) are not patient to the above conditions. Please discuss the details with the sponsor in advance.

In case of any inconsistency with the dose modification specified in the protocol, the Investigator is advised to discuss and confirm with the sponsor in advance. Patients who have dose interruption or permanently discontinue treatment due to adverse events or clinically significant laboratory abnormalities are recommended to be followed weekly (more frequent visits are

allowed as required by the study site or as clinically indicated) until the AE resolves or stabilizes, whichever occurs first.

Table 5 Dose Modification Guidelines

Toxicity Grade (Per CTCAE 5.0)	Dose Modification Recommendations
ALT/AST increased	
Grade 2	Hold study drug, administer appropriate supportive care or treatment, and monitor liver function at least once weekly until recovery to \leq Grade 1 or baseline, <ul style="list-style-type: none"> – Restart at the same dose level if recovered within 14 days; in the event of 2 relapse, restart at one dose level lower or discuss with the sponsor. – Restart at one dose level lower if recovered after 14 days; in the event of 2 relapse, discussion with the sponsor is required.
Grade 3	Hold study drug, administer appropriate supportive care or treatment, and monitor liver function at least once weekly until recovery to \leq Grade 1 or baseline, <ul style="list-style-type: none"> – Restart at one dose level lower if recovered within 14 days; subsequent recurrence of Grade 3 AEs should be discussed with the sponsor. – If recovered after 14 days, discussion with the sponsor is required.
Grade 4	Permanently discontinue the study drug.
Bilirubin increased	
Grade 2	Hold study drug, administer appropriate supportive care or treatment, and monitor liver function at least once weekly until recovery to \leq Grade 1 or baseline, <ul style="list-style-type: none"> – Restart at one dose level lower if recovered within 14 days; subsequent recurrence of Grade 2 AEs should be discussed with the sponsor. – If recovered after 14 days, discussion with the sponsor is required.
\geq Grade 2 Concurrent ALT or AST elevation \geq Grade 3	Permanently discontinue the study drug.
Grade 3 or 4	Permanently discontinue the study drug.
CK increased	

Grade 2	<p>Closely monitor clinical symptoms (abnormal renal function or signs of myocardial and skeletal muscle injury) and continue study drug at the current dose. Hold study drug and monitor CK levels at least once a week until recovery to \leq Grade 1 or baseline if accompanied with clinical symptoms.</p> <ul style="list-style-type: none"> – If recovered within 14 days, restart at the same dose level. – If not recovered within 14 days, discussion with the sponsor is required. <p>If recurrence of \geq Grade 2 accompanied with clinical symptoms after restart dosing, discussion with the sponsor is required.</p>
Grade 3	<p>Closely monitor clinical symptoms (abnormal renal function or signs of myocardial and skeletal muscle injury) and continue the treatment at the current dose level if without clinical symptoms. If need, monitor CK levels at least once weekly until recovery to \leq Grade 1 or baseline, or until the investigators assesses that CK monitor can be discontinued. If clinical symptoms accompanied, hold the study drug.</p> <p>For patients with asymptomatic CK increased:</p> <ul style="list-style-type: none"> – If recovered within 14 days, restart at the same dose level; subsequent recurrence of Grade 3 AE should be discussed with the Sponsor. – If not recovered within 14 days, discussion with the sponsor is required. <p>For patients with CK increased associated with clinical symptoms:</p> <ul style="list-style-type: none"> – Restart at a reduced dose after recovered to Grade 1 or baseline. If recurrence of \geq Grade 2 accompanied with clinical symptoms after restart dosing, discussion with the Sponsor is required.
Grade 4	<p>Hold study drug and closely monitor clinical symptoms (signs of abnormal kidney function or heart and skeletal muscle damage), and monitor CK levels at least once weekly until recovery to \leq Grade 1 or baseline.</p> <p>For patients with asymptomatic CK increased:</p> <ul style="list-style-type: none"> – If recovered within 14 days, restart at the same dose level or 1 dose level lower. – If not recovered within 14 days, discussion with the sponsor is required. <p>For patients with CK increased associated with clinical symptoms:</p> <ul style="list-style-type: none"> – Restart at a reduced dose after recovered to Grade 1 or baseline. If recurrence of \geq Grade 2 accompanied with clinical symptoms after restart dosing, discussion with the Sponsor is required.
Non-hematologic toxicity (except ALT/AST, bilirubin, or CK increased)	
Grade 1	Administer appropriate supportive care or treatment and continue study drug at the current dose.

Grade 2	<p>Administer appropriate supportive care or treatment and continue study drug at the current dose.</p> <p>Hold study drug if not improved within 7 days:</p> <ul style="list-style-type: none"> – If the AE recovers to Grade 1 or baseline within 14 days, restart at the same dose level. – If the AE recovers to Grade 1 or baseline after 14 days, restart at one dose level lower. <p>If the AE relapses to Grade 2 after resuming dosing, discussion with the sponsor is required.</p>
≥ Grade 3	<p>Administer appropriate supportive care or treatment and hold study drug:</p> <ul style="list-style-type: none"> – If the AE recovers to Grade 1 or baseline within 14 days, restart at the same dose level lower. – If the AE recovers to Grade 1 or baseline after 14 days, discussion with the sponsor is required. <p>Permanently discontinue study drug if the AE relapses to ≥ Grade 3 after resuming dosing. If, in the opinion of the Investigator, it is in the best interest of the patient to resume dosing, it must be discussed with the sponsor to determine whether the study drug can be restarted.</p>
Grade 4	<p>Administer appropriate supportive care or treatment and hold study drug:</p> <ul style="list-style-type: none"> – If the AE recovers to Grade 1 or baseline within 14 days, restart at the same dose level lower. – If the AE recovers to Grade 1 or baseline after 14 days, permanently discontinue study drug. If, in the opinion of the Investigator, it is in the best interest of the patient to resume dosing, it must be discussed with the sponsor to determine whether the study drug can be restarted.
Hematologic toxicity	
≤ Grade 2	Administer appropriate supportive care or treatment and continue treatment with study drug at the current dose.
≥ Grade 3	<p>Administer appropriate supportive care or treatment and hold study drug:</p> <ul style="list-style-type: none"> – If the AE recovers to Grade 1 or baseline within 14 days, restart at the same dose level. – If the AE recovers to Grade 1 or baseline after 14 days, restart at one dose level lower. <p>If the AE relapses to ≥ Grade 3 after resuming dosing, it should be discussed with the sponsor.</p>

Note: dose level reductions will be determined based on the dose level at the onset time AE.

5.6 Randomized Treatment Assignment

After the Investigator has confirmed that the patient meets all eligibility criteria, in Part 1 of the study, patients will be randomized in a 2:1 ratio to ABSK021 treatment or matching placebo according to the randomization schedule provided by an independent statistician. Randomization will be performed between all sites using a central interactive web response system (IWRS). Randomization will be stratified by China sites and non-China sites.

At screening, the IWRS will assign a unique screening number to each patient. The screening number will be used in all study-related documents, including the electronic case report form (eCRF). The screening number will not be reused. In addition, a randomization number will be assigned to each screened eligible patient. This randomization number correlates the patient's eCRF and the assignment of treatment group.

If a patient does not receive study drug according to the assigned treatment group, the reason must be clearly documented in the eCRF. The patient may still participate in the study and continue to receive the same study drug, and all data will be collected for this patient and subsequent follow-up will be performed according to the study schedule.

The first dose of study drug (Part 1-C1D1) should be administered within 3 days of the date of randomization.

In Part 2 of the study, all patients will receive open-label treatment with ABSK021.

5.7 Blinding and Unblinding

5.7.1 Blinding

Part 1 will be a randomized, placebo-controlled, double-blind study, where treatment assignment will remain unknown to the patients, Investigators, study site personnel, safety laboratory personnel, central imaging readers and reviewers, and the sponsor. The appearance of ABSK021 and placebo capsules will be identical.

5.7.2 Unblinding

5.7.2.1 Emergency Unblinding

In case of emergency where, in the opinion of the Investigator, immediate unblinding of treatment is necessary in order to evaluate further course of action, the Investigator should access the IWRS to initiate patient unblinding. Whenever possible, the Investigator should communicate emergency unblinding with the sponsor as early as possible. Under the premise of the patient's safety, the unblinding should be limited to the minimum number of personnel.

The Investigator should enter in the IWRS system:

- Confirm to continue with unblinding
- Patient ID

The IWRS will provide:

- Patient's randomized treatment group
- IWRS transaction confirmation

The Investigator may also contact the sponsor's medical monitor for information related to ABSK021 adverse effects in making the decision to unblind. It is important to note that, once unblinded, a patient cannot receive further study treatment and must discontinue from the study.

The Investigator should promptly document and report to the Sponsor any unblinding for emergency reasons (e.g., accidental unblinding, unblinding due to SAE, etc.).

In the event of an emergency unblinding, the date and reason for unblinding must be fully documented in the source document and eCRF. The Investigator should make every effort to ensure that study site personnel do not mention patient treatment group assignment to sponsor staff or relevant personnel involved in the conduct of the study.

5.7.2.2 End of Part 1 Unblinding

After completing the assessments of Part 1, patients who meet eligibility criteria and are willing to continue in the open-label study (Part 2) may receive open-label ABSK021. After all patients complete Part 1 and reach the primary efficacy analysis time point, unblinding (for the sponsor and contract research organizations only) and analysis will be performed after data cleaning and database lock.

5.8 End of Study and Treatment Discontinuation

The study consists of Part 1, Part 2 and Part 3. In Part 1, all patients who have completed 24 weeks of dosing and week 25 follow-up, and meet eligibility criteria will be eligible to enter Part 2 (for patients who have not completed dosing and follow-up due to imaging disease progression, please refer to 4.3.1). In Part 2, all patients who complete 24 weeks of dosing and week 25 follow-up will be eligible to enter Part 3 to continue longer treatment and safety follow-up. A patient may be discontinued from treatment if the Investigator assesses that the patient cannot benefit from continued treatment.

Part 3 is an extension treatment phase, and all patients will continue to receive open-label ABSK021 once daily until any of the following events occurs: disease progression, experiencing unacceptable toxicity, withdrawal of informed consent form, commercialization of the study drug for the treatment of TGCT approved by the local regulatory authorities, decision by the sponsor to terminate the study, or until 2 years after the last patient enters Part 3, whichever occurs first.

The study will end when all subjects have completed the study (including completion of all treatments and all visits required by the protocol) or have early withdrawn from the study, or the Sponsor decides to terminate the study, whichever occurs first.

5.9 Concomitant therapy

5.9.1 Permitted Medications

In general, in addition to prohibited medications and treatments specified in the protocol, the Investigator may provide supportive care for disease-related symptoms as clinically indicated, and care should be performed according to the site standard of care procedures. Patients may also receive medication for symptom relief (e.g., antidiarrheals, antiemetics, etc.).

5.9.2 Medications to be Avoided or Taken with Caution

The following medications should be avoided or taken with caution during the course of the study:

- Due to the high protein binding of ABSK021, close monitoring is required if warfarin is required.
- Low molecular weight heparin should be used under monitoring.
- For the use of H2-receptor antagonists, such as ranitidine, famotidine, or cimetidine, ABSK021 should be administered 2 hours before or 10-12 hours after H2-receptor antagonist administration.
- Gastric antacids such as aluminum hydroxide/magnesium hydroxide/dimethylsilicone oil or calcium carbonate should be avoided whenever possible but, if necessary, these medications should be administered 2 hours before or after ABSK021 administration.
- CYP2C9 and CYP2C19 substrates should be used with caution during treatment with ABSK021 (reference: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>).

5.9.3 Prohibited Medications and Substances

The following medications are prohibited during the course of the study:

- Strong inhibitors or inducers of cytochrome CYP3A4 are prohibited from 14 days prior to the initial dose of ABSK021 until the end of treatment with ABSK021 (reference: <https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers>).

- Proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole, or dexlansoprazole, are prohibited from 7 days prior to the initial dose of ABSK021 until the end of treatment with ABSK021.
- Antitumor therapies other than ABSK021 (including traditional Chinese medicine preparations).
- Study drugs other than ABSK021 or any kind of investigational therapy.
- Patients are prohibited from heavy alcohol consumption (more than 2 standard alcohol consumption per day, equivalent to alcohol consumption of more than 20 grams per day or more than 140 grams per week) since at least 7 days prior to the first dose of ABSK021 throughout the study treatment period.
- Cannabis drugs (e.g., medical marijuana), whether used as medication or for other purposes, are prohibited.

6 Study Procedures

6.1 Study Schedule

The specific study procedures are presented in [Table 1](#), [Table 2](#), [Table 3](#) and [Table 4](#) describes the PK sample collection time points. The following subsections detail the study procedures such as efficacy, safety, PK assessments, in this study.

The Investigator may request additional safety or efficacy assessments to determine the relationship between the onset or duration of a clinical event and the study drug.

6.2 Randomization

In Part 1 of the study, patients will be randomized in a 2:1 ratio to ABSK021 group or matching placebo group. Randomization will be stratified by China sites and non-China sites. Please refer to [5.6](#) for randomization.

6.3 Efficacy Evaluation

Efficacy evaluations in Part 1 will be performed according to the schedule shown in [Table 1](#), and efficacy evaluations in Part 2 will be performed according to the schedule shown in [Table 2](#). In Part 3, MRI examinations will be performed as shown in [Table 3](#). Once every 3 months in the first 6 months, and then once every 6 months until the end of the study. The MRI examination results will be assessed by the Investigator and BIRC (optional) separately. Additional measurements may be performed at the discretion of the Investigator based on the actual situation.

6.3.1 Tumor Response Evaluation (Part 1)

All MRI examination results will be evaluated by BIRC and Investigators according to

RECIST v1.1, respectively. In addition, all MRI examination results will be evaluated by BIRC based on TVS for tumor response. For patients who have disease progression (including radiographic disease progression or clinical progression) as assessed by the Investigator, the radiographic disease progression will be confirmed by BIRC. The specific reading procedures will be specified in the BIRC charter.

6.3.1.1 Response per RECIST v1.1 criteria

All MRI scans will be assessed according to RECIST v1.1 by BIRC and Investigator, respectively. Patient eligibility will be determined by the Investigator based on baseline MRI findings, and all subsequent MRI findings in Part 1 will be assessed separately by the Investigator and BIRC in a manner blinded to treatment assignment. Since Part 1 is a randomized controlled study, patients who achieve complete response (CR) or partial response (PR) per RECIST v1.1 do not need to be confirmed. A patient who has a tumor assessment of PR at Week 13 and subsequently has neither sufficient shrinkage to achieve CR nor sufficient increase to achieve PD (i.e., non-CR/non-PD/non-NE) at Week 25 will be considered as PR in efficacy endpoint evaluation. The evaluation details are shown in [Table 6](#) below.

Table 6 Definition of Efficacy Responses in TGCT Patients (Part 1)

Response at Week 13	Response at Week 25	Tumor response
CR or PR	CR	Response (CR)
CR or PR	PD	Non-response (PD)
PR	Non-CR/Non-PD/Non-NE	Response (PR)
SD	CR or PR	Response (CR or PR)
SD	SD	Non-response (SD)
SD	PD	Non-response (PD)
CR, PR, SD or NE	NE	Non-response (NE)
PD	Any	Non-response (PD)
NE	CR or PR	Response (CR or PR)
NE	SD or PD	Non-response (SD or PD)

CR = complete response; NE = Not evaluable (including MRI scan is not done); PD = progressive disease; PR = partial response; SD = stable disease

All MRI scans assessed by BIRC will be read in a blinded manner according to the procedures outlined in a separate BIRC charter.

6.3.1.2 Response per TVS criteria

MRI findings will also be assessed by BIRC in a blinded manner based on tumor volume score (TVS), a novel evaluation system specifically developed for TGCT. TVS is a semi-quantitative MRI scoring system that describes tumor mass and is an extension of the 4-point synovitis scale of the well-established and widely used multifeatured score RAMRIS, originally developed for rheumatoid arthritis, and WOMBS, originally developed for osteoarthritis. The extended scale, the TVS, will be based on 10% increments of the estimated volume of the maximally distended synovial cavity or tendon sheath involved. Thus, a tumor that is equal in volume to that of a maximally distended synovial cavity or tendon sheath will be scored 10, whereas a tumor that is 70% of that volume will be scored 7, a tumor that is twice the volume of the maximally distended synovial cavity or tendon sheath will be scored 20, and so on. A score of “0” means no evidence of tumor. Individual patient outcomes by TVS will be classified according to the following criteria inspired by RECIST v1.1:

- Complete response: Lesion completely gone.
- Partial response: $\geq 50\%$ decrease in volume score relative to baseline.
- Progressive disease: $\geq 30\%$ increase in volume relative to lowest score during the study whether at baseline or some other visit.
- Stable disease: Tumor volume decrease does not meet the above criteria for PR or volume increase does not meet the above criteria for PD.
- NE: TVS not evaluable due to inadequate imaging or imaging missing.

TVS-based tumor response assessments are similar to RECIST v1.1 and will be assessed according to Table 6. All MRI scans will be read in a blinded manner according to the procedures outlined in a separate BIRC charter.

6.3.2 Tumor Response Evaluation (Part 2)

In Part 2, all MRI scans will be assessed according to RECIST v1.1 by BIRC and Investigator, respectively. In addition, all MRI scans will be assessed by BIRC for tumor response per TVS.

Readings of MRI scans will be performed during or after the patient completes the study. For patients with Investigator-assessed disease progression (including radiographic disease progression or clinical progression), radiographic disease progression will be confirmed by BIRC.

Specific reading procedures will be specified in the BIRC Charter.

6.3.3 Tumor Response Evaluation (Part 3)

In Part 3, MRI examinations will be performed once every 3 months for the first 6 months, and once every 6 months thereafter until the end of the study. All MRI examination results will be

evaluated by the Investigators according to RECIST v1.1. In addition, all MRI examination results will be evaluated by BIRC according to RECIST v1.1 and TVS as needed (optional).

Readings of MRI scans will be performed during or after the patient completes the study. For patients who are assessed to have disease progression by the Investigator (including radiographic disease progression or clinical progression), the patient's radiographic disease progression can be confirmed by BIRC as needed (optional). Specific procedures will be stipulated in the BIRC Charter.

6.3.4 Range of motion (ROM) assessment

For patients in Part 1, the range of motion of the affected joint or tumor site will be assessed using a goniometer under blinded conditions. Measurements will be recorded in degrees. The assessments will be performed at time points specified in [Table 1](#).

For patients in Part 2, the mobility of the same affected joint will continue to be assessed in the same manner as Part 1 under open-label conditions. Measurements will still be recorded in degrees. The assessments will be performed at time points specified in [Table 2](#).

For patients in Part 3, the mobility of the same affected joint will continue to be assessed in the same manner as Part 1 and Part 2 under open-label conditions. Measurements will still be recorded in degrees. The assessments will be performed at time points specified in [Table 3](#).

Measurements of ROM will be standardized by a ROM standard reference value to obtain relative ROM values. Relative ROM value = $100 \times (\text{absolute ROM value}) / (\text{ROM standard reference value})$ ²⁶.

6.3.5 Patient-Reported Outcome (PRO) Assessment

6.3.5.1 Worst Stiffness Numeric Rating Scale (Worst-Stiffness-NRS)

Stiffness will be assessed using the Worst-Stiffness-NRS. Patients will be asked to recall the degree of stiffness at the tumor site over the past 24 hours. On all study visit days requiring a Numerical Rating Scale, including the screening, the patients are recommended to complete the evaluation of the Numerical Rating Scale prior to any invasive clinical procedure. Please refer to [Table 1](#), [Table 2](#) and [Table 3](#) for specific assessment time points, and [Appendix 12.5](#) for a sample instrument.

The mean score of evaluations completed prior randomization (at least 4 of 7 consecutive days during the 2 weeks prior to randomization) and on C1D1 will be used as baseline. If there are multiple consecutive 7-day assessments, baseline will be calculated from the most recent 7-day assessments as well as C1D1. In addition, mean score (at least 4 of 7 consecutive days) of Worst-Pain-NRS ≥ 4 or mean score (at least 4 of 7 consecutive days) of Worst-Stiffness-NRS ≥ 4 within 2 weeks prior to randomization (not include C1D1) is required for eligibility confirmation.

6.3.5.2 Worst Pain Numeric Rating Scale (BPI-Worst-Pain-NRS)

For the BPI-Worst-Pain-NRS assessment, patients will be asked to recall their worst pain at the tumor site over the past 24 hours. On all study visit days requiring a Numerical Rating Scale, including the screening, the patients are recommended to complete the evaluation of the Numerical Rating Scale prior to any invasive clinical procedure. Please refer to [Table 1](#), [Table 2](#) and [Table 3](#) for specific assessment time points, and Appendix 12.4 for a sample instrument.

The mean score of evaluations completed prior randomization (at least 4 of 7 consecutive days during the 2 weeks prior to randomization) and on C1D1 will be used as baseline. If there are multiple consecutive 7-day assessments, baseline will be calculated from the most recent 7-day assessments as well as C1D1. In addition, mean score (at least 4 of 7 consecutive days) of Worst-Pain-NRS ≥ 4 or mean score (at least 4 of 7 consecutive days) of Worst-Stiffness-NRS ≥ 4 within 2 weeks prior to randomization (not include C1D1) is required for eligibility confirmation.

6.3.5.3 PROMIS Physical Functioning Scale score

The PROMIS Physical Functioning Scale includes two different sets of topics for the upper (see Appendix 12.6 for example) and lower extremities (see Appendix 12.6 for example). Items assessing lower extremity function will be used for patients with lower extremity tumors, and the items for assessing upper extremity function will be used for patients with upper extremity tumors. The mean score of evaluations during the screening period (within 14 days prior to randomization) and on C1D1 will be used as baseline. On all study visit days requiring an evaluation scale, including the screening, the patients are recommended to complete the evaluation of the evaluation scale prior to any invasive clinical procedure(s). Please refer to [Table 1](#), [Table 2](#) and [Table 3](#) for specific assessment time points.

6.3.5.4 EQ-5D-5L Health Scale Score

The EQ-5D-5L (EuroQol Working Group, www.euroqol.org) is a preference-based general health status or health-related quality of life instrument consisting of two parts. The first part comprises five domains (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which can have five levels ranging from no problems through profound difficulties. The second part of the EQ-5D-5L is a Visual Analogue Scale on which the patient rates their current health, with 0 representing the “worst health you can imagine” and 100 representing the “best health you can imagine.”

The EQ-5D-5L health scale will be performed at the time points indicated in [Table 1](#), [Table 2](#) and [Table 3](#). The mean score of evaluations during the screening period (within 14 days prior to randomization) and on C1D1 will be used as baseline. On all study visit days requiring an evaluation scale, including the screening, the patients are recommended to complete the evaluation scale prior to any invasive clinical procedure(s).

6.3.6 Progressive Disease Follow-up

Patients who discontinue treatment prematurely for reasons other than disease progression will be followed for disease progression until disease progression, death, loss to follow-up, or the patient receives alternative anti-tumor therapy (including surgery), whichever occurs first. Disease progression follow-up will be conducted every 12 weeks (± 7 days). In principle, the maximum follow-up time will not exceed 12 months.

For patients who withdraw from the study after prematurely treatment discontinuation and plan to undergo surgery, it is recommended to perform the surgery at least 3 weeks after the last dose (for patients in Part 1, the Investigator and the sponsor will jointly decide whether emergency unblinding is needed). Details of the surgery will be collected, including but not limited to, the reason for surgery, date, surgery name, copies of the surgical report and pathological reports (if any), ROM and PRO assessments (if any). Surgically resected tumor samples will be collected to assess the effect of this study drug on tumor cells, and disease recurrence will also be followed up by telephone (every 3 months) for a maximum follow-up period up to 12 months after the surgery (not applicable for placebo-treated patients).

6.4 Safety assessment

Safety assessments will include demographic information and disease history, physical examination, ECOG score, vital signs, 12-lead ECG and echocardiography/MUGA, laboratory safety assessments, pregnancy tests, concomitant medications and therapies, adverse events (AEs) and related items in NCI-PRO-CTCAE. Safety assessments will be performed according to the time points indicated in Table 1, [Table 2](#) and Table 3. Any persistent abnormalities with clinical significance at the end of treatment will be followed up by the Investigator until the abnormality relieves, stabilizes, or has a clear outcome based on clinical judgment or the end of the study.

6.4.1 Demographic Information and Disease History

Demographic information includes the patient's sex, year of birth, age, ethnicity, and race (as permitted by the local laws and regulations).

Demographic information, prior and current medical history as well as detailed tumor history, including prior anti-tumor therapy, will be collected at screening.

6.4.2 Physical examination

Physical examination may be performed by a qualified physician, physician assistant, or registered nurse. The examination includes general condition, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, blood vessels, and nervous system. Additional rectal, external genital, breast, and pelvic examinations are required if indicated by medical history or clinical symptoms. Physical examination is recommended to

focus on primary tumor sites, areas of known abnormalities, or informed by clinical findings and/or patients.

Weight information will be collected at each physical examination and height will only be collected at screening. A general physical examination will be performed at subsequent visits. Investigators may perform more frequent examinations if clinically indicated.

6.4.3 ECOG score

ECOG score (Appendix 12.1) will be performed concurrently with the physical examination.

6.4.4 Vital signs

Vital signs include sitting blood pressure, pulse, respiratory rate, and pre-dose body temperature. When PK sampling is performed, vital signs are recommended to be measured after ECG and before PK sampling.

6.4.5 12-Lead Electrocardiogram (ECG)

The 12-lead ECG will be performed at screening, all on-study visits, and at the EOT visit. ECGs will be performed pre-dose (within 1-hour pre-dose) and post-dose (3 ± 0.5 hours post -dose) on Cycle 1 Day 1 (C1D1) and Cycle 1 Day 15 (C1D15) in Part 1, and ECGs at the remaining time points will be performed at any time on the day of the visit. Additional ECG tests may be performed as clinically indicated. Blood draws for vital signs, PK, and safety are recommended to be performed after the ECG, if applicable. Patients are advised to remain supine or semi-recumbent for at least 5 minutes prior to ECG testing. ECG results will include heart rate (HR), RR interval, PR interval, QRS interval, QT interval, and QTcF interval.

6.4.6 Echocardiography (or MUGA)

In Part 1, echocardiography or MUGA will be performed at screening, C4D1 (± 7 days), and C7D1 (± 7 days). In Part 2, echocardiography or MUGA will be performed on C1D1 ($- 2$ days), C4D1 (± 7 days) and C7D1 (± 7 days). In Part 3, echocardiography or MUGA will be performed on C4D1 (± 7 days), C7D1 (± 7 days) and subsequent visits. Results will include clinically important findings and left ventricular ejection fraction (LVEF). The same examination (echocardiography or MUGA) should be used throughout the study. If the time interval between the current examination and the previous examination does not exceed 7 days, repeated examination is not needed.

6.4.7 Laboratory Safety Assessments

Clinical laboratory tests include pregnancy test (6.4.8), hematology, blood chemistry, myocardial enzymes, coagulation, urinalysis, thyroid function test, and virology. Specific evaluation requirements are as follows:

- Hematology includes red blood cell count, hemoglobin concentration, hematocrit, white blood cell count, differential and absolute value of white blood cells (including neutrophils count, lymphocytes count, monocytes count, eosinophils count, and basophils count), and platelet count.
- Blood chemistry includes sodium, potassium, chloride, bicarbonate/ $\text{CO}_2/\text{CO}_2\text{CP}$, BUN/Urea, glucose, creatinine, AST, ALT, LDH, gamma-glutamyl transferase, alkaline phosphatase, total and direct bilirubin, total protein, albumin, calcium, magnesium, phosphorus, cholesterol, triglycerides, lipase, and amylase (if lipase and amylase cannot be tested simultaneously, one of which can be selected according to local site conditions). In the event of \geq Grade 2 transaminase elevations, more frequent liver function tests (e.g., twice weekly transaminase tests, etc.) are recommended until recovery.
- Myocardial Enzyme tests include creatine kinase (CK) and creatine kinase isoenzyme (CK-MB). Cardiac troponin-T or cardiac troponin-I will be measured at baseline and further evaluation is recommended during the study if ECG morphology shows the possibility of myocardial ischemia or infarction, or if CK increases \geq Grade 3.
- Coagulation will be performed according to time points specified in [Table 1](#), [Table 2](#) and [Table 3](#). Tests included prothrombin time (PT), international normalized ratio (INR), activated partial thromboplastin time (APTT), fibrinogen (Fbg), and thrombin time (TT).
- Urinalysis includes specific gravity, glucose, total protein, ketones, and red blood cells. If urine protein is $\geq 2+$ at any visit time point, further evaluation is recommended, such as 24-hour urine protein quantification, at the Investigator's discretion.
- Thyroid function tests include TSH, FT3, and FT4. This will be performed according to time points specified in [Table 1](#), [Table 2](#) and [Table 3](#).
- Virological testing includes testing for HIV, HBV, and HCV infection. HIV infection will be tested by HIV-Ab. HBV infection will be tested by the hepatitis B virus surface antigen (HBsAg). If the test result of hepatitis B expressed antigen is positive, HBV-DNA test is required. HCV infection will be detected by hepatitis C virus antibody (confirmed by Western Blot or ELISA). If the test result is positive, hepatitis C RNA testing should be supplemented. Virological testing will be performed at screening.

6.4.8 Pregnancy test

For women of childbearing potential, a pregnancy test will be performed at the times indicated in [Table 1](#), [Table 2](#) and [Table 3](#) and will also be performed at the end of treatment. Of these, pregnancy tests at screening should be completed within 7 days prior to randomization. Refer to [8.2.2](#) for pregnancy reporting during the study.

Female patients of non-childbearing potential must meet either of the following and can be exempt from pregnancy testing:

- Postmenopausal women: spontaneous menopause for at least 12 consecutive months with serum FSH levels ≥ 40 mIU/mL.
- Hysterectomy or bilateral oophorectomy/salpingo-oophorectomy performed.
- Bilateral tubal ligation for at least 6 months.

All other female patients, including those with bilateral tubal ligation within 6 months and without hysterectomy, will be considered of childbearing potential.

6.4.9 Contraception

Patients participating in this study need to agree to use effective methods of contraception from at least 14 days prior to randomization until 6 months after the last dose of ABSK021. According to the requirement of the European authorities, patients from Europe need to agree to use of a highly effective contraceptive measure from at least 14 days prior to randomization until 6 months after the last dose of ABSK021. Methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods.

Contraception methods can be exempt in following situations:

- If the patient has become accustomed to daily absolute abstinence lifestyle. Periodic abstinence (abstinence adjusted according to ovulation period) and extracorporeal ejaculation are not exempt from contraceptive measures.
- If a male patient has undergone bilateral orchiectomy or if the patient has no vas deferens confirmed by semen examination or ultrasound, which means the patient is not of childbearing potential prior to the first dose of study drug.
- Female patients of non-childbearing potential who meet either of the following conditions:
 - Postmenopausal women: spontaneous menopause for at least 12 consecutive months with serum FSH levels ≥ 40 mIU/mL.
 - Hysterectomy or bilateral oophorectomy/salpingo-oophorectomy has been performed.
 - Bilateral tubal ligation for at least 6 months.

Note: all other female patients, including those with bilateral tubal ligation within 6 months and without hysterectomy, will be considered of childbearing potential.

Acceptable highly effective contraception methods ²⁷:

- Hormonal contraception that inhibits ovulation, combined use of estrogen and progesterone^{*}:
 - Oral
 - Intravaginal
 - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation^{*}:
 - Oral
 - Injection
 - Implantation
- Continuous use of an intrauterine device (non-hormonal) or an intrauterine hormone-releasing system (IUS) for at least 6 months^{*}.
- Bilateral tubal ligation for at least 6 months.
- Vasectomised partner^{**}.
- Sexual abstinence^{***}.
- Vasectomy for 6 months or more, with negative postoperative semen analysis.

^{*}: Hormonal contraceptives can be used as highly effective methods of birth control unless they are already prohibited in Section 5.9.3, as the efficacy of hormonal contraceptives may be affected by potential drug-drug interactions with ABSK021. Intrauterine devices and intrauterine hormone releasing systems are acceptable methods of contraception in the absence of definitive drug interaction studies when hormone exposures from intrauterine devices do not alter contraception effectiveness.

^{**}: Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success. If not, an additional highly effective method of contraception should be used.

^{***}: Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Acceptable contraception methods:

- Male/female condoms with or without spermicide ingredients.
- Barrier contraception (e.g., diaphragm, cervix cap, or contraceptive sponge) and spermicide.

- Barrier contraception without spermicide is acceptable in participating countries that do not use spermicides.

Other precautions:

- The above acceptable methods of contraception are only provided as examples. Some of these measures may be prohibited in accordance with local requirements. If there are any questions, the sponsor may be contacted.
- Female condoms should not be used with male condoms (as a dual contraceptive method), due to risk of condom(s) tearing.
- Patients who are not sexually active at screening should agree to comply with the contraceptive requirements of this study when having sex with the opposite sex.
- Other contraceptive requirements are required in accordance with local regulations and/or requirements, as applicable.
- Male patients should not donate sperm from the start of the first dose of study drug through the entire study and for 6 months after the last dose of study drug.
- Female patients and female partners of male patients must not plan to become pregnant within 6 months after the last dose of study drug.
- Contraceptive requirements must be met if the female partner of a male patient becomes pregnant through documented in vitro fertilization (sperm donation) or cryopreserved sperm (collected prior to receiving study drug). In this case, male patients must use an acceptable method of birth control (to ensure that the fetus does not come into contact with the study drug) during the study until 6 months after receiving the last dose of study drug.

Special circumstances that do not meet the above description need to be discussed with the sponsor.

A female or male patient of childbearing potential cannot be included in the study if there is doubt about strict compliance with contraceptive requirements.

6.4.10 Prior and Concomitant Medications and Therapies

In Part 1, all concomitant medications and therapies should be collected from randomization until 30 days after the last dose of study drug (or before the start of Part 2). Medications and therapies taken within 28 days prior to the randomization are considered prior medication and therapies, and will also be collected.

In Part 2, all concomitant medications and therapies should be collected from the first dose of study drug up to 30 days after the last dose of study drug (or before Part 3). Medications and therapies prior to the first dose of study drug in Part 2 should have been collected in Part 1.

In Part 3, all concomitant medications and therapies should be collected from the first dose of study drug up to 30 days after the last dose of study drug. Medications and therapies prior to the first dose of study drug in Part 3 should have been collected in Part 2.

In addition, analgesic use will be collected (including but not limited to name and dosage of analgesics) for assessment of patient pain relief.

6.4.11 Adverse Events (AEs)

Adverse events (AEs) will be collected from the time the patient signs the informed consent form until 30 days (including Day 30) after the last dose of study drug. Please refer to Section 8 for the definition and reporting of adverse events.

6.4.12 NCI-PRO-CTCAE Items

NCI-PRO-CTCAE is a patient-reported outcome (PRO) measurement system developed to evaluate symptomatic toxicity in patients ²⁸. Ten relevant NCI-PRO-CTCAE items which representing 6 symptomatic toxicities drawn from the CTCAE were included in this study based on the frequency of symptomatic AEs observed in early clinical data. Each AE includes up to 3 discrete questions, separately representing the frequency, severity, and/or interference with daily activities of the event. In addition, a free-text question is added as the last question to mitigate concerns for missing important symptom items. It will be assessed during the screening period (within 14 days prior to randomization), on C1D1 (-1 day), C1D8(±1 days), C1D15 (±1 days), C1D22 (±1 days), C2D1 (±2 days), C2D8(±2 days), C2D15 (±2 days), and C2D22 (±2 days), C3D1 (±7 days), C4D1 (±7 days), C5D1 (±7 days), C6D1 (±7 days), C7D1 (±7 days), and EOT visit respectively. Please refer to Table 1 for specific assessment time points, and Appendix 12.8 for a sample instrument.

6.5 Pharmacokinetic (PK) assessment

6.5.1 PK blood sampling

PK samples will be collected according to the time points in Table 4.

In addition to the predefined samples, one or more unscheduled PK samples (up to 4 samples per cycle) may be collected to investigate the relationship between ABSK021 and suspected toxicities if agreed by both the Investigator and the sponsor. In addition to suspected toxicities, unscheduled PK samples may be collected due to disease progression, unscheduled tumor assessments, and dose interruption due to planned medical procedures or toxicity. For PK sampling after a dose modification, the PK sample is recommended to be collected at 3 hours post-dose in the most recent visit following the modification.

The PK sample collection time, corresponding dosing time, and the time of morning food intake on the PK collection days will be recorded in the CRF.

6.5.2 Sample analysis

An amount of 2 ml whole blood will be drawn at each sampling point. Plasma samples will be used to test ABSK021 concentrations and identify metabolites, if applicable.

6.5.3 Sample Handling, Storage and Shipment

PK plasma samples will be analyzed using validated, specific, and sensitive methods designated by the sponsor. Further information on PK plasma sample collection, processing, labeling, and shipment will be included in the laboratory manual.

7 Statistical Methods

7.1 Sample Size Determination

The sample size of this study is calculated based on the primary objective of the study, which is to compare the objective response rate within 25 weeks after treatment with ABSK021 or placebo in TGCT patients.

The target ORR of 40% for ABSK021-301 was anticipated from this study (i.e., 85% of the lower limit of 95% CI for interim ORR in ABSK021-101) based on the following considerations: a) Limited sample size in ABSK021-101 interim analysis; b) The inclusion of TGCT patients in the Phase 3 study will be more stringent than ABSK021-101 study which could lead to the enrolment of patients with a more severe condition. This may have a detrimental influence on treatment effectiveness; c) A single region preliminary ORR results from ABSK021-101 may not completely reflect the true response from the multi-region trial in a placebo control study.

Patients will be randomized in a 2:1 ratio to ABSK021 treatment group or placebo group. Assuming a 25-week ORR of 6% (P_0) (the upper 95% CI of the placebo group in the ENLIVEN study²³) in the placebo group and 40% (P_1) for ABSK021, by using Fisher's exact test with a two-sided significance level α of 0.05, a sample size of 75 evaluable patients provides a 90% power to detect the difference in the ORR between the two groups ($H_0: P_1 = P_0$ vs. $H_a: P_1 \neq P_0$). The power is calculated using the binomial distribution enumeration method (PASS 2021, v21.0.3). Considering a dropout rate of about 15%, approximately 90 TGCT patients need to be enrolled, including 60 patients in the ABSK021 treatment group and 30 patients in the placebo group.

7.2 Analysis sets

Intent-to-treat Analysis Set (ITT): ITT includes all randomized patients. The analyses for the ITT analysis set will be conducted according to the randomly assigned treatment regardless of whether the patient received study treatment or was compliant with the protocol. The ITT analysis set is the primary analysis set for the primary and key secondary efficacy analyses.

Per Protocol Set (PPS): the PPS is a subset of ITT and includes all patients who received at least one dose of study drug and had no major protocol deviations that may affect the efficacy assessment.

Safety Analysis Set (SST): includes all randomized patients who received at least 1 dose of study drug. Analyses using the SST will be conducted according to the actual treatment received. All safety analyses will be evaluated using the SST.

PK Analysis Set (PKS): includes all patients who received at least 1 dose of study drug and had at least one PK sample for PK Analysis.

7.3 Planned Analyses

No formal interim analysis is planned for this study. Data analyses will be performed according to the following analysis plan to support the study objectives.

7.3.1 First Planned Analysis

The first planned analysis is the primary analysis of this study, which will be performed after all randomized patients have either completed Part 1 of treatments for 24 weeks and a follow-up MRI scan at Week 25 visit or have withdrawn from informed consent or died. The effect of ABSK021 on ORR will be primarily evaluated in this analysis. All data up to the data cut-off date for the primary analysis (including all data from Part 1 and available data from Part 2) will be cleaned before treatment codes are unblinded for the analysis, but this unblinding will only apply to the sponsor and contract research organization (CRO).

7.3.2 Second Planned Analysis

The second planned analysis (i.e., the final analysis) will be performed after the completion of study Part 2 to supplement a long-term efficacy, safety, and tolerability profile. All data prior to the cut-off date will be cleaned and analyzed after database lock.

7.3.3 End of Study Analysis

End-of-study analysis will be performed after all patients complete the study or the study is terminated. All collected data will be cleaned before the database is locked. End-of-study analysis will be used for supplementary purposes to assess the long-term efficacy and safety of ABSK021.

7.4 Statistical Analysis Methods

7.4.1 General Considerations

The categorical variables will be summarized by counts and percentages, the continuous variables will be summarized by mean, standard deviation (SD), median, and minimum and maximum values by treatment group.

All available data will be included in the data listings. In general, missing data will not be imputed and only observed data will be analyzed, unless otherwise specified. Any patient excluded from the summary and/or statistical analyses will be documented in the clinical study report along with the reason for exclusion.

In general, the baseline for an efficacy variable is the last non-missing value prior to randomization. In addition, baseline values for PRO variables are the mean of non-missing values within 14 days prior to randomization and non-missing values prior to the first dose of C1D1. Unless otherwise specified, the baseline value for a safety variable will be the last non-missing value prior to the first dose of study treatment.

Patients will be randomized according to the stratification factor of China sites versus non-China sites. When appropriate, the stratification factor will be included in the statistical model for efficacy analyses with the strata information as entered in IWRS at the time of randomization. All statistical tests will be two-sided at the alpha of 0.05 level of significance.

Details of the analyses of all endpoints will be provided in the Statistical Analysis Plan (SAP).

7.4.2 Patient Disposition, Demographics, and Baseline Characteristics

Patient disposition will be descriptively summarized by treatment group and overall. The summary will include the number of all screened patients, and number and percentage of patients who were randomized, received study drug, discontinued from study drug and reasons, and discontinued from study and reasons.

Demographic and disease baseline characteristics will be descriptively summarized by treatment group and overall based on the ITT. The summary will include age, sex, ethnicity, race, disease diagnosis, and prior lines of treatment.

7.4.3 Drug Exposure

Based on the SST, descriptive summaries of the actual total dose, duration of drug exposure, and relative dose intensity will be provided by treatment group.

7.4.4 Efficacy Analysis

The ITT will be used as the primary analysis set for the primary and secondary efficacy analyses. The PPS will be used for the supportive analysis of the primary efficacy analysis.

7.4.4.1 Primary Estimand

7.4.4.1.1 Definition of Primary Estimand

- **Population:** Patients with TGCT who meet the eligibility criteria.
- **Treatment:** Randomized treatment (ABSK021 or placebo).
- **Variable:** Objective Response (OR) within 25 Weeks based on RECIST v1.1 as assessed by BIRC in Part 1. OR is defined as the patients achieving the best overall response of CR or PR.
- **Intercurrent Events and Management Strategies**

Table 7 Intercurrent Events and Management Strategies for Estimated Objectives

Intercurrent Events	Management Strategy	Comments
Dose modifications (including dose interruption and dose reduction) due to toxicity	Treatment policy strategy Continue to collect and use the data even if the patient experiences intercurrent events.	Reflects clinical practices.
Early discontinuation of treatment not due to PD	Treatment policy strategy Continue to collect and use the data even if the patient experiences intercurrent events.	Patients who discontinue treatment prematurely not due to PD in Part 1 will be encouraged to remain in the study and followed up as scheduled until complete study Part 1.
Receiving an alternative anti-tumor therapy (including surgery)	While on treatment strategy Data before the intercurrent event will be used.	Focus on treatment effects before the intercurrent event, outcomes after the intercurrent event are regarded as unrelated to the treatment.

- **Population-level summary:** Treatment difference (ABSK021 – Placebo) in 25-Week ORR by BIRC (RECIST v1.1)

7.4.4.1.2 Analysis of Primary Efficacy Endpoint

Analysis set

ITT Analysis Set.

Primary Statistical Analysis

The primary efficacy endpoint, 25-Week ORR by BIRC (RECIST v1.1), will be summarized by treatment group and its exact two-sided 95% CI will be calculated using the Clopper-Pearson method. The primary efficacy endpoint will be compared at a two-sided significance level of 0.05 using Fisher's exact test. The 95% CI in ORR difference (ABSK021 - placebo) will be calculated using the Wilson method.

If patients discontinue treatment before Week 24, the data collected after treatment discontinuation will be included in analyses according to the treatment policy strategy. For intercurrent events as "receiving an alternative anti-tumor therapy (including surgery)", data before the intercurrent event will be used according to the while on treatment strategy. Patients with missing MRI data at Week 25 will be considered as non-responders.

Sensitivity Analysis

In addition, considering the effect of stratification factors (China sites vs. non-China sites), the ORR difference will be tested using the Cochran-Mantel-Haenszel (CMH) method as a sensitivity analysis, in which the ORR difference between ABSK021 and placebo group will be calculated, with its two-sided 95% CI calculated using the CMH weighting method²⁹. Fisher's exact test will be considered more appropriate if the expected response event is less than 5 in any stratified group. The treatment effect on the BIRC-25-Week ORR will be evaluated using Fisher's exact test with applying mid p-value correction³⁰.

Subgroup Analysis

Subgroup analyses for the 25-Week ORR will also be performed in (including but not limited to) the following subgroups:

- Age (< 65 years vs. ≥ 65 years; < 40 years vs. ≥ 40 years);
- Sex (Female vs. Male);
- China sites vs. non-China sites;
- Lower extremity tumors vs. upper extremity tumors.

In each subgroup defined above, the same approach for the primary analysis of ORR as described above will be used. These analyses will be considered exploratory and will not involve multiplicity adjustment. If any subgroup contains an insufficient number of patients, the subgroups will be analyzed descriptively.

7.4.4.2 Key Secondary Efficacy Analysis

The following key secondary efficacy endpoints will be tested in the following order:

- 1) 25-week ORR by BIRC based on TVS (TVS-ORR);
- 2) Mean change from baseline in ROM (presented as relative to ROM, refer to [6.3.3](#)) of the affected joint at Week 25;
- 3) Mean change from baseline in Worst-Stiffness-NRS score at Week 25;
- 4) Mean change from baseline in the BPI Worst Pain Numeric Rating Scale (NRS) score at Week 25;
- 5) Mean change from baseline in PROMIS Physical Function scale score at Week 25.

A hierarchical gatekeeping testing procedure will be applied to test the treatment effect on these secondary endpoints. Therefore, the treatment effect on the second endpoint #1 can only be evaluated if the statistically significant treatment effect on the 25-Week ORR by BIRC has been established at the 2-sided significance level of 0.05 ($P < 0.05$); and the treatment effect on the second endpoint #2 will be evaluated only if the statistically significant treatment effect on the second endpoint #1 has been established at the 2-sided significance level of 0.05. Similarly, all remaining secondary endpoints can be sequentially tested at a two-sided significance level of 0.05 in the pre-specified order. A statistical test for any subsequent secondary endpoint (s) will not be performed if the treatment effect on any preceding secondary endpoint is not statistically significant. Categorical endpoint TVS-ORR will be analyzed using the same analysis method as the primary efficacy endpoint ORR; continuous endpoints, including change from baseline in relative ROM, Worst-Stiffness-NRS, BPI Worst-Pain-NRS and PROMIS, will be analyzed using mixed models for repeated measures (MMRM). For all of these continuous variables, the model will include change from baseline as the dependent variable, and treatment, baseline, visit, stratification-factor of China sites vs. non-China sites, and treatment-by-visit interaction, and the baseline-by-visit interaction as fixed effects. In addition, for the endpoint of relative ROM, additional fixed terms of joint type category will be added to the MMRM. An unstructured variance-covariance matrix will be used. Formal statistical comparisons between groups will be made at Week 25.

Intercurrent events and management strategies for key secondary endpoints are the same as the primary estimand. For intercurrent events of “Early discontinuation of treatment” or “Dose modification due to toxicity”, treatment policy strategy will be used with all observed data; for intercurrent event of “Receiving an alternative anti-tumor therapy (including surgery)”, while on treatment policy will be used, focusing on treatment effects and data collected before the intercurrent event.

The primary analysis of key secondary endpoints is under the treatment policy strategy. This primary analysis includes all data until the Week 25 visit or patients withdraw from the study regardless of if they discontinue from randomized treatment. For the tumor response key secondary endpoint, BIRC-25-Week ORR based on TVS, patients with missing MRI data at the Week 25 visit will be considered as non-responders. As for the continuous key secondary endpoints, the primary analysis of these endpoints includes all data captured during the study Part 1 up to the Week 25 visit regardless of if they discontinue from randomized treatment. The Mixed Model for Repeated Measures (MMRM) will be employed with the restricted maximum likelihood (REML) estimation and the unstructured covariance structure under the MCAR and MAR assumptions.

Sensitivity analyses will be performed to examine the robustness of the results obtained from the primary analysis of continuous key primary endpoints. These sensitivity analyses will take into account possible departures from the underlying assumptions, specifically under missing not at random (MNAR) scenarios. Control-based pattern mixture models (PMM) such as Jump to Reference (J2R), Copy Reference (CR), and the tipping point analysis will be used.

7.4.5 Other Secondary Efficacy Analyses

7.4.5.1 Tumor Response by Investigators

In addition to tumor responses by BIRC based on both RECIST v1.1 and TVS, the BOR and ORR based on RECIST v1.1 will be determined based on the investigator's assessments for 25 weeks (Part 1) and subsequent analyses beyond Week 25.

The Investigator-ORR based on RECIST v1.1 will be analyzed using the same method as the primary endpoint of BIRC-ORR based on the ITT analysis set.

To compare the discrepancy of response assessments, a summary of concordance between the BICRC and Investigator review of radiographic images will be provided.

7.4.5.2 Duration of Response (DOR)

The DOR for responders is defined as the time interval between the date of the first documentation of objective response (CR/PR) and the date of first documentation of radiographic disease progression, or death, whichever occurs earlier. Patients who have no record of disease progression or death at the time of data cutoff date for a planned analysis will be censored.

The following DORs will be derived for all patients with an objective response.

- DOR by BIRC based on RECIST v1.1
- DOR by BIRC based on TVS

- DOR by Investigator based on RECIST v1.1

Analysis of DOR will be conducted for patients with an objective response in the ITT analysis set. The 25th, median, 75th percentile of the time, and their associated 95% CIs (Brookmeyer and Crowley, 1982)³¹ will be estimated using Kaplan-Meier method adjusting for censoring. In addition, the probability of DOR at landmarks of month 3, 6, 9, 12 and 24, and their corresponding two-sided 95% CIs (Kalbfleisch, 1980)³² will be provided.

The analysis of DOR will be analyzed in the following 3 groups:

- 1) For patients randomized to the ABSK021 treatment group, include both Part 1 and Part 2 data.
- 2) For patients randomized to placebo group, include Part 1 data only.
- 3) For patients in the placebo group who further enter Part 2 and receive ABSK021, include Part 2 data only.

7.4.5.3 EQ-5D-5L

The EQ-5D-5L instrument will be analyzed according to the recommendations of the authors (www.euroqol.org). The change from baseline in EQ-VAS will be analyzed using similar MMRM models as for BPI. Missing data will not be imputed.

7.4.6 Correlation Analyses for Key Secondary Endpoints

To investigate the correlation between the treatment effect on tumor responses and improvements in key secondary clinical outcome assessments (COA), including change from baseline to Week 25 in relative ROM, Worst-Stiffness-NRS, Worst-Pain-NRS, and PROMIS-PF T-scores (named change below), the following descriptive summaries and subgroup analyses will be carried out at Week 25. For the tumor response assessment, BIRC evaluations based on the RECIST v1.1 criteria will be used unless specified otherwise.

- A scatter plot of percent change in tumor size vs. change in each COA.
- Spearman's rank-order correlation coefficients will be provided between the change in tumor size and the change for each COA.
- Descriptive responder summary of the change by potential thresholds of clinically meaningful within-patient change for each COA.

Responder subgroup analysis of the change by tumor responder status may be conducted. The evaluation will use a similar approach for the primary analysis of each endpoint, with the addition of two fixed factors (subgroup and subgroup-by-treatment) into the corresponding MMRM model.

7.4.7 Safety Analysis

Safety and tolerability will be assessed by adverse events, dose modifications, laboratory tests, vital signs, electrocardiograms, Echocardiography and related items in NCI-PRO-CTCAE. Data from both scheduled and unscheduled visits will be included in the safety analysis. All safety data will be summarized descriptively based on the Safety Analysis Set.

Safety summaries primarily include on-treatment measurements/events. The on-treatment measurements /events are defined as any measurements /events assessed between the date of the first study dose and 30 days after the last dosing date of the study drug. If the last dosing date is missing, the measurements/events that occur after the start of study drug administration will be considered as on-treatment measurements/events.

7.4.7.1 Treatment-emergent Adverse Events (TEAEs)

A treatment-emergent adverse event (TEAE) is defined as any adverse event that occurs or worsens after the initiation of treatment in this study until 30 days after the last dose of the study drug. Adverse event (AE) data will be coded to system organ class (SOC) and preferred term (PT) using the most recent version of MedDRA. The severity of AEs (toxicity grade 1-5) will be graded by the Investigator according to NCI-CTCAE version 5.0. Any treatment-emergent adverse events, study treatment-related adverse events, adverse events leading to discontinuation of study drug, adverse events leading to dose modification, serious adverse events, etc., will be summarized by SOC, PT, and CTCAE version 5.0 grade.

The summary of TEAEs will be performed for the following groups:

- 1) For patients who received ABSK021 in Part 1, include Part 1 data only.
- 2) For patients who received placebo in Part 1, include Part 1 data only.
- 3) For patients who received ABSK021 in Part 1 and Part 2, include Part 1 and Part 2 data for these patients.
- 4) For patients who received placebo in Part 1 and treated with ABSK021 in Part 2, include Part 2 data only.
- 5) For all patients who received at least one dose of ABSK021 in Part 1 and/or Part 2, include the data on ABSK021 treatment in Part 1 and Part 2, and exclude the data on placebo treatment in Part 1.
- 6) For all patients who received at least one dose of ABSK021 in Part1, Part 2 and/or Part 3, include the data on ABSK021 treatment form Part 1 to Part 3, and exclude the data on placebo treatment in Part 1.

7.4.7.2 Analyses of Other Safety Endpoints

Observations and changes from baseline in vital signs and laboratory tests including hematology, blood chemistry, and liver function measures will be summarized by treatment group for each scheduled visit, the maximum and minimum post-treatment values and the values at the End of Treatment visit.

Blood chemistry and hematology laboratory tests will be graded according to CTCAE (toxicity grade 1 to 5) Version 5.0, if applicable. The number and percentage of patients within each CTCAE grade will be summarized by throughout the whole study and by scheduled visit. The worst grade will be reported if a patient has multiple laboratory assessments during the interval analyzed.

For vital signs and ECG, the proportion of patients with potentially clinically significant (PCS) findings will be summarized by treatment group. Vital signs and ECG findings of potentially clinical significance are defined by post-baseline assessments or whether changes from baseline meet prespecified thresholds. The criteria for PCS will be detailed in the SAP.

For NCI-PRO-CTCAE, scores for each attribute (frequency, severity and/or interference) will be presented descriptively.

7.4.8 PK analysis

PK data analysis will be based on PKS. Plasma concentrations at each time point will be summarized descriptively using the scheduled sampling time points. The impact of food condition on safety will be explored if data allowed.

If needed, population pharmacokinetic analysis and exposure-response analysis will be performed based on the pooled dataset with other clinical trial data. These analysis results will be presented in a separate report.

8 Adverse Event Reporting

8.1 Definition

8.1.1 Definition and Classification of Adverse Events

8.1.1.1 Adverse Events (AEs)

An adverse event is any untoward medical occurrence, regardless of causal relationship to the investigational drug, that occurs in a patient from the time of signing the informed consent form until 30 days (including Day 30) after the last dose of study drug. Adverse events include the following:

- 1) Worsening of the original (before entering the clinical trial) medical conditions/diseases

(including aggravation of symptoms, signs, laboratory abnormalities);

2) Any new adverse medical condition (including symptoms, signs, newly diagnosed diseases);

3) Abnormal laboratory test results (e.g. blood chemistry, urinalysis) or other safety assessments (e.g. radiological examination, ECG, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator. Not every abnormal laboratory test result qualifies as an adverse event. However, laboratory test result must be reported as an adverse event if it meets any of the following criteria:

- Is associated with accompanying symptoms.
- Requires clinical intervention, further investigation, or additional diagnostic testing.
- Leads to a change in study dosing or discontinuation from the study intervention.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as Adverse Event. If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event.

8.1.1.2 Serious Adverse Events (SAEs)

An SAE is any adverse event, regardless of causality, occurring at any dose that:

- Results in death (excluding death that occurred after the Day 30 follow-up visit after the last dose, or due to confirmed disease progression/health status, instead of the study drug).
- Is life-threatening. Life-threatening refers to an event in which the patient is at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires hospitalization or prolongation of existing hospitalization. A planned hospitalization and/or surgical procedure prior to the patient's entry into the study will not be considered an adverse event provided there is no unexpected worsening during the study (e.g., surgery performed earlier than scheduled). Social and/or convenience admission to a hospital without untoward medical occurrence will not be considered an adverse event.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is medically important. Medically important events are those that may not result in death or be life-threatening or require hospitalization, but may jeopardize the patient or may require intervention to prevent any of the outcomes listed in the definition of an SAE based on appropriate medical judgment and are also considered SAEs. Examples of such medical events include allergic bronchospasm requiring intensive

treatment in an emergency room or at home, blood cachexia or convulsions that do not require hospitalization, or development of drug dependence or drug abuse.

8.1.1.3 Suspected Unexpected Serious Adverse Reactions (SUSARs)

Suspected unexpected serious adverse reaction (SUSAR) refers to a suspected and unexpected serious adverse reaction in which the nature and severity of the clinical manifestation exceeds the available information such as the Investigator's Brochure of the investigational drug, the package insert of a marketed drug, or a summary of product characteristics.

8.1.2 Causality Definition

The investigator is obligated to assess the causality between study intervention and each AE/SAE.

The Investigator will determine the relationship to study drug administration according to the following criteria:

Related: there is a reasonable possibility of causal relationship between the study drug and the AE.

Unrelated: there is no reasonable possibility of causal relationship between the study drug and the AE.

“Reasonable possibility of causal relationship” means there are evidence to suggest a causal relationship.

The investigator will consider and investigate alternative causes, temporal association and use clinical judgment to determine the causal relationship.

The investigator should always make a causality assessment for every event before transmission of the SAE data to the sponsor, even if the investigator has minimal information to provide in the initial report.

The investigator may change causality opinion after follow-up information is received and send updated causality assessment in the SAE follow-up report.

8.1.3 Severity Criteria

The adverse events will be assessed for severity according to NCI CTCAE Version 5.0. For AEs not listed in CTCAE v5.0, assess the severity according to below criteria:

Grade	Clinical Description of Severity
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental Activities of Daily Living (ADL)*.

Grade	Clinical Description of Severity
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL **.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

**Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.*

***Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.*

8.1.4 Safety Reporting Period

The AE reporting period begins from the time that the patient provides signed informed consent, (i.e., prior to undergoing any study-related procedure/or receiving study drug), throughout the study and until 30 days (inclusive) after the last administration of study drug. Any serious adverse events that occur after the reporting period must also be reported immediately if a causal relationship with the study drug is suspected.

If a patient starts a new anti-tumor therapy, the safety report should end at the start of the new treatment.

8.2 Special Reporting Situations

8.2.1 AE and SAE Reporting Procedures

Each patient must be carefully monitored for any adverse events. This information should be obtained in the form of non-leading questions (e.g., "How do you feel?"), as well as from signs and symptoms detected during each examination, observations by researchers, and spontaneous reports from patients.

All adverse events (serious and non-serious) spontaneously reported by the patient must be recorded and/or identified by answering open-label questions raised by the study personnel, or by observation, physical examination, or other diagnostic procedures. Whenever possible, signs and symptoms with common pathological features should be considered a composite event. Concomitant signs or symptoms (e.g., abnormal laboratory values) should not be reported as additional adverse events. If the diagnosis is unknown, one or more symptoms may be reported as separate adverse events. If the subsequently reported symptom is confirmed, the reported symptom term must be modified to "attributed to" or "due to" the diagnosis.

For all SAEs occurring during the reporting period, whether initial or follow-up, regardless of causality, the Investigator must report the SAE to the sponsor or designated CRO within 24 hours of the knowledge of the SAE. SAEs must be followed until resolution, stable disease, or until the

Investigator decides that follow-up is not required. For study analysis, if the event has not resolved by the end of the study reporting period, it must be recorded as ongoing (recovering or not recovered). Follow-up information must be reported. A follow-up report should be sent as soon as more information becomes available.


Follow-up information will include sufficient details to allow for a complete medical assessment and independent determination of causality. Any relevant information, such as concomitant medications and illnesses, must be provided. For deaths, a summary of autopsy or other post-mortem findings, when available, must be submitted as soon as possible.

Events that are clearly consistent with the expected condition of disease progression should not be recorded as adverse events. These data can only be used as efficacy assessment data. In most cases, disease progression is based on RECIST v1.1. In rare cases, disease progression is determined by worsening symptoms. However, whenever possible, objective criteria should be used to document disease progression.

If it is uncertain whether the event is due to disease progression, it should be reported as an adverse event based on its diagnosis or symptoms rather than using the term "disease progression".

SAE initial and follow-up reports should be submitted via email (contact details below). CRO contact details may vary depending on vendor.

All SAEs must be reported, whether or not considered causally related to study drug. Follow-up information on SAEs may be requested by the sponsor or designated CRO.

Contact Information	
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In the event of a suspected unexpected serious adverse reaction (SUSAR), Abbisko or its authorized representative will follow the requirements of local regulatory authorities to ensure that the relevant regulatory authorities and all personnel involved in the study are notified as soon as possible. Ethics Committee (EC)/ Institution Review Board (IRB) will be notified of SUSARs or other required information in accordance with local regulations and institutional policies.

8.2.2 Exposure During Pregnancy

Patients are obligated to inform the Investigator of any pregnancy that occurs during study treatment and up to 6 months after the last dose of study drug. Pregnancy beyond 6 months after the last dose of study drug, or pregnancy due to sperm donation/sperm preservation prior to study drug exposure, are not required to be reported.

Any female patient becomes pregnant during the clinical study must promptly discontinue the study drug and be withdrawn from the study. If the female partner of a male patient becomes pregnant during the study, the patient must immediately notify the Investigator, the male patient

can continue the clinical study. Male patients must commit to use an acceptable method of contraception (to avoid or prevent fetal exposure to study drug) during the study and up to 6 months after the last dose of study drug. The Investigator must notify the sponsor, the CRO, or designated third party pharmacovigilance personnel within 1 working day of the knowledge of the pregnancy of the patient (or his partner).

If confirmed to be on active drug, the patient or partner must be followed until the end of the pregnancy and the infant must be followed 1 year after the birth, provided informed consent is obtained. A separate informed consent form (ICF) must be provided to explain these follow-up activities. Pregnancy itself does not constitute an AE. However, if there is any adverse pregnancy outcome, such as stillbirth, spontaneous abortion and fetal malformation, it is considered as SAE and needs to be reported in accordance with SAE reporting requirements. SAE report form and pregnancy report form are completed respectively, and the reporting time is the same as SAE report.

8.2.3 Death

All deaths occurring during the adverse event reporting period, whether related to study treatment or not, must be recorded on the Adverse Event eCRF and immediately reported to the sponsor as SAEs.

If the death occurs after the safety reporting period, but it is considered related to the study drug, serious adverse events (SAEs) should be reported.

9 Data Management and Electronic Systems

9.1 Data Management

9.1.1 Data Collection

An electronic data capture (EDC) system, or electronic case report form (eCRF), will be used for the collection of study data in this study. The sponsor or designee will test all aspects of the EDC system database, including system functions, data entry interface, raw datasets, and system edit checks. The EDC system database will only go live until it has been tested and approved by relevant personnel. When the EDC system database is available, the sponsor or designee will grant accounts to the Investigators and other project members as needed, and the sponsor or designee will maintain the central management of the accounts to ensure the security of study data. The EDC system will record all audit trails of any data entry and modification; the EDC system vendor will perform maintenance of the system and back up the database periodically during the study. The sponsor will provide CRF completion guidelines to Investigators.

9.1.2 Data Review and Query Management

Data management personnel will develop plans or processes for data verification, medical coding and SAE reconciliation, etc., in order to review the integrity, validity and accuracy of data entered by study personnel into the EDC system, and generate queries in the EDC system for all identified issues. The Investigators will review queries in the EDC system, respond to the identified questions, or make appropriate data modifications. Relevant personnel such as Data Management and Medical Monitors shall review the responses to queries or data modifications in the EDC system, and close the queries after confirming the problems are resolved; If the responses or modifications are identified with errors, are inadequate or inappropriate, follow up queries should be generated in the EDC system until all queries are resolved and closed.

9.1.3 Data Cleaning and Database Lock

The data manager will develop a database lock checklist according to the steps required in database cleaning; urge study personnel to complete the steps required by the database lock checklist before completion of the study or other phases requiring database lock; when the database lock has been approved by the applicable personnel, the database administrator be notified to lock the database.

9.2 Electronic system

Electronic systems will be used to process and/or collect data in this study, which may include the following:

- EDC System-Data Acquisition
- Statistical Analysis Software (SAS) — Statistical Analysis and Summary
- Pharmacovigilance and Clinical Safety Software System-Collection and Reporting of Safety Data
- Centralized Interactive Web Response System (IWRS System)

10 Administrative Requirements

10.1 Good Clinical Practice

This study will be conducted in strict compliance with Good Clinical Practice, ICH-GCP and local regulatory requirements. The Investigator needs to be fully familiar with the drug information and administration methods described in the protocol and the Investigator's Brochure. Essential documents will be retained to demonstrate the compliance of the study and the integrity of data. Essential documents of the study should be established at the beginning and be retained for the duration required by regulations.

10.2 Ethical considerations

The study will strictly follow the ethical principles of the Declaration of Helsinki. The IRB/IEC will review the study to safeguard the rights, safety and welfare of patients. This study will be conducted only at sites approved by the IRB/IEC. The protocol, Investigator's Brochure, informed consent form, advertisements (if applicable), written information given to patients (including diary cards), safety updates, progress reports, and other documents as well as the amendments of these documents will be submitted to the IRB/IEC for review.

10.3 Patient Information and Informed Consent Form

Patients should fully understand the contents of the study and sign the informed consent form before participating in the study. The method of obtaining and documenting informed consent and the materials will be in compliance with ICH-GCP and all applicable regulations. If new information that may impact patients' continuing participation in the trial becomes available during the course of the study, the patient will be informed of in a timely manner and such records will be maintained.

10.4 Patient Confidentiality Measures

To protect patient privacy, all CRFs, study drug records, study reports, and correspondence will use assigned patient numbers to identify patients. The investigator will grant the sponsor (e.g. monitor), the IEC/IRB, or its designee, and regulatory authorities (e.g., inspectors) access to the patient's original medical records to verify data collected in the CRFs and to review the data collection process. Patient privacy will be strictly protected from disclosure to the extent permitted by applicable laws and regulations.

10.5 Protocol compliance

The Investigator will conduct the study in compliance with the protocol provided by the sponsor, which is also approved by the IRB/IEC and appropriate regulatory authorities. The protocol may not be modified without the prior agreement of the sponsor and the Investigator. Protocol amendments need to be approved or agreed to by the IRB/IEC, unless there is an immediate threat to the safety, rights and interests of patients. The sponsor will submit necessary protocol amendments to regulatory authorities in accordance with laws and regulatory requirements and will not implement the amended protocol until there has been agreement or approval from the regulatory authorities and the IRB/IEC.

When a protocol deviation is necessary to immediately prevent direct hazard to the patient, the

Investigator should contact the sponsor to discuss the action plan when possible. All deviations from the protocol need to be fully documented.

10.6 Direct access to source data

The sponsor will conduct monitoring and reviews during the study to ensure that the study complies with GCP guidelines.

Monitoring activities will be conducted by monitors designated by the sponsor or third parties, including on-site review of the completeness and clarity of CRFs, cross-checking with source documents, and clarification of administrative matters, etc. Monitoring of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

The monitor will ensure that the Investigator complies with the protocol and its amendments, GCP and regulatory requirements through frequent correspondence (e.g., email, letter, telephone, fax).

Regulatory authorities, IRBs/IECs, and/or authorized representatives of the sponsor (or designated third parties) (e.g., monitors) will have direct access to all source documents, CRFs, and other study documents at the time of inspection, monitoring, or audit. The Investigator or institution will need to ensure direct access to these documents at any time to support these activities.

10.7 Case Report Form

An electronic data capture (EDC) system, the electronic case report form (eCRF), will be used for the collection of study data in this study. Upon completion of the study, the Investigator will retain a copy of the case report form.

10.8 Records and Documents Retention

The Investigator will retain all study records (including essential documents) as required by China GCP, ICH-GCP and applicable regulations. Study records will be retained for at least 2 years (5 years in China) after approval for marketing without unresolved questions, or 2 years after formal discontinuation of clinical development of the product (5 years in China), or in accordance with applicable regulatory requirements. Any study records are prohibited from being destroyed or discarded during record retention without the written agreement of the sponsor. If the Investigator no longer assumes responsibility for the retention of study records, the regulatory obligation needs to be transferred to other personnel willing to assume responsibility, i.e., a change in custody occurs and the sponsor needs to be notified in writing.

10.9 Liability and insurance

The sponsor has subscribed to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards.

10.10 Publication of Study Results and Use of Information

All ABSK021 product and study-related information provided to the Investigator by the sponsor are confidential. The Investigator may use this information to complete the study and may not use for any other purposes without the agreement of the sponsor. The Investigator is obligated to provide the sponsor with the complete data obtained from the study. Information obtained during the clinical study will be used for the development of ABSK021 and may be disclosed to regulatory authorities, other Investigators, business partners, and consultants as needed.

The results of this study are expected to be presented in scientific conferences and/or published in a peer reviewed scientific or medical journal. The Investigator and sponsor will form a publications committee as appropriate to oversee the publication of study results which will reflect the experience of all study sites. Subsequently, the individual Investigator may publish the study results in accordance with his/her agreement with the sponsor.

A prepublication manuscript is to be provided to the Sponsor at least 30 days prior to the submission of the manuscript to a publisher. Similarly, the sponsor will provide a company prepared manuscript to the Investigator for review at least 30 days prior to submission to a publisher.

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12 Appendix

12.1 ECOG PERFORMANCE STATUS (ECOG PS)

GRADE	ECOG PERFORMANCE STATUS
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 house work, 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

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655

12.2 RECIST v1.1

The text below was obtained from the following reference: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228-247.

DEFINITIONS

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (Version 1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term “evaluable” in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (when superficial).
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm 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.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal

masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

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

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, 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 locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. Target lesions should be

selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm 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 2 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 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm 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.

Non-target Lesions

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” (more details to follow). In addition, it is possible to record multiple non-target 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”).

GUIDELINES FOR EVALUATION OF MEASURABLE DISEASE

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.

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 examination.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm 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 examination and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the trial.

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.

Computed tomography, 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 5 mm 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).

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 subject 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 CA-125 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.

RESPONSE CRITERIA

Evaluation of Target Lesions

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

Partial Response (PR): At least a 30% decrease in the sum of 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.

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 10 mm 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 < 10 mm. Case report recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. 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., 2 mm). 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 them as being “too small to measure”. When this occurs it is important that a value be recorded on the eCRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm 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 5 mm 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 5 mm.

Lesions that split or coalesce on treatment. 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 obtaining maximal diameter measurements of each 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”.

Evaluation 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 (<10 mm 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).

When the subject 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 qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the subject has only non-measurable disease, this circumstance arises in some Phase III trials when it is not a criterion of trial entry to have measurable disease. The same general concept applies 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 subjects 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 disease from localized to widespread, or may be described in protocols as “sufficient to require a change in therapy”. If “unequivocal progression” is seen, the subject 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.

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 trial 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 subject who has visceral disease at baseline and while on trial has a CT or MRI brain ordered which reveals metastases. The subject’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 fluorodeoxyglucose-positron emission tomography (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:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- 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.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of ABSK-021 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 subject’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 trial and the protocol requirements, it may also require confirmatory measurement. 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”.

The best overall response is determined once all the data for the subject 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 subject 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 subject's best response depends on the subsequent assessments. For example, a subject 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 subject lost to follow-up after the first SD assessment would be considered unevaluable.

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; and PD = progressive disease.

Note:

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 subjects with CR may not have a total sum of “zero” on the eCRF.

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 subject with time point responses of PR-NE-PR as a confirmed response.

Subjects 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 trial therapy.

Conditions that define “early progression, early death, and unevaluability” are trial 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.

CONFIRMATORY MEASUREMENT/DURATION OF RESPONSE

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. However, in all other circumstances, i.e., in randomized trials (Phase II or III) or trials 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 trials which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after trial entry at a minimum interval (in general not less than 6 to 8 weeks).

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.

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 subjects 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 PFS 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 consider many parameters including disease types and stages, treatment periodicity, and standard practice. However, these limitations of the precision of the measured endpoint should be considered if comparisons between trials are to be made.

12.3 COCKCROFT-GAULT FORMULA

The Cockcroft and Gault formula was developed in 1973 to predict creatinine clearance from serum creatinine in adult males:

$$C_{cr} = \frac{(140 - age)(wt\ kg)}{72 \times S_{cr}(mg/100\ ml)}$$

For females, the result should be multiplied by 85%.

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

12.4 Sample of BRIEF PAIN INVENTORY (BPI) WORST PAIN NUMERIC RATING SCALE (NRS) ITEM (BPI-Worst-Pain-NRS)

For TGCT patients, the following question asks about pain at the site of tumor (below sample is for reference only).

STUDY ID #: _____ DO NOT WRITE ABOVE THIS LINE HOSPITAL #: _____

Worst Pain Numeric Rating Scale

Date: ____ / ____ / ____

Time: _____

Name _____

Last

First

Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes

2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.

3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No										Pain as bad as
Pain										you can imagine

Statement: The Worst Pain Numeric Rating Scale were taken from the English version of Brief Pain Inventory Short Form (BPI-SF).

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Pain Research Group
All rights reserved

12.5 Sample of WORST STIFFNESS NRS ITEM

For TGCT patients, the following question asks about stiffness at the site of tumor (below sample is for reference only).

Patient ID: _____	Hospital Number: _____																																																							
Do not write above this line.																																																								
Worst Stiffness Numeric Rating Scale																																																								
<table style="width: 100%;"><tr><td style="width: 50%;">Date: _____</td><td style="width: 50%;">Time: _____</td></tr><tr><td colspan="2">Name: _____</td></tr></table>		Date: _____	Time: _____	Name: _____																																																				
Date: _____	Time: _____																																																							
Name: _____																																																								
1. Have you had stiffness in the last 24 hours?																																																								
1. Yes 2. No																																																								
2. Please rate your stiffness by circling the one number that best describes your stiffness at its worst in the last 24 hours.																																																								
<table style="width: 100%;"><tr><td>0</td><td>1</td><td>2</td><td>3</td><td>4</td><td>5</td><td>6</td><td>7</td><td>8</td><td>9</td><td>10</td></tr><tr><td>No</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>Stiffness</td></tr><tr><td>Stiffness</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>as bad as</td></tr><tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>you can</td></tr><tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>imagine</td></tr></table>		0	1	2	3	4	5	6	7	8	9	10	No										Stiffness	Stiffness										as bad as											you can											imagine
0	1	2	3	4	5	6	7	8	9	10																																														
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Worst Stiffness NRS																																																								

12.6 PROMIS Physical Function Scale

12.6.1 Sample of PROMIS Physical Functioning (Lower Extremity)

Please respond to each item by marking one box per row.

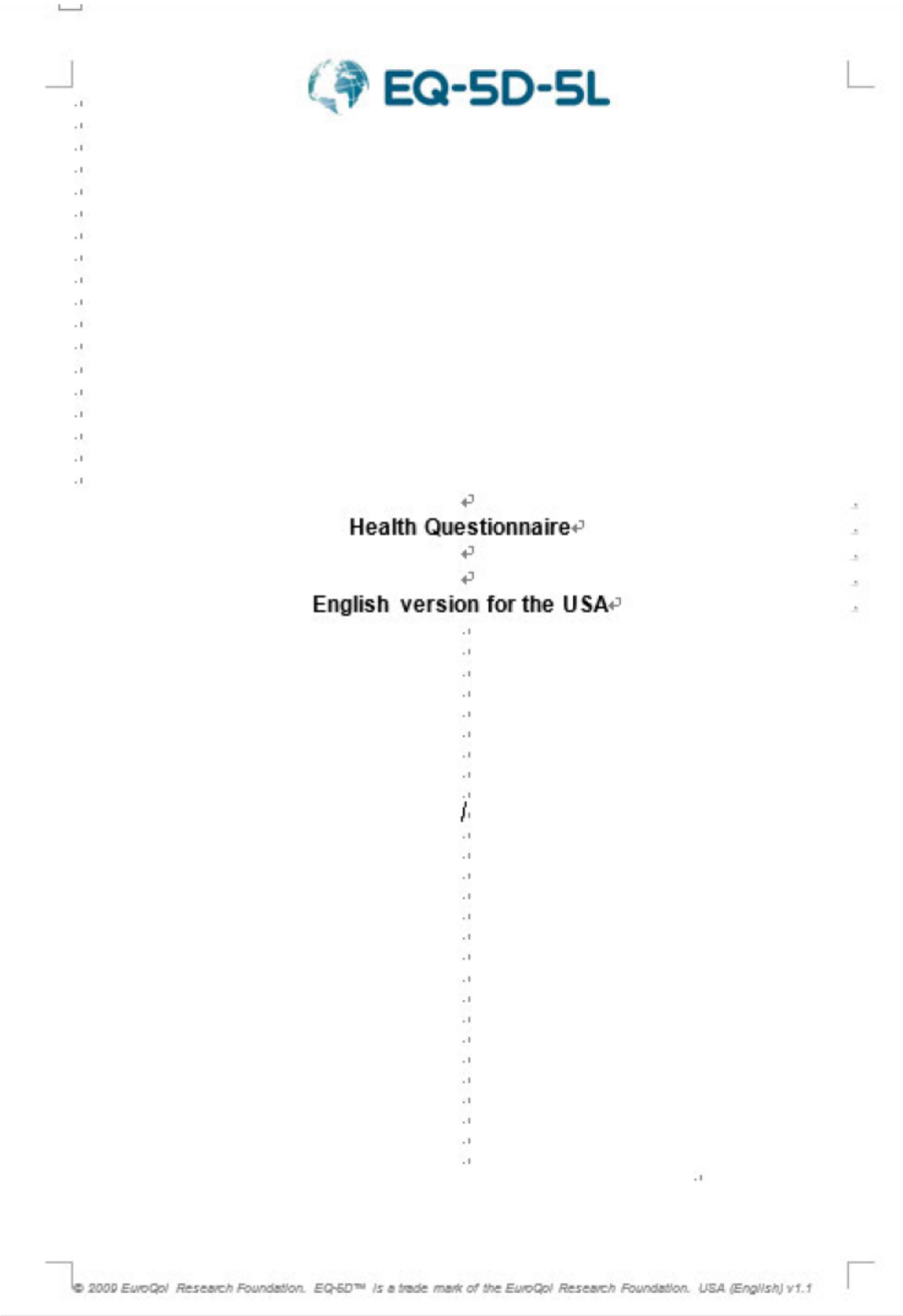
		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFA23	Are you able to go for a walk of at least 15 minutes?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA16r1	Are you able to dress yourself, including tying shoelaces and buttoning up your clothes?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA12	Are you able to push open a heavy door?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA14r1	Are you able to carry a heavy object (over 10 pounds/5 kg)?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA21	Are you able to go up and down stairs at a normal pace?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA42	Are you able to carry a laundry basket up a flight of stairs?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA10	Are you able to stand for one hour?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA13	Are you able to exercise for an hour?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
		Not at all	Very little	Somewhat	Quite a lot	Cannot do
PFB54	Does your health now limit you in going OUTSIDE the home, for example to shop or visit a doctor's office?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA4	Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFB1	Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA5	Does your health now limit you in lifting or carrying groceries?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA3	Does your health now limit you in bending, kneeling, or stooping?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1

12.6.2 Sample of PROMIS Physical Functioning (Upper Extremity)

Please respond to each item by marking one box per row.

		Without any difficulty	With a little difficulty	With some difficulty	With much difficulty	Unable to do
PFB34	Are you able to change a light bulb overhead?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA16r1	Are you able to dress yourself, including tying shoelaces and buttoning up your clothes?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA12	Are you able to push open a heavy door?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFB28r1	Are you able to lift 10 pounds (5 kg) above your shoulder?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA14r1	Are you able to carry a heavy object (over 10 pounds/5 kg)?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA42	Are you able to carry a laundry basket up a flight of stairs?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA13	Are you able to exercise for an hour? ..	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
		Not at all	Very little	Somewhat	Quite a lot	Cannot do
PFB54	Does your health now limit you in going OUTSIDE the home, for example to shop or visit a doctor's office?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA4	Does your health now limit you in doing heavy work around the house like scrubbing floors, or lifting or moving heavy furniture?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFB1	Does your health now limit you in doing moderate work around the house like vacuuming, sweeping floors or carrying in groceries?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1
PFA5	Does your health now limit you in lifting or carrying groceries?	<input type="checkbox"/> 5	<input type="checkbox"/> 4	<input type="checkbox"/> 3	<input type="checkbox"/> 2	<input type="checkbox"/> 1

12.7 Sample of EQ-5D-5L



Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY.

I have no problems walking.

☐

I have slight problems walking.

☐

I have moderate problems walking.

☐

I have severe problems walking.

☐

I am unable to walk.

☐

SELF-CARE.

I have no problems washing or dressing myself.

☐

I have slight problems washing or dressing myself.

☐

I have moderate problems washing or dressing myself.

☐

I have severe problems washing or dressing myself.

☐

I am unable to wash or dress myself.

☐

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities).

I have no problems doing my usual activities.

☐

I have slight problems doing my usual activities.

☐

I have moderate problems doing my usual activities.

☐

I have severe problems doing my usual activities.

☐

I am unable to do my usual activities.

☐

PAIN / DISCOMFORT.

I have no pain or discomfort.

☐

I have slight pain or discomfort.

☐

I have moderate pain or discomfort.

☐

I have severe pain or discomfort.

☐

I have extreme pain or discomfort.

☐

ANXIETY / DEPRESSION.

I am not anxious or depressed.

☐

I am slightly anxious or depressed.

☐

I am moderately anxious or depressed.

☐

I am severely anxious or depressed.

☐

I am extremely anxious or depressed.

☐

The best health you can imagine..

100

95

90

85

80

75

70

65

60

55

50

45

40

35

30

25

20

15

10

5

0

The worst health you can imagine..

- We would like to know how good or bad your health is TODAY..
- This scale is numbered from 0 to 100..
- 100 means the best health you can imagine. ↓
0 means the worst health you can imagine..
- Mark an X on the scale to indicate how your health is TODAY..
- Now, please write the number you marked on the scale in the box below..

YOUR HEALTH TODAY =

12.8 Sample of NCI-PRO-CTCAE Items

This is a sample of NCI-PRO-CTCAE items for this study, and local language versions will be available according to different study regions.

NCI-PRO-CTCAE® CUSTOM SURVEY

Item subset derived from PRO-CTCAE® Item Library Version 1.0

English

Form Created on 11-January-2023

<https://healthcaredelivery.cancer.gov/pro-ctcae/builder.html>

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please select the one response that best describes your experiences over the past 7 days...

1a. In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Very severe
1b. In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
<input type="radio"/> Not at all	<input type="radio"/> A little bit	<input type="radio"/> Somewhat	<input type="radio"/> Quite a bit	<input type="radio"/> Very much

2a. In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Very severe
2b. In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
<input type="radio"/> Not at all	<input type="radio"/> A little bit	<input type="radio"/> Somewhat	<input type="radio"/> Quite a bit	<input type="radio"/> Very much

3a. In the last 7 days, how OFTEN did you have NAUSEA?				
<input type="radio"/> Never	<input type="radio"/> Rarely	<input type="radio"/> Occasionally	<input type="radio"/> Frequently	<input type="radio"/> Almost constantly
3b. In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Very severe

4a. In the last 7 days, how OFTEN did you have VOMITING?				
<input type="radio"/> Never	<input type="radio"/> Rarely	<input type="radio"/> Occasionally	<input type="radio"/> Frequently	<input type="radio"/> Almost constantly
4b. In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Very severe

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5a. In the last 7 days, how OFTEN did you have ARM OR LEG SWELLING?				
<input type="radio"/> Never	<input type="radio"/> Rarely	<input type="radio"/> Occasionally	<input type="radio"/> Frequently	<input type="radio"/> Almost constantly
5b. In the last 7 days, what was the SEVERITY of your ARM OR LEG SWELLING at its WORST?				
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Very severe
5c. In the last 7 days, how much did ARM OR LEG SWELLING INTERFERE with your usual or daily activities?				
<input type="radio"/> Not at all	<input type="radio"/> A little bit	<input type="radio"/> Somewhat	<input type="radio"/> Quite a bit	<input type="radio"/> Very much

6a. In the last 7 days, did you have any RASH?	
<input type="radio"/> Yes	<input type="radio"/> No

7a. In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Very severe

8a. In the last 7 days, what was the SEVERITY of your DIZZINESS at its WORST?				
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Very severe
8b. In the last 7 days, how much did DIZZINESS INTERFERE with your usual or daily activities?				
<input type="radio"/> Not at all	<input type="radio"/> A little bit	<input type="radio"/> Somewhat	<input type="radio"/> Quite a bit	<input type="radio"/> Very much

9a. In the last 7 days, what was the SEVERITY of your INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) at its WORST?				
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Very severe
9b. In the last 7 days, how much did INSOMNIA (INCLUDING DIFFICULTY FALLING ASLEEP, STAYING ASLEEP, OR WAKING UP EARLY) INTERFERE with your usual or daily activities?				
<input type="radio"/> Not at all	<input type="radio"/> A little bit	<input type="radio"/> Somewhat	<input type="radio"/> Quite a bit	<input type="radio"/> Very much

10a. In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
<input type="radio"/> None	<input type="radio"/> Mild	<input type="radio"/> Moderate	<input type="radio"/> Severe	<input type="radio"/> Very severe
10b. In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
<input type="radio"/> Not at all	<input type="radio"/> A little bit	<input type="radio"/> Somewhat	<input type="radio"/> Quite a bit	<input type="radio"/> Very much

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OTHER SYMPTOMS	
Do you have any other symptoms that you wish to report?	
<input type="radio"/> Yes	<input type="radio"/> No
Please list any other symptoms:	
1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? <input type="radio"/> None <input type="radio"/> Mild <input type="radio"/> Moderate <input type="radio"/> Severe <input type="radio"/> Very Severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? <input type="radio"/> None <input type="radio"/> Mild <input type="radio"/> Moderate <input type="radio"/> Severe <input type="radio"/> Very Severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? <input type="radio"/> None <input type="radio"/> Mild <input type="radio"/> Moderate <input type="radio"/> Severe <input type="radio"/> Very Severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? <input type="radio"/> None <input type="radio"/> Mild <input type="radio"/> Moderate <input type="radio"/> Severe <input type="radio"/> Very Severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST? <input type="radio"/> None <input type="radio"/> Mild <input type="radio"/> Moderate <input type="radio"/> Severe <input type="radio"/> Very Severe

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12.9 Exit Interview Protocol

Please see attachment 1 for more details.

12.10 Exit Interview Guide

Please see attachment 2 for more details.