Official Title: Single-Center, Single-Arm, Two-Stage, Prospective Phase II Clinical Study of AK112 Combined with GAP Regimen as Conversion Therapy for Locally Advanced Gallbladder Cancer

NCT number: Not yet assigned

Protocol Version: V2.1

Version Date: July 4, 2026

Informed Consent Form

Version V2.1, Date: July 4, 2026

Trial Title: Single-Center, Single-Arm, Two-Stage, Open-Label, Prospective Phase II Clinical Study of AK112 Combined with GAP Regimen as Conversion Therapy for Locally Advanced Gallbladder Cancer

Study Institution: The First Affiliated Hospital of Xi'an Jiaotong University

Principal Investigator: Geng Zhimin

Consent Form Version: V2.1, July 4, 2026

Subject ID: _____

Dear Prospective Trial Subject,

We invite you to participate in a clinical trial conducted by the Department of Hepatobiliary Surgery, The First Affiliated Hospital of Xi'an Jiaotong University, titled "Single-Center, Single-Arm, Two-Stage, Open-Label, Prospective Phase II Clinical Study of AK112 Combined with GAP Regimen as Conversion Therapy for Locally Advanced Gallbladder Cancer". This trial will be fully conducted at our institution, with a planned total evaluable enrollment of 29 subjects. This trial protocol and this informed consent document have been reviewed and fully approved by the Institutional Review Board (IRB) / Medical Ethics Committee of The First Affiliated Hospital of Xi'an Jiaotong University.

Your participation is completely voluntary with no mandatory obligation. You retain the right to accept or decline trial enrollment without any penalty. Prior to making your final decision, please read and fully comprehend this document. This form comprehensively describes trial rationale, all trial-related procedures, potential clinical benefits, foreseeable risks, and your statutory rights as a trial subject. You may discuss all contents with your family members, legal representatives or friends, and consult your designated trial physician to clarify any questions you have before signing consent. Declining enrollment or withdrawing from the trial at any time will not lead to discrimination, withholding or downgrade of your standard medical care for gallbladder cancer. If you choose to participate, you will receive a fully signed duplicate copy of this informed consent form for permanent personal retention.

1 Rationale for Conducting This Clinical Trial

Gallbladder cancer is an aggressive digestive malignancy with insidious onset, and most patients lose the opportunity for curative radical surgery at diagnosis, resulting in poor long-term survival. Conversion therapy is an innovative preoperative treatment strategy utilizing anti-tumor therapy (chemotherapy, immunotherapy, etc.) to shrink and downstage initially unresectable tumors, enabling eligible patients to undergo curative radical surgery.

AK112 is a novel humanized bispecific monoclonal antibody that simultaneously blocks the PD-1 immune checkpoint pathway and VEGF angiogenesis signaling pathway, exerting synergistic dual anti-tumor activity combining immunotherapy and anti-angiogenesis effects. A previous domestic Phase II clinical trial of AK112 combined with chemotherapy for advanced biliary tract cancer (BTC) demonstrated robust anti-tumor efficacy and acceptable safety profiles: investigator-assessed objective response rate (ORR) reached 63.6%, and disease control rate (DCR) reached 100%.

The GAP regimen is a standard first-line chemotherapy combination for gallbladder cancer, consisting of three cytotoxic agents: gemcitabine, cisplatin, and albumin-bound paclitaxel. This trial aims to prospectively investigate whether adding AK112 to the GAP regimen can improve the R0 radical resection rate in subjects with locally advanced gallbladder cancer, and generate high-level evidence-based treatment options for this high-mortality patient population.

The principal investigator, has long-term experience in clinical practice and translational research focusing on biliary tract malignancies, with extensive expertise in standardized diagnosis and comprehensive management of gallbladder cancer. This trial will be fully designed, implemented and supervised by the Department of Hepatobiliary Surgery at our hospital.

2 Trial-Related Procedures and Subject Responsibilities

Trial Design Overview

This is a single-arm, open-label Phase II trial; all enrolled eligible subjects will receive uniform AK112 plus GAP combination therapy, with no separate randomized control arm. The trial adopts the validated Simon two-stage optimal statistical design: a small initial cohort will be enrolled first for interim efficacy evaluation. If the primary endpoint meets pre-specified efficacy thresholds, additional subjects will be enrolled to complete the total sample size. This design allows early trial termination when the regimen demonstrates insufficient clinical benefit, to maximize the safety and rights of all trial subjects.

Trial Timeline

(1) Overall trial period:

Global trial execution window: June 2026 – June 2028. Your individual participation will consist of three distinct sequential phases: screening phase (maximum 28 calendar days), treatment phase (approximately 4–6 months), and long-term survival follow-up phase.

(2) Step-by-Step Trial Workflow

① Screening Period: Sign informed consent, complete all eligibility assessments including physical examination, ECG, echocardiogram, blood laboratory testing, cross-sectional imaging (CT/MRI) and tumor tissue biomarker sampling.

② Treatment Phase: Each treatment cycle is defined as 21 days (Q3W), with a planned treatment course of 4–6 cycles. AK112 intravenous infusion will be administered on Day 1 of every cycle. A mandatory minimum 15-minute washout interval must be maintained after AK112 infusion before sequential intravenous administration of gemcitabine, albumin-bound paclitaxel, and cisplatin. Cross-sectional tumor efficacy assessment per RECIST v1.1 criteria will be performed every 2 treatment cycles, followed by MDT comprehensive re-evaluation of surgical feasibility.

③ Radical Surgery Eligibility Assessment: Upon completion of the planned conversion therapy cycles, the multidisciplinary team (MDT) will conduct a comprehensive joint discussion to evaluate whether curative radical surgery can be safely performed. If surgical resection is feasible, radical surgery will be scheduled for you. If conversion therapy fails to achieve tumor downstaging to resectable status, the MDT will formulate individualized standard subsequent anti-tumor therapy tailored to your disease status.

④ Post-Treatment Follow-Up Phase: Regular scheduled follow-up visits will be conducted after the last cycle of study drug (or post-surgery), including safety follow-

up, long-term survival follow-up, and dedicated recurrence monitoring for subjects who receive radical resection.

(3) Required Participant Compliance

Disclose full medical history and current physical symptoms truthfully to research staff;

Immediately report any new discomfort or adverse symptoms to your research physician during trial participation;

Attend all scheduled hospital visits for treatment and testing as specified in the trial schedule;

Notify research staff promptly if you enroll in any other clinical trial during participation;

All female subjects of childbearing potential must use reliable contraceptive measures throughout the entire treatment period and for 120 calendar days after the last study drug administration.

(4) Patient Safety Protections During Trial

All diagnosis and treatment decisions will be supervised by a multidisciplinary medical team with extensive hepatobiliary oncology experience;

Full baseline physical function assessment will be completed prior to every cycle of drug administration to confirm treatment safety;

Standardized tiered adverse event intervention protocols will be activated timely upon detection of any treatment-related toxicity;

Specialists from surgery, medical oncology, radiology and pathology will jointly participate in all MDT clinical decision-making throughout your trial participation.

Scheduled Trial Visit Schedule

Visit Stage	Timing	Core Assessments
Screening Period	Within 28 calendar days pre-enrollment	Informed consent signature, physical exam, vital signs, ECG, echocardiogram, full laboratory panel, cross-sectional tumor imaging, tumor tissue biomarker sampling
Treatment Cycles	Every 21 calendar days (Q3W)	Study drug administration, vital sign monitoring, concomitant medication documentation, adverse event recording
Efficacy Evaluation	Every 2 cycles (6 weeks)	CT/MRI tumor imaging, RECIST v1.1 tumor response assessment
Surgical Eligibility Review	30 calendar days after last study drug administration	Full MDT multidisciplinary discussion to evaluate radical surgical feasibility
Safety Follow-Up	30 calendar days after last study	Physical examination, vital
	drug administration	signs, laboratory testing, tumor imaging
Survival Follow-Up	Every 90 calendar days post safety follow-up	Survival status, record of all subsequent anti-tumor treatments
Postoperative Follow-Up	Synchronized with survival follow-up frequency	Recurrence monitoring, survival status update for surgical patients

3 Eligibility Criteria for Trial Participation

You may only enroll if you meet all of the following requirements:

(1) Voluntarily provide written informed consent;

(2) Age ≥18 years and ≤75 years at enrollment;

(3) Histologically or cytologically confirmed gallbladder adenocarcinoma;

(4) Radiological imaging demonstrating any of the following locally advanced unresectable features:

a. Hepatic invasion requiring extensive hepatectomy with unacceptable surgical risk;

b. Biliary tract invasion extending beyond bifurcation requiring extensive hepatectomy that the patient cannot tolerate;

c. Fused bulky regional lymph nodes (max diameter >2 cm) compressing/infiltrating critical vessels/biliary tracts precluding radical lymphadenectomy;

d. Primary tumor vascular invasion: main/left portal vein invasion without reconstructive options; proper/common hepatic artery invasion >180°, or <180° invasion combined with mandatory portal vein reconstruction; right portal/hepatic artery invasion with intolerance to extensive hepatectomy;

e. Direct invasion of adjacent visceral organs (pancreas, stomach, duodenum, colon);

(5) MDT consensus confirming initial non-resectability with anticipated tumor downstaging potential after conversion therapy;

(6) ECOG performance status score of 0 or 1 (ambulatory, capable of mild daily activity);

(7) No prior systemic anti-tumor therapy for locally advanced gallbladder cancer;

(8) At least one measurable target lesion per RECIST v1.1 suitable for repeated serial imaging measurement;

(9) Adequate global organ function to tolerate AK112+GAP conversion therapy;

(10) Estimated overall survival ≥3 months;

(11) Willing and able to comply with all scheduled trial visits, treatment cycles, laboratory testing and other protocol requirements;

(12) Adequate hematologic, renal, hepatic, coagulation and cardiac lab parameters (no blood product/growth factor support within 7 days prior to screening labs):

a. Hematology: ANC ≥1.5×10⁹/L; PLT ≥100×10⁹/L; Hb ≥90 g/L;

b. Renal: CrCl ≥50 mL/min (Cockcroft-Gault formula); urine protein ≤1+ or 24h

urine protein <1.0 g;

c. Hepatic: TBil ≤2×ULN; AST/ALT ≤2.5×ULN; ALB ≥28 g/L;

d. Coagulation: INR, APTT ≤1.5×ULN;

e. Cardiac: LVEF ≥50%.

Please consult your research physician for detailed clarification of any eligibility criteria you do not fully understand.

4 Trial Exclusion Criteria (Any single item disqualifies enrollment)

You are ineligible to participate if any of the following apply to you:

(1) Histological/cytological diagnosis of non-adenocarcinoma gallbladder malignancy (squamous carcinoma, neuroendocrine neoplasm, lymphoma, sarcoma);

(2) Radiological evidence of distant metastatic disease;

(3) Prior radiotherapy, chemotherapy, targeted therapy or immunotherapy administered for gallbladder cancer;

(4) Concurrent secondary malignant tumor diagnosis unrelated to gallbladder cancer;

(5) Severe uncontrolled biliary tract infection or untreated obstructive jaundice;

(6) Major surgery or severe traumatic injury within 30 days before first study drug administration:

a. Definitions:

Major surgery: All open/laparoscopic procedures requiring general endotracheal anesthesia entering thoracic/abdominal/pelvic cavities;

Severe trauma: Deep tissue/visceral injury requiring hospitalization or surgical repair (fractures, extensive soft tissue contusion, closed abdominal trauma);

b. Permitted minimally invasive procedures with mandatory washout intervals:

Diagnostic biopsy (lymph node, liver/gallbladder FNAB, EUS biopsy): minimum 7 days between procedure and first drug infusion, no active hemorrhage/hematoma;

Biliary decompression (PTCD, ERCP stent/nasobiliary drain): minimum 14 days between procedure and first drug infusion, no active bleeding, peritonitis or biliary leak confirmed clinically and radiologically;

(7) Active systemic disease requiring continuous treatment: active autoimmune disorders, active inflammatory bowel disease, immunodeficiency, active tuberculosis, untreated syphilis, solid organ/allogeneic hematopoietic stem cell transplant history, non-infectious interstitial lung disease requiring chronic systemic corticosteroids;

(8) Severe bleeding diathesis or coagulation disorder history:

a. Screening lab abnormalities: PLT <100×10⁹/L; INR >1.5 (off anticoagulants); APTT >1.5×ULN; fibrinogen <1.5 g/L;

b. CTCAE Grade ≥2 active bleeding event within 3 months pre-enrollment, or uncontrolled major vascular complications;

(9) Confirmed hypersensitivity or anaphylaxis to any active pharmaceutical ingredient or excipient of AK112, gemcitabine, cisplatin or albumin-bound paclitaxel;

(10) Pregnant or breastfeeding female patients;

(11) Severe untreated psychiatric disorders, substance abuse history, or other conditions impairing long-term trial compliance.

5 Circumstances for Termination of Individual Trial Participation

The overall trial will conclude once the final participant completes all scheduled follow-up assessments and data collection. For your individual participation, trial discontinuation may occur under the following circumstances:

(1) Voluntary self-withdrawal (written withdrawal of informed consent): You retain full rights to exit the trial at any time without stated reason, with no negative impact on your standard clinical care;

(2) Documented Progressive Disease (PD): Continued study treatment provides no further anti-tumor benefit;

(3) Intolerable Grade 3/4 treatment-related adverse events refractory to standardized supportive intervention;

(4) Clinical deterioration or new comorbidities rendering you unfit for continued protocol treatment;

(5) Perioperative contraindications to radical surgery identified post-conversion therapy (new distant metastasis, irreversible organ failure);

(6) Severe protocol non-compliance or major protocol deviation (failure to attend scheduled treatment, imaging or follow-up visits for multiple consecutive cycles).

You may voluntarily exit the trial at any time. Your trial physician may also recommend trial discontinuation to protect your safety. Prior to early termination, additional safety laboratory and imaging assessments will be arranged to ensure your clinical stability. The trial sponsor, institutional IRB or national regulatory authorities reserve the right to fully terminate the entire trial for safety or administrative reasons at any time.

6 Alternative Standard Treatment Options Available to You

If you decline enrollment in this trial, standard alternative treatment options for your locally advanced gallbladder cancer include:

(1) Single-agent or doublet chemotherapy regimens (GC regimen, GAP chemotherapy alone);

(2) Alternative PD-1/PD-L1 immunotherapy combined with chemotherapy;

(3) Palliative symptomatic supportive care only;

(4) Enrollment in other independent clinical trials for biliary tract malignancies.

Your attending physician will review all personalized alternative treatment options based on your individual tumor characteristics and physical condition.

7 Potential Risks of Trial Participation

(1) Drug-Related Toxicities

All investigational and standard chemotherapy agents carry potential unforeseen severe adverse reactions. Based on pooled clinical safety data for AK112 monotherapy, common adverse events (incidence ≥10%) include proteinuria (33.7%), hypertension (22.3%), elevated AST (19.4%), elevated ALT (15.0%), hypercholesterolemia (14.8%), hyperbilirubinemia (14.3%), anemia (14.3%), hypothyroidism (13.3%), rash (11.9%), hyperglycemia (10.9%), elevated amylase (10.7%), thrombocytopenia (10.2%). Most monotherapy toxicities are CTCAE Grade 1–2. The most frequent Grade ≥3 adverse events include hypertension (6.1%), proteinuria (3.1%), liver

function abnormalities (2.4%), anemia (2.2%), hyperbilirubinemia (1.2%), hypertriglyceridemia (1.2%), lipase elevation (1.2%), infusion-related reaction (1.0%).

When AK112 is combined with GAP chemotherapy, overall toxicity profiles overlap with standard chemotherapy, with increased incidence of fatigue, nausea and rash but maintained clinical tolerability. Common combined regimen adverse events (≥10% incidence): anemia (34.5%), leukopenia (30. 1%), neutropenia (29.4%), elevated AST (25.0%), thrombocytopenia (22.5%), proteinuria (19.6%), rash (13.6%), decreased appetite (13.3%), elevated amylase (12.7%), epistaxis (12.3%), hypothyroidism (12.0%), elevated GGT (12.0%), hypercholesterolemia (10.8%), fatigue (10.4%). The most frequent Grade ≥3 toxicities: neutropenia (18.7%), leukopenia (12.0%), anemia (11. 1%), thrombocytopenia (8.5%), lymphopenia (4.4%), hypertension (3.2%), rash (2.2%), elevated GGT (2.2%), interstitial lung disease (1.6%), hypertriglyceridemia (1.3%), infusion-related reaction (1.3%).

For PD- 1 immune checkpoint inhibitors, immune-related adverse events (irAEs) occur in 30–40% of all patients, with severe irAEs observed in 5–10% of treated individuals, potentially affecting lungs (immune pneumonitis: cough, dyspnea), gastrointestinal tract (immune colitis: diarrhea, abdominal pain), liver (immune hepatitis: transaminitis), skin (rash, pruritus) and endocrine organs (thyroid dysfunction, hypopituitarism). Most mild-moderate irAEs are fully controllable with standardized intervention protocols, though rare life-threatening severe irAEs have been documented.

The GAP chemotherapy regimen has a well-characterized toxicity spectrum: myelosuppression (neutropenia 60–70%, Grade 3/4 neutropenia 30–40%), gastrointestinal toxicity (nausea/vomiting 40–50%), peripheral neurotoxicity (15–25%), hepatic/renal injury, hypersensitivity and alopecia. Concurrent AK112 administration increases the incidence of fatigue, nausea, rash and alopecia relative to chemotherapy alone.

Additional risks for bispecific monoclonal antibody AK112 include infusion-related reactions presenting with chills, fever, facial/extremity cyanosis, headache, nausea/vomiting; severe rare reactions include hypotension, shock and respiratory failure. As a humanized bispecific antibody, AK112 is anticipated to have low incidence and mild severity of infusion reactions.

(2) Procedure-Related Risks

Tumor biopsy carries small risks of hemorrhage or infection (1–3% incidence). Post-radical surgery risks include surgical site infection, intraoperative hemorrhage and biliary fistula (3–5% incidence).

(3) Venipuncture Risks

Peripheral blood draws may cause local pain, bruising, or rare vasovagal syncope.

(4) Unforeseen Unknown Risks

Additional uncharacterized adverse effects of AK112+GAP combination therapy may emerge during trial participation that cannot be predicted at this stage.

Risk Mitigation Measures: Full pre-treatment physical assessment prior to every

drug cycle; continuous vital sign monitoring during AK112 infusion with emergency resuscitation supplies readily available; dose delay/reduction protocols for treatment-emergent toxicities; tiered standardized management pathways for all adverse events to enable timely clinical intervention.

8 Potential Benefits of Trial Participation

Direct Individual Benefit

You may achieve tumor shrinkage and successful downstaging after AK112 + GAP conversion therapy, which may grant you access to curative radical surgery and improve your long-term overall survival prognosis. This is an exploratory Phase II trial; no guaranteed clinical therapeutic benefit can be promised to all enrolled subjects.

Population-Level Social Benefit

Data collected from your trial participation will expand global clinical understanding of gallbladder cancer conversion therapy, generating evidence-based treatment guidelines to improve outcomes for future patients with locally advanced gallbladder cancer.

9 Trial-Related Cost Responsibilities

Per national clinical trial regulatory requirements, participants shall not be charged fees for trial-specific research procedures. Cost breakdown:

(1) AK112 and GAP chemotherapy agents are standard commercial products; no complimentary supply of investigational drugs provided by the trial sponsor;
(2) All trial-mandated testing (imaging, laboratory panels) shall be covered by the participant or their medical insurance;
(3) Radical surgery, perioperative medications and inpatient hospital care costs are borne by the participant or medical insurance;
(4) All standard treatment and testing required for unrelated comorbidities shall be covered by the participant or medical insurance.

Please consult your research physician for full clarification of all trial-associated financial obligations prior to enrollment.

10 Trial Follow-Up Compensation

A fixed follow-up subsidy of RMB 200 will be provided to participants upon completion of every scheduled two-cycle efficacy assessment visit.

11 Management of Trial-Related Injury

If you sustain physical harm directly related to trial treatment or procedures, immediate necessary medical intervention will be provided by the trial team. If the injury is confirmed causally associated with trial drugs or research procedures, the trial sponsor shall cover all associated medical expenses and provide reasonable financial compensation in accordance with national laws and the trial clinical liability insurance policy. The trial maintains full clinical trial insurance coverage for all enrolled subjects; consult your research physician for full insurance policy details and claim procedures.

12 Biological Tissue Samples

Tumor tissue and peripheral blood samples will be collected from you for trial biomarker analysis:

(1) Sample source: Tumor biopsy tissue or surgical resection specimens, serial peripheral blood draws;

(2) Testing purpose: Quantify intratumoral PD-L1 expression, TMB and VEGF pathway molecular alterations to identify predictive biomarkers of treatment response and resistance;

(3) Residual sample disposal: All leftover biological specimens will be processed per institutional biobank regulations upon trial completion;

(4) Secondary research use: Any utilization of your residual samples for research outside this trial will require separate written informed consent and formal IRB approval.

13 Notification of Emerging Critical Trial Safety Information

If new safety data emerges that may alter your ability to continue trial treatment, the research team will notify you promptly. If protocol or informed consent revisions are required, updated documents will be IRB-approved and re-signed by all active participants as needed.

14 Trial Result Disclosure to Participants

Upon full trial completion, a written summary of overall trial outcomes will be provided to you upon request. All peer-reviewed publications and conference presentations will fully de-identify all participant personal data to protect confidentiality.

15 Personal Information Confidentiality

All individually identifiable personal health information collected during the trial will be fully de-identified using unique anonymous study numbers in place of your full legal name. All trial data is stored in encrypted electronic databases with restricted access limited exclusively to authorized trial research staff. All trial personnel execute formal confidentiality agreements. No personal identifying information will be disclosed in any public trial report or publication.

Authorized parties (investigators, trial monitors, IRB, national regulatory inspectors) may review your full medical records only after executing formal confidentiality agreements as required by clinical trial oversight regulations. Your signature on this informed consent document constitutes voluntary authorization for such regulated data review.

16 Voluntary Participation Right

Your enrollment in this trial is entirely voluntary. You may refuse participation without any negative impact on your standard medical care for gallbladder cancer. Even after signing informed consent, you retain the unconditional right to withdraw

trial participation at any time without penalty or disruption to routine clinical treatment. If you elect to withdraw, please notify your research physician promptly to receive clinical guidance on subsequent standard care.

The research team may also mandate your trial discontinuation if new clinical conditions, severe adverse toxicities or disease progression render continued trial participation unsafe for you. You retain full rights to request regular updates on trial progress and emerging safety findings throughout your participation.

17 Contact Information for Trial Inquiries

For questions regarding this study, please refer to the contact information provided in the ClinicalTrials.gov record.

Signature Page of Informed Consent

Participant Statement：I confirm that I have fully read the entire informed consent document, all trial procedures, potential benefits, risks, financial terms, injury compensation policies and confidentiality clauses have been fully explained to me by the research physician. All my questions have been answered completely to my satisfaction. I voluntarily agree to participate in this clinical trial.

Participant Printed Full Name: _____

Participant Signature: _____

Date: _____ Year _____ Month _____ Day

Participant Mobile Phone Number: _____

Legal Guardian Section (if applicable)

Guardian Printed Full Name: _____

Relationship to Participant: _____

Guardian Signature: _____

Date: _____ Year _____ Month _____ Day

Reason for legal guardian signature: _____

Witness Section (if applicable)

Witness Printed Full Name: _____

Witness Signature: _____

Date: _____ Year _____ Month _____ Day

Reason for witness signature: _____

Investigator Confirmation Statement

I confirm that I have fully explained all trial details to the prospective participant, including all potential risks, clinical benefits, financial obligations, injury compensation and ethical confidentiality standards outlined in this informed consent document. The participant fully understands all trial information and voluntarily consents to enrollment. A fully executed copy of this informed consent form has been provided to the participant for personal retention.

Investigator Signature: _____

Date: _____ Year _____ Month _____ Day