

REG/2025/CT/DCGI/VB/589

23 December 2025

To,
Drugs Controller General (India)
Central Drugs Standard Control Organization
FDA Bhawan, CHEB Campus
Kotla Road, New Delhi 110002

Clinical Study Protocol (CSP): D702NC00001, CSP Version 1.0 dated 08 Aug 2025 and
Local CSP - Addendum Version 1.0 India dated 07 Oct 2025

Protocol Title: “Phase III, Randomized, Open-label, Global, Multicenter Study of Rilvegostomig or Durvalumab in Combination With Chemotherapy as a First-line Treatment for Patients With Advanced Biliary Tract Cancer (ARTEMIDE-Biliary02)”

Subject: Global Clinical Trial Application seeking:

- Permission to conduct Phase III Global Clinical Trial under New Drugs and Clinical Trial Rules, 2019
- Test License for Import of Investigational Medicinal Products for Clinical Trial under Rule 67 of New Drugs and Clinical Trial Rules, 2019

Dear Sir,

We AstraZeneca Pharma India Limited, hereby submit an application in Form CT-04 to your esteemed Directorate, seeking permission to conduct a “Phase III, Randomized, Open-label, Global, Multicenter Study of Rilvegostomig or Durvalumab in Combination With Chemotherapy as a First-line Treatment for Patients With Advanced Biliary Tract Cancer (ARTEMIDE-Biliary02)”

This study will be conducted in compliance with the Study Protocol, New Drugs and Clinical Trials Rules, 2019, and the current regulatory requirements and guidelines in India.

Background: Biliary tract cancer (BTC)

India bears a disproportionately high burden of biliary tract cancer (BTC), particularly gallbladder cancer (GBC), with endemic hotspots in the North, Northeast, and Gangetic plains and rising incidence that exceeds many Western regions. Indian patients often present younger, with a female predominance in GBC and geographic clustering that implicates unique environmental and genetic cofactors. Distinct risk exposures—high gallstone prevalence, chronic Salmonella typhi carriage, Helicobacter pylori, polluted water and soil, and dietary factors—support a “toxic environment × susceptible host” model for carcinogenesis in India. Real-world Indian cohorts show late-stage presentation, low curative resection rates, and poor survival (overall median 16.1 months; metastatic 9.6 months), compounded by barriers to second-line therapy and supportive care. Against this backdrop, global benchmarks highlight the limits of current first-line immunochemotherapy: TOPAZ-1 showed durvalumab + GemCis improved OS vs GemCis alone (HR 0.80; median 12.9 vs 11.3 months; $p=0.021$), yet 3-year OS remained low (14.6% vs 6.9%), and approximately half of patients received no further therapy after discontinuation; similar patterns were observed in KEYNOTE-966. The similar survival benefits had also been witnessed from real world study (Muddu et al), which underscores the urgent need for more effective first-line regimens in India where post-progression treatment rates are limited. Dual checkpoint inhibition targeting convergent immunosuppressive PD-1 and TIGIT pathways is biologically compelling, and TIGIT is overexpressed in cholangiocarcinoma relative to normal tissue [12,13]. Rilvegostomig, a bispecific that co-engages PD-1 and TIGIT, offers potential advantages over separate antibodies through assured co-distribution, reduced infusion burden, and cooperative binding that may enhance immune activation. Indian molecular profiles—KRAS ~25%, TP53 ~16%, rare MSI-H/TMB-high, variable PD-L1, and lower frequencies of FGFR/IDH—

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warrant population-specific evaluation and correlative biomarker studies [4]. Trial participation can expand molecular testing capacity, including tissue and cfDNA/bile assays, addressing infrastructure gaps. Including Indian sites improves external validity, ensures representation of GBC-rich populations justify Indian participation to address unmet needs and enhance the global applicability of trial results.

Note: Kindly refer to Annexure I for List of abbreviations.

Investigational Medicinal Product (IMP): Rilvegostomig (AZD2936) Concentrate for solution for infusion 50 mg/mL (750 mg/vial)

Rilvegostomig is a monovalent, bispecific, humanized, IgG1 triple-mutant mAb against human PD-1 and TIGIT. Rilvegostomig was constructed on the backbone of the DuetMab molecule, and its antigen-binding fragment portions are comprised of the variable domains of the anti-TIGIT (COM902) and anti-PD-1 LO115 antibodies. The IgG1 Fc domain carries the triple mutation (L234F/L235E/P331S) designed to reduce Fc-mediated immune effector functions. In the preclinical studies, dual blockade of TIGIT and PD-1 by rilvegostomig enhanced human T cell function and promoted antitumor immune responses.

The TIGIT receptor is a member of the Ig superfamily, which plays a critical role in limiting T cell and NK cell effector functions. Preclinical studies have demonstrated that TIGIT is a key inhibitor of antitumor responses that can hinder multiple steps of the cancer immunity cycle.

Evidence has been found that dual inhibition of PD-1 or PD-L1 and the novel immune checkpoint TIGIT show promising results across multiple tumor types without major increases in high-grade toxicity compared to PD-1 or PD-L1 inhibition alone. In terms of GC, high TIGIT expression is found to be associated with relapsed GC and poor prognosis. Downregulation of CD155 in GC cells combined with PD-L1 blockade mediated synergistic effects in terms of the inhibition of tumor progression and increased survival compared with the effects of downregulation of CD155 in GC cells or PD-L1 blockade alone. Preliminary efficacy signals have also been observed in clinical studies involving GC.

The use of an anti-TIGIT/anti-PD-1 bispecific antibody is an innovative approach for targeting the converging, immunosuppressive PD-1 and TIGIT pathways at the same time. This approach has some potential advantages as compared with the co-administration of separate anti-TIGIT and anti-PD-L1 antibodies. Along with the ease of drug delivery (a single administration replacing 2 administrations), there is a certainty of equal biodistribution of a single molecule targeting both receptors.

The efficacy of rilvegostomig in combination with chemotherapy has been evaluated in GEMINI-Gastric, a Phase II platform study in previously untreated patients with locally advanced or metastatic GC/GEJC. As of the DCO of 04 July 2024, the preliminary efficacy data had been reviewed in 40 patients treated with rilvegostomig 750 mg combined with CAPOX or FOLFOX regimen. The confirmed response rate was 62.5% in all patients and increased to 81.3% in patients with PD-L1 CPS $\geq$ 5. The safety profile of rilvegostomig in the GEMINI-Gastric study was tolerable and consistent with other studies evaluating rilvegostomig, and no new safety signals were found.

Rilvegostomig (AZD2936) is available as concentrate for solution for infusion in a 750 mg vial in this clinical study.

Study Rationale:

Despite advances in first-line BTC, overall survival remains poor and many patients receive no therapy after discontinuing standard care, underscoring a high unmet need. In TOPAZ-1, adding durvalumab to GemCis improved OS versus chemotherapy alone (HR 0.80; median OS 12.9 vs 11.3 months; $p=0.021$),

yet 3-year OS was only 14.6% vs 6.9%. In TOPAZ-1 and KEYNOTE-966 (pembrolizumab plus GemCis vs GemCis in first-line BTC), approximately 50% of patients who discontinued the current SoC did not

receive any additional lines of treatment (1,2,3). Due to the poor survival post first-line progression, improved therapies in the first-line setting are needed.

Emerging data indicate that dual blockade of the converging immunosuppressive PD-1 and TIGIT pathways may enhance immune checkpoint efficacy, with TIGIT overexpressed in cholangiocarcinoma. (4,5). The bispecific, antibody rilvegostomig targets both receptors in one molecule, potentially offering advantages over separate antibodies—reduced infusion burden, assured equal biodistribution, and cooperative binding that may yield novel biological effects— supported by nonclinical antitumor activity exceeding parental-antibody combinations. Preliminary results from the BTC substudy (Cohort 2A) of the Phase II GEMINI Hepatobiliary platform (NCT05775159) combining rilvegostomig with GemCis show efficacy favorable to historical TOPAZ-1 and KEYNOTE-966 benchmarks and a tolerable safety profile without new signals (6,7,8).

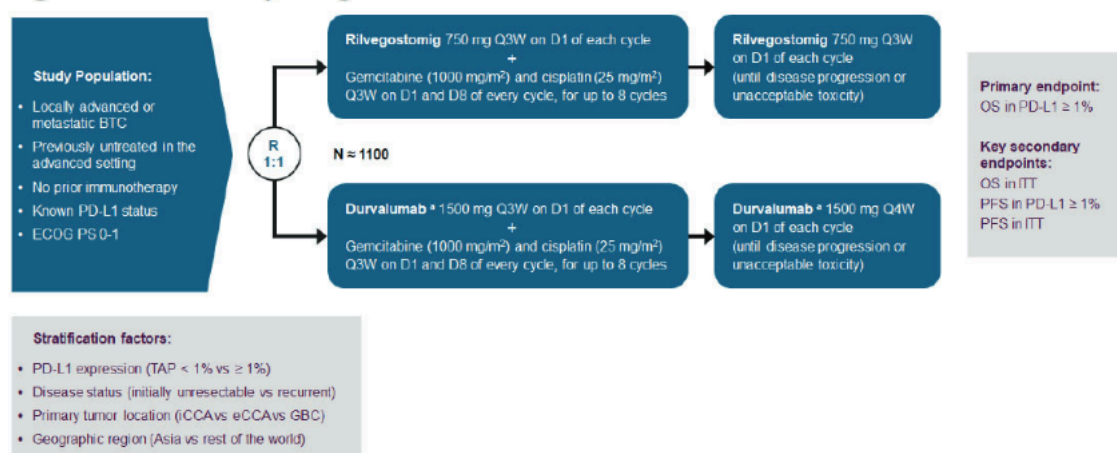
Study Design:

This is a Phase III, two-arm, randomized, open-label, multicenter, global study, assessing the efficacy and safety of rilvegostomig in combination with gemcitabine and cisplatin chemotherapy compared with durvalumab in combination with gemcitabine and cisplatin chemotherapy in participants with advanced BTC.

Approximately 1100 participants will be randomized in a 1:1 ratio to one of the following intervention arms:

1.2 Schema

Figure 1 Study Design



* Durvalumab is administered Q3W on Day 1 of each cycle in combination with chemotherapy for up to 8 cycles, followed by Q4W on Day 1 of each cycle as a single-agent. If weight falls to ≤ 30 kg, the participant should receive weight-based dosing of 20 mg/kg of durvalumab (for full details, see Section 6.6).

Treatment plan:

Study interventions in both arms will begin administration on Day 1 of each cycle, Q3W, after all procedures/assessments have been completed as detailed in the SoA of Clinical Study Protocol.

Arm A – Experimental arm: Rilvegostomig in combination with gemcitabine plus cisplatin. Participants will receive rilvegostomig 750 mg IV Q3W on D1 of each cycle starting on C1D1 in combination with chemotherapy for up to 8 cycles, after which participants will receive rilvegostomig 750 mg IV Q3W as a single-agent, until disease progression or unacceptable toxicity. Gemcitabine 1000 mg/m² IV Q3W plus cisplatin 25 mg/m² IV Q3W will be administered on D1 and D8 of each cycle starting on C1D1 for up to 8 cycles.

Arm B - Control arm: Durvalumab in combination with gemcitabine plus cisplatin. Participants will receive durvalumab 1500 mg IV Q3W on D1 of each cycle starting on C1D1 in combination with chemotherapy for up to 8 cycles, after which participants will receive durvalumab 1500 mg IV Q4W as a single-agent, until disease progression or unacceptable toxicity. Gemcitabine 1000 mg/m² IV Q3W plus cisplatin 25 mg/m² IV Q3W will be administered on D1 and D8 of each cycle starting on C1D1 for up to 8 cycles.

All randomized participants in both arms of the study will receive study interventions until RECIST v1.1-defined PD or unacceptable toxicity, withdrawal of consent, or other criteria for discontinuation are met.

Description of Treatment:

	Rilvegostomig	Durvalumab	Gemcitabine	Cisplatin
Arm Name	Arm A	Arm B	Arm A & B	Arm A & B
Dosing regimen	750 mg Q3W with with chemotherapy for up to 8 cycles followed by Rilvegostomig 750 mg Q3W as a single-agent	1500 mg Q3W with chemotherapy for up to 8 cycles followed by durvalumab 1500 mg Q4W as a single-agent	1000 mg/m ² Q3W on D1 and D8 of each 21-day cycle, for up to 8 cycles	25 mg/m ² Q3W on D1 and D8 of each 21-day cycle, for up to 8 cycles
Route of administration	IV Infusion	IV infusion	IV infusion	IV infusion
Use	Experimental	Control	Experimental & Control	Experimental & Control
Sourcing	Provided centrally by AstraZeneca		Provided locally by the study site, subsidiary, or designee	
Current/former name(s) or alias(es)	AZD2936	MEDI4736	NA	NA

Objectives & Endpoints for the Safety Lead-in Period:

Objectives	Estimands descriptions/Endpoints
Primary	
To demonstrate the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of OS in the PD-L1 $\geq 1\%$ population.	OS is defined as time from randomization until the date of death due to any cause. The analysis will include all randomized participants in the PD-L1 $\geq 1\%$ population. All deaths will be included, regardless of whether the participant withdraws from therapy or receives another anticancer therapy. The measure of interest is the HR of OS.
Secondary	
To demonstrate the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of OS in the ITT population.	OS is defined as time from randomization until the date of death due to any cause. The analysis will include all randomized participants. All deaths will be included, regardless of whether the participant withdraws from therapy or receives another anticancer therapy. The measure of interest is the HR of OS.
To demonstrate the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus	PFS is defined as the time from randomization until radiological progression per RECIST 1.1 as assessed by Investigator, or death due to any cause (in the absence of progression), whichever occurs first.

chemotherapy by assessment of PFS in the PD-L1 $\geq$ 1% population.	The analysis will include all randomized participants in the PD-L1 $\geq$ 1% population. All events will be included regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to radiographic progression per RECIST 1.1. However, if the participant progresses or dies immediately after 2 or more consecutive missed visits, the participant will be censored at the time of the latest evaluable assessment prior to the 2 missed visits. PFS will also be assessed by BICR for supplementary/sensitivity analysis. The measures of interest is the HR of PFS.
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Objectives and Endpoints for the Randomised Period:

Objectives	Estimands descriptions/Endpoints
Primary	
To characterize and compare the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of DoR in the PD-L1 $\geq$ 1% population.	DoR is defined as the time from the date of first documented response until the date of documented progression per Investigator assessments using RECIST 1.1 or death due to any cause (in the absence of progression), whichever occurs first. The analyses will include all randomized participants who have a confirmed response in the PD-L1 $\geq$ 1% population. The end of response coincides with the date of progression or death from any cause used for the PFS endpoint. The measure of interest is the median of DoR.
Key Secondary	
To demonstrate the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of OS in the ITT population.	OS is defined as time from randomization until the date of death due to any cause. The analysis will include all randomized participants. All deaths will be included, regardless of whether the participant withdraws from therapy or receives another anticancer therapy. The measure of interest is the HR of OS.
To demonstrate the efficacy of rilvegostomig plus chemotherapy relative to durvalumab plus chemotherapy by assessment of PFS in the PD-L1 $\geq$ 1% population.	PFS is defined as the time from randomization until radiological progression per RECIST 1.1 as assessed by Investigator, or death due to any cause (in the absence of progression), whichever occurs first. The analysis will include all randomized participants in the PD-L1 $\geq$ 1% population. All events will be included regardless of whether the participant withdraws from therapy, receives another anticancer therapy, or clinically progresses prior to radiographic progression per RECIST 1.1. However, if the participant progresses or dies immediately after 2 or more consecutive missed visits, the participant will be censored at the time of the latest evaluable assessment prior to the 2 missed visits. PFS will also be assessed by BICR for supplementary/sensitivity analysis. The measures of interest is the HR of PFS.

For more details on Secondary, Tertiary/Exploratory objectives and estimands descriptions/endpoints, see Section 3 of the protocol.

Number of Participants:

Total number of patients to be randomized globally in the study is **approximately 1100 patients**. Similarly, from **India 55 patients** are planned to be randomized in the clinical study.

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Global and India Regulatory Status of IMP: *Rilvegostomig (AZD2936) Concentrate for solution for infusion 50 mg/mL (750 mg/vial) and Durvalumab (MEDI4736) Concentrate for solution for infusion 500mg/vial (50mg/mL).*

Rilvegostomig has not been marketed or approved for clinical use by any country.

Durvalumab (MEDI4736): As of 30 April 2025, across the indications of UC, unresectable stage III NSCLC, ES-SCLC, BTC, unresectable HCC, metastatic NSCLC, endometrial cancer, resectable Stage II and III NSCLC, LS-SCLC and MIBC, durvalumab is approved in more than 100 countries including India vide permission no. BIO/IMP/18/000001 dated 01-Jun-2018.

Global Regulatory Status of Proposed Clinical Study:

The study is planned to be conducted in approximately 19 countries worldwide and following is the list participating countries: Australia, Belgium, Brazil, Canada, China, France, Germany, India, Italy, Japan, Netherlands, Poland, South Korea, Spain, Taiwan, Thailand, Turkey, United Kingdom & United States of America *For detailed information, kindly refer to section 1.9.2.2 of SUGAM application).*

We also wish to inform that, upon approval from your kind directorate we shall import the Investigational Medicinal Product from *M/s Fisher Clinical Services UK Limited, Langhurstwood Road Horsham RH12 4QD United Kingdom and Fisher Clinical Services GmbH, Zweigniederlassung Rheinfelder Niederlassungsnummer: 0001, Marie-Curie-Str. 16, D-79618 Rheinfelden (Baden)Germany* shall be used exclusively for the purpose of clinical trial and no part of it shall be diverted to the domestic market.

Based on the rationale provided above, we request your kind Directorate to grant us with the permission for the conduct of the above-mentioned Global Clinical Trial in accordance with CSP No. D702NC00001, Version 1.0 dated 08 Aug 2025 and Local CSP - Addendum 1.0 India, Version 1.0 dated 07 Oct 2025 and also issue the test license for the import of study drug at the earliest and oblige.

Thanking you,

Regards,

For AstraZeneca Pharma India Ltd.

Pranali Mohite

Electronically signed by: Pranali Mohite
Reason: I approve this document
Date: 24-Dec-2025 10:50:18 GMT+5.5

Pranali Mohite, Lead-Regulatory Affairs

VB

Enclosures:

As per SUGAM checklist