

Efficacy and Safety of the MDM2–p53 Antagonist Brigimadlin (BI 907828) in Patients with Advanced Biliary Tract Cancer: A Case Series

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Background: In patients with advanced biliary tract cancer (BTC), first-line chemotherapy plus immunotherapy has improved outcomes; however, second-line options that reflect the disease's molecular heterogeneity are still needed. One emerging target is *MDM2*, amplified in ~5–8% of BTC cases.

Methods: This is a subset analysis of two ongoing Phase Ia/Ib trials assessing patients treated with brigimadlin (BI 907828; a highly potent, oral MDM2–p53 antagonist) ± ezabenzimab (PD-1 inhibitor) ± BI 754111 (anti-LAG-3; n = 1).

Results: Results from 12 patients with BTC are shown (monotherapy: n = 6/combination: n = 6). Six patients achieved partial response (monotherapy: n = 2/combination: n = 4), four had stable disease; responses were durable. Brigimadlin had a manageable safety profile. Seven patients had dose reductions due to adverse events, but no treatment-related adverse events led to treatment discontinuation.

Conclusion: Brigimadlin demonstrated anti-tumor activity in patients with advanced *MDM2*-amplified BTC, and warrants further investigation.

Plain Language Summary: Biliary tract carcinoma (BTC) is a cancer that affects the bile ducts which are part of the digestive system. Usually, the first treatment for advanced BTC (ie cannot be removed surgically and/or has spread) is chemotherapy in combination with immunotherapy. However, if chemotherapy does not work, or stops working, there are few treatment options available in second-line. Accordingly, intensive research is ongoing to try and find effective drugs. One potential medicine, called brigimadlin (or BI 907828), is a tablet that activates a molecule in tumor cells called p53. The normal function of p53 is to kill cells when they first start to become cancerous. However, if p53 is turned off by genetic mutations, or other mechanisms, then cancer can develop. Although p53 is rarely mutated in BTC tumors, it is inactivated by another molecule called MDM2 which is usually present at abnormally high levels in BTC. Brigimadlin prevents interaction between MDM2 and p53. This activates p53 and causes the cancer to die. Two clinical trials are currently assessing brigimadlin in a range of cancers, including BTC, with the aim of identifying a safe dose that can be examined in more detail in larger trials. So far, 12 patients with BTC have been treated. The patients' tumors significantly shrank in six of these patients and remained stable in a further four patients. Side effects were as expected and could be tolerated by pausing treatment or lowering the dose. These results show that brigimadlin should be tested further in patients with advanced BTC.

Keywords: biliary tract cancer, MDM2-p53 antagonist, brigimadlin, ezabenzimab, *MDM2*, MDM2-amplified

Introduction

Biliary tract cancer (BTC) refers to several cancers of the biliary system, and covers a range of invasive adenocarcinomas, including intrahepatic cholangiocarcinoma (iCCA), extrahepatic cholangiocarcinoma, gallbladder carcinoma, and ampullary carcinoma. Cholangiocarcinoma incidence is low in high-income countries, with only around 0.35–2 cases per 100,000 people, but is up to 40 times higher in endemic regions of Thailand and China.¹ Symptoms of BTC are dependent on the location of the primary tumor and any metastases, and are usually observed at an advanced stage of the disease due to their non-specificity.¹ Until recently, the first-line standard of care for most patients with advanced BTC was gemcitabine/cisplatin. Addition of the programmed cell death-ligand 1 (PD-L1) inhibitor durvalumab to gemcitabine/cisplatin was recently approved as a first-line treatment option based on the results of the Phase III TOPAZ-1 trial. This study demonstrated that the treatment combination significantly improved overall survival (OS) versus gemcitabine/cisplatin alone.² In the Phase III KEYNOTE-966 trial, the immunochemotherapy regimen of pembrolizumab plus gemcitabine/cisplatin significantly improved OS versus chemotherapy alone, with no new safety signals; however, the difference in response rate between the two groups was not significant.³ Envafoleimab plus gemcitabine/oxaliplatin (NCT03478488; another immunochemotherapy regimen) and triplet chemotherapy regimens (NCT03768414; NCT02182778) are also currently being assessed in Phase III trials. Despite these advances, there is a lack of effective options for second and subsequent lines of treatment for patients with advanced/metastatic disease, with no clear global standard, especially for patients without targetable molecular aberrations.^{4–7}

BTC is highly heterogeneous, and selection of second-line treatment depends on the molecular characteristics of the tumor. Some patients have targetable aberrations such as fibroblast growth factor receptor (*FGFR*; 0–12.5%) or isocitrate dehydrogenase mutations (*IDH*; 0–23%).⁸ In these cases, pemigatinib, futibatinib (*FGFR2* inhibitors) or ivosidenib (*IDH* inhibitor) are approved therapies.^{9,10} Other genetic aberrations that have been identified include *TP53* mutations (44–47%), *KRAS* mutations (11–47%), *BRAF* substitutions (1–5%), and *HER2* amplification (3–16%).⁸ The molecular complexity of BTC highlights the need for comprehensive genomic characterization of tumors to help drive appropriate treatment decisions.

The E3 ubiquitin ligase mouse double minute 2 (*MDM2*) is a potential drug target in some patients with BTC. *MDM2* is an endogenous negative regulator of p53, hence aberrations of the *MDM2* gene can result in inappropriate silencing of wild-type p53, potentially leading to tumorigenesis.¹¹ *MDM2* amplification has been observed in around 5–8% of BTCs,^{12,13} with *TP53* mutations being mostly mutually exclusive.¹² Prevalence of *MDM2* amplification varies depending on the anatomical location of the tumor, ranging from 2% to 6% in iCCA,^{14,15} to 16% in ampullary carcinoma.¹⁶ Other studies have reported *MDM2* amplification in 13–14% of gallbladder cancer cases.^{17,18} *MDM2* amplifications are generally mutually exclusive to other clinically targetable alterations, including *FGFR2*-fusions, *HER2* amplifications, and *IDH1* mutations.¹² In addition, aberrant activity of *MDM2* can be caused by the loss of its negative regulator, p14ARF, due to mutations in the cyclin dependent kinase inhibitor 2A gene, which occur in around 10% of BTCs.¹⁹

Brigimadlin (BI 907828) is a highly potent, oral *MDM2*–p53 antagonist that binds to *MDM2*, leading to stabilization of p53, followed by target gene induction, cell-cycle arrest, and apoptosis in tumor cells. Brigimadlin also promotes a pro-immunogenic tumor microenvironment.²⁰ Preliminary dose-escalation results from two Phase Ia/Ib trials investigating brigimadlin as monotherapy, and in combination with ezabenlimab (a programmed cell death protein-1 [PD-1] inhibitor), demonstrated a manageable safety profile and preliminary signs of efficacy in patients with advanced solid tumors.^{21,22} In the dose-escalation part of the monotherapy trial, the maximum tolerated dose was 60 mg orally, once every 3 weeks (Q3W);²³ maximum tolerated dose was not reached in the combination trial.²² Key inclusion criteria included adult patients with *TP53* wild-type status and either *MDM2*-amplified or non-amplified tumors.

Here, we present detailed case descriptions of the first 12 patients with advanced BTC treated with brigimadlin alone, or in combination with checkpoint inhibitors, and safety data from the overall population, in these two ongoing trials.

Methods: Trial Designs of I403–0001 and I403–0002

The Phase Ia/Ib, open-label, multicenter, dose-escalation/expansion studies I403–0001 (NCT03449381) and I403–0002 (NCT03964233) assessed brigimadlin in patients with advanced solid tumors as monotherapy or combined with the PD-1 inhibitor ezabenlimab, respectively (Figure 1). Briefly, both trials had Phase Ia (dose escalation) and Phase Ib (dose expansion) parts.

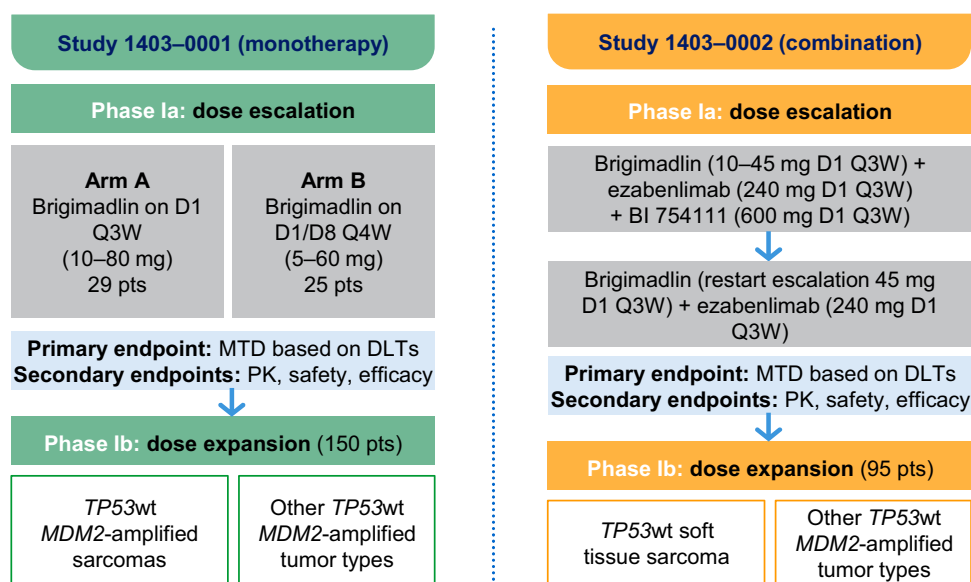


Figure 1 Trial design of brigimadlin as monotherapy (1403-0001) and in combination with ezabenlimab (1403-0002*).

Notes: *Some patients in 1403-0002 also received BI 754111.

Abbreviations: D1/8, Day 1/8; DLTs, dose-limiting toxicities; *MDM2*, murine double minute 2 homolog; MTD, maximum tolerated dose; PK, pharmacokinetics; pts, patients; Q3W, every 3 weeks; Q4W, every 4 weeks; TP53, tumor protein 53; wt, wild-type.

In 1403-0001, patients with *TP53* wild-type solid tumors were assigned to receive 10–80 mg brigimadlin either Q3W (Arm A) or on Days 1 and 8 every 4 weeks (Arm B). In 1403-0002, 10–45 mg brigimadlin was administered with 240 mg ezabenlimab (and 600 mg BI 754111 in some patients) Q3W. In the dose-expansion phase of 1403-0001, patients with wild-type *TP53*, *MDM2*-amplified tumors are being recruited into two cohorts: sarcoma (Cohort 1) or other tumor types (Cohort 2). In 1403-0002, patients with *TP53* wild-type tumors are also being recruited to two dose expansion cohorts: those with soft tissue sarcomas (Cohort 1), and those with other tumor types (Cohort 2). The Phase Ia primary endpoint for both trials is the maximum tolerated dose based on dose-limiting toxicities in Cycle 1. Secondary endpoints include pharmacokinetics, safety, and efficacy. Inclusion and exclusion criteria for both studies are largely similar. Key inclusion criteria include adult patients with an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0/1, and with adequate organ function. Key exclusion criteria include previous administration of brigimadlin or any other *MDM2*–p53 or *MDMX* (*MDM4*)–p53 antagonist, brain metastases, and history of bleeding diathesis.

Patients provided formalin-fixed paraffin-embedded (FFPE) samples to determine eligibility. Fluorescence in situ hybridization (FISH) or FoundationOne CDx (Foundation Medicine Inc.,) next-generation sequencing (NGS; 1403-0002 Phase Ia only) was used to determine *MDM2* amplification status. *TP53* mutation status was evaluated with NGS (1403-0001: local-assessment; 1403-0002: Phase Ia, FoundationOne CDx; Phase Ib, NGS Panel, Almac Sciences).

The studies were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines, were approved by local ethics committees, (National Cancer Center Hospital Institutional Review Board (IRB), Tokyo, Chuo-ku, Japan; Central IRB: Advarra IRB Maryland, USA; Local IRB: Salus IRB Texas, USA, CEIC Área 7 Hospital Clínico San Carlos de Madrid, Madrid, Spain) and all patients provided written informed consent to publish.

Results

Case Presentations

A total of 12 cases are presented, 6 from the 1403-0001 brigimadlin monotherapy trial and 6 from the 1403-0002 combination trial. The data cut-off for Patients 1–10 was December 2022; patients 11 and 12 were added at a later stage (data cut-off February 2023). An overview of cases is shown in Table 1.

Table I Patient and Disease Characteristics

Patient	Sex	Age at enrollment, years	Details of cancer	MDM2 CN	Previous treatments [best response if known]
I403–0001					
1	M	51	iCCA with liver metastases	9	7 cycles of cisplatin/gemcitabine [SD]; 3 cycles of tegafur/gimeracil/oteracil (TS-I) [SD]; 2 cycles of an unknown investigative product [PD]; Brigimadlin [PR]
2	M	51	Poorly differentiated ampullary adenocarcinoma with liver and lymph node metastases	15	Whipple surgery with lymph nodes and hepatic artery excision; Endoscopic retrograde cholangiopancreatography with stent exchange in 2019, 12 cycles of adjuvant mFOLFIRINOX; Brigimadlin [PR]
3	F	69	Biliary tree adenocarcinoma with liver metastases.	Unknown	22 cycles of cisplatin/gemcitabine; Brigimadlin [SD]
4	M	78	Moderately differentiated ampullary adenocarcinoma with liver and lymph node metastases	Unknown	Whipple procedure, 12 cycles of adjuvant FOLFOX [SD]; Fluorouracil maintenance; 39 cycles of fluorouracil/leucovorin [SD]; Brigimadlin [PD]
5	F	72	Undifferentiated ampullary carcinoma with liver and lymph node metastases.	13	FOLFIRINOX for 2 months; Gemcitabine for 2.5 months [PD]; Brigimadlin [SD]
6	M	74	Bile duct adenocarcinoma with liver and lymph node metastases.	Amplified (CN unknown)	Brigimadlin [PD]
I403–0002					
7	F	57	iCCA with liver, lung, and lymph node metastases	36	15 cycles of cisplatin/gemcitabine; TS-I; Gemcitabine; Radiotherapy for left cervical lymph nodes; Brigimadlin + ezabenlimab [PR]
8	M	66	Gallbladder adenocarcinoma with lymph node metastases	14	Gallbladder resection, hepatectomy, bile duct resection and D2 dissection, 4 cycles of adjuvant TS-I; TS-I; 7 cycles of second-line cisplatin/gemcitabine [SD]; Brigimadlin + ezabenlimab [PR]
9	M	67	iCCA with liver and lymph node metastases	7	10 cycles cisplatin/gemcitabine [PR]; Brigimadlin + ezabenlimab [PR]
10	F	56	iCCA with liver, pancreatic, and lymph node metastases	9	7 cycles of cisplatin/gemcitabine; 15 cycles of FOLFOX; Brigimadlin + ezabenlimab [SD]
11	M	59	Moderately differentiated iCCA	Amplified (CN unknown)	18 cycles of cisplatin/gemcitabine [PR]; 4 cycles of Sym021 and Sym023 [SD]; 5 cycles of FOLFOX [SD]; Brigimadlin + ezabenlimab [PR]
12	M	74	Poorly differentiated gall bladder carcinoma. Pancreatic and abdominal metastases reported at time of trial entry	Amplified (CN unknown)	Cholecystectomy, lymphadenectomy, and resection of liver segments IVB and V; Cisplatin/gemcitabine; FOLFOX; 1 cycle of irinotecan; Brigimadlin + ezabenlimab [SD]

Abbreviations: CN, copy number; F, female; FOLFIRINOX, folinic acid fluorouracil irinotecan and oxaliplatin; FOLFOX, folinic acid fluorouracil and oxaliplatin; iCCA, intrahepatic cholangiocarcinoma; M, male; MDM2, mouse double minute 2; PD, progressive disease; PR, partial response; SD, stable disease.

I403–0001 Trial (Brigimadlin Monotherapy; n = 6: All Received Brigimadlin Q3W)

Patient 1 (Japan)

A 51-year-old Asian male presented with anemia and was diagnosed with iCCA with liver metastases. Molecular analysis of the tumor demonstrated amplified *MDM2* (copy number 9) and wild-type *TP53*. The patient received three prior lines of systemic therapy: 7 cycles of cisplatin/gemcitabine, with a best response of stable disease (SD); 3 cycles of tegafur/gimeracil/oteracil (TS-1) with a best response of SD; and 2 cycles of an unknown investigative product with a best response of progressive disease (PD). The patient then received brigimadlin 80 mg Q3W on 14 December 2020, which was reduced to 45 mg Q3W during Cycle 2 due to decreased platelet and neutrophil counts (both grade 4). The patient achieved a best response of confirmed partial response (PR) by Day 22 (Figure 2A), which was still apparent on Day 360. Maximum tumor shrinkage was –73%. The patient remained on treatment for 12.0 months and discontinued due to PD. Progression-free survival (PFS) was 13.3 months. Analysis of CA19.9 blood levels demonstrated a drop from 17,000 U/mL at baseline to undetectable until Day 260 (114 U/mL). Grade ≥ 3 treatment-related adverse events (TRAEs) were grade 4 decreased platelet, neutrophil, and white blood cell counts, and grade 3 anemia and febrile neutropenia.

Patient 2 (USA)

A 51-year-old Hispanic male presented with suspected choledocholithiasis or bile duct stricture with obstructive jaundice and cholangitis. Bilirubin and aspartate transaminase (AST)/alkaline phosphatase were elevated. The patient had hypertension, hyperlipidemia, and nephrolithiasis. He was diagnosed with poorly differentiated ampullary adenocarcinoma with liver and lymph node metastases. *MDM2* was amplified (copy number 15). The patient underwent Whipple surgery with lymph nodes and hepatic artery excision, and subsequently received endoscopic retrograde cholangiopancreatography with stent exchange in 2019, followed by 12 cycles of adjuvant mFOLFIRINOX. The patient started brigimadlin 45 mg Q3W on 25 May 2021, and treatment was ongoing at the data cut-off date. The patient achieved a confirmed PR on Day 38 that was still apparent at Day 581 (Figure 2B). Maximum tumor shrinkage is currently –61%, and treatment has been administered for 19.1 months so far. No grade ≥ 3 TRAEs have been reported.

Patient 3 (Japan)

A 69-year-old Asian female presented with hypertension, hyperlipidemia, elevated AST/alkaline phosphatase, and dysesthesia. She was diagnosed with biliary tree adenocarcinoma with liver metastases. *MDM2* was reported as amplified (copy number unknown). The patient received one prior line of systemic therapy: 22 cycles of cisplatin/gemcitabine. Treatment was discontinued because of AEs. Treatment with brigimadlin was initiated on 12 February 2019 at 45 mg Q3W. Cycle 2 was delayed with a subsequent dose reduction to 30 mg Q3W due to grade 3 thrombocytopenia and grade 2 neutropenia. There was a second dose reduction to 20 mg Q3W during Cycle 4 due to grade 3 thrombocytopenia. Best response was SD (maximum tumor shrinkage: –13%) up to Day 162. Treatment was administered for 6.0 months before discontinuation due to patient withdrawal. Grade ≥ 3 TRAEs were grade 3 and 4 decreased neutrophil count, grade 3 decreased platelet count, and grade 3 decreased white blood cell count.

Patient 4 (USA)

A 78-year-old white male with a history of type 2 diabetes, hypertension, hyperlipidemia, dyspnea on exertion, and non-cardiac chest pain was diagnosed with moderately differentiated ampullary adenocarcinoma with liver and lymph node metastases. *MDM2* amplification status was unknown. The patient underwent the Whipple procedure followed by 12 cycles of adjuvant FOLFOX with a best response of SD, then fluorouracil maintenance. He later received 39 cycles of fluorouracil/leucovorin with a best response of SD. Treatment with brigimadlin was initiated on 25 May 2021 at 45 mg Q3W. Best response was PD and treatment was administered for 0.8 months. PFS was 1.3 months. The patient discontinued due to PD. No grade ≥ 3 TRAEs were reported in this patient.

Patient 5 (Poland)

A 72-year-old white female with a history of cholecystectomy and hypertension was diagnosed with undifferentiated ampullary carcinoma with liver and lymph node metastases. *MDM2* was amplified (copy number 13); *TP53* was wild-type.

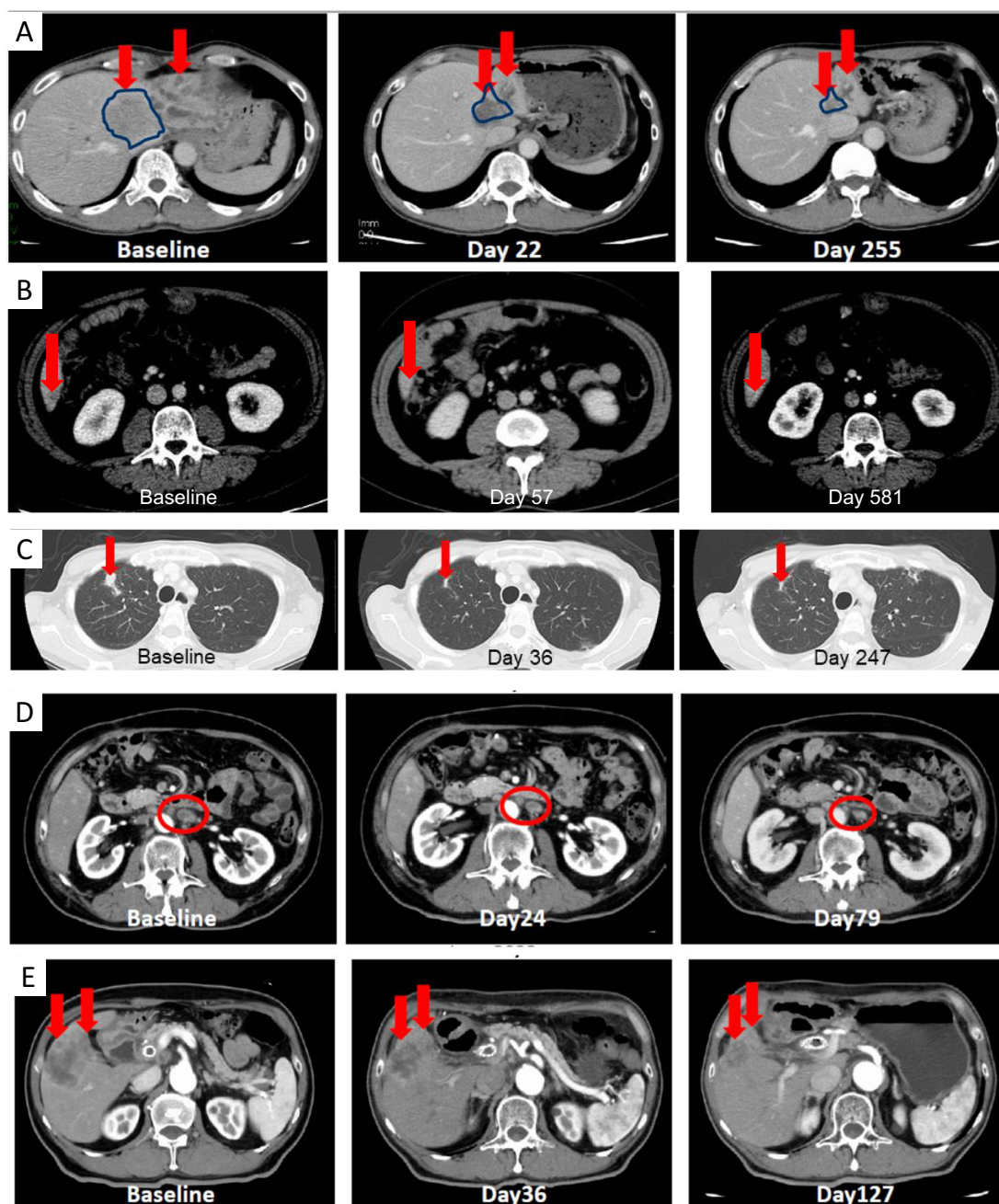


Figure 2 Computed tomography images of (A) Patient 1 at baseline, and showing a partial response at Day 22 and at Day 255 of treatment with brigimadlin monotherapy; (B) Patient 2 at baseline, showing a partial response at Day 57 and 581 of treatment with brigimadlin monotherapy; (C) Patient 7 at baseline, showing partial response at Day 36 and 247 of treatment with brigimadlin + ezabenlimab; (D) Patient 8 at baseline, showing stable disease at Day 24 and a partial response at Day 79 of treatment with brigimadlin + ezabenlimab; (E) Patient 9 at baseline, showing stable disease at Day 36 and a partial response at Day 127 of treatment with brigimadlin + ezabenlimab. Red arrows and red circles indicate lesion location. Blue lines indicate border of lesion.

The patient received first-line FOLFIRINOX for 2 months until treatment was stopped due to thrombocytopenia. Second-line treatment was gemcitabine for 2.5 months, which was discontinued due to PD. Treatment with brigimadlin was initiated in July 2022 at 45 mg Q3W, which was reduced to 30 mg during Cycle 3 due to grade 3 increased alanine transaminase and grade 2 increased AST; treatment was ongoing at the data cut-off date. Best response so far is SD, and treatment has been administered for 5.0 months. Grade ≥ 3 AEs were grade 3 neutropenia and grade 3 thrombocytopenia.

Patient 6 (Japan)

A 74-year-old Asian male with a history of anemia and thrombocytopenia was diagnosed with bile duct adenocarcinoma with liver and lymph node metastases. *MDM2* was reported as amplified (copy number unknown); no mutations were detected in *TP53*. First-line treatment with brigimadlin 45 mg Q3W was initiated on 6 July 2022. Treatment was administered for 1 day, but was suspended due to hematologic AEs. Treatment was later discontinued due to PD. PFS was 1.3 months. Grade 3/4 TRAEs were anemia and hypokalemia (both grade 3).

I403–0002 Trial (Brigimadlin + Ezabenlimab; n = 6)**Patient 7 (Japan)**

A 57-year-old Asian female with a history of arrhythmia, anemia, thrombocytopenia, and hypoalbuminemia was diagnosed with iCCA with liver, lung, and lymph node metastases. *MDM2* was amplified (copy number 36); *TP53* was wild-type. The patient received 15 cycles of cisplatin/gemcitabine, which was stopped due to toxicity. She subsequently received second-line TS-1, third-line gemcitabine, and radiotherapy for left cervical lymph nodes. Treatment with brigimadlin 30 mg and ezabenlimab 240 mg Q3W was initiated on 22 November 2021. The brigimadlin dose was reduced to 20 mg Q3W during Cycle 3 due to grade 1 thrombocytopenia and grade 2 neutropenia. The patient achieved confirmed PR up to Day 247 (Figure 2C). Treatment was administered for 8.2 months before discontinuation due to AEs. PFS was 9.6 months. Maximum tumor shrinkage was –54%. Grade 3/4 TRAEs (related to brigimadlin) were grade 4 neutropenia and grade 3 reduced white blood cell count.

Patient 8 (Japan)

A 66-year-old Asian male with a history of angina pectoris, dyslipidemia, lower leg edema, and elevated AST was diagnosed with gallbladder adenocarcinoma with lymph node metastases. *MDM2* was amplified (copy number 14). No mutations were detected in *TP53*. The patient underwent gallbladder resection, hepatectomy, bile duct resection and D2 dissection followed by 4 cycles of adjuvant TS-1. He subsequently received first-line TS-1 and 7 cycles of second-line cisplatin/gemcitabine with a best response of SD. The patient then received brigimadlin starting on 9 June 2021 at 45 mg and ezabenlimab 240 mg Q3W. Cycle 3 was delayed and the brigimadlin dose was reduced to 30 mg Q3W due to grade 3 thrombocytopenia. Best response was PR up to Day 227, with maximum tumor shrinkage of –50% (Figure 2D). Treatment was administered for 4.6 months, and then suspended due to hematologic AEs. Treatment was later discontinued due to PD. PFS was 7.9 months. Grade 3/4 TRAEs (related to brigimadlin) were grade 3 and grade 4 decreased neutrophil count, grade 3 and grade 4 thrombocytopenia, grade 3 reduced white blood cell count, grade 3 elevated AST, and grade 3 anemia.

Patient 9 (Japan)

A 67-year-old Asian male with a history of anemia and hypoalbuminemia was diagnosed with iCCA with liver and lymph node metastases. *MDM2* was amplified (copy number 7); no mutations were detected in *TP53*. The patient received 10 cycles of first-line cisplatin/gemcitabine with a best response of PR. He then received 7 cycles of second-line gemcitabine/TS-1. Treatment with brigimadlin and ezabenlimab was initiated on 28 April 2021 at 45 mg and 240 mg Q3W, respectively. Cycle 3 was delayed and the dose of brigimadlin was reduced to 30 mg Q3W due to grade 3 thrombocytopenia. The patient achieved SD on Day 36, and PR up to Day 162 (Figure 2E). The maximum tumor shrinkage was –49%. The patient was on treatment for 4.2 months; however, due to hematologic AEs the treatment was suspended, and was later discontinued due to PD. PFS was 7.6 months. Grade 3/4 TRAEs (related to brigimadlin) were decreased platelet count, anemia, and hypoxia (all grade 3). Additionally, in November 2021 the patient underwent nasobiliary drainage for cholangitis and had a central venous catheterization for pancreatitis.

Patient 10 (USA)

A 56-year-old Caucasian female presented with biliary obstruction for which a stent was fitted in 2019. She was diagnosed with iCCA with liver, pancreatic, and lymph node metastases. *MDM2* was amplified (copy number 9) and there were no *TP53* mutations. First-line treatment was 7 cycles of cisplatin/gemcitabine; second-line treatment was 15

cycles of FOLFOX. A left neck lymph node resection was undertaken in 2020. Treatment with brigimadlin 45 mg, ezabenlimab 240 mg, and BI 754111 600 mg Q3W was initiated on 29 July 2020. The best response was SD on Days 36, 110, and 148. Treatment was administered for 4.1 months before discontinuation due to physician decision, and the patient was then transferred to a hospice. PFS was 5.9 months. Grade 3/4 TRAEs (related to brigimadlin) were anemia, and decreased neutrophil and white blood cell counts (all grade 3).

Patient 11 (Spain)

A 59-year-old Caucasian male was diagnosed with moderately differentiated iCCA in February 2020. *MDM2* was amplified and there were no *TP53* mutations. The patient underwent right hepatectomy and hepatic hilum lymphadenectomy followed by adjuvant capecitabine. First-line treatment was 18 cycles of cisplatin/gemcitabine with PR as best response, second-line treatment was 4 cycles of Sym021 (targeting PD-1) and Sym023 (targeting TIM3), and third-line therapy was 5 cycles of FOLFOX; best response for second- and third-line therapy was SD. Treatment with brigimadlin 45 mg and ezabenlimab 240 mg Q3W was initiated on 21 October 2022, and was ongoing at the data cut-off date. The dose of brigimadlin was reduced to 30 mg due to grade 2 neutropenia. Liver and lymph node metastases were reported at time of trial entry. The patient achieved a confirmed PR starting on Day 48 that was still apparent at Day 127, with maximum tumor shrinkage of −39%. Treatment has been administered for 4.2 months so far. Grade 3/4 TRAEs (related to brigimadlin) were grade 3 and 4 thrombocytopenia, and grade 3 neutropenia.

Patient 12 (Spain)

A 74-year-old Asian male was diagnosed with poorly differentiated gall bladder carcinoma in February 2021. *MDM2* and *HER2* were amplified and there were no *TP53* mutations. The patient underwent cholecystectomy, lymphadenectomy, and resection of liver segments IVB and V. First-line treatment was cisplatin/gemcitabine from December 2021 to May 2022, second-line treatment was cycles of FOLFOX from May to September 2022, and third-line therapy was 1 cycle of irinotecan. Treatment with brigimadlin 45 mg and ezabenlimab 240 mg Q3W was initiated on 24 October 2022, and was ongoing at the data cut-off date. Pancreatic and abdominal metastases were reported at time of trial entry. The patient had confirmed SD starting on Day 36 that was still apparent at Day 128, with best percentage change from baseline of 5%. Treatment has been administered for 4.1 months so far. No Grade 3/4 TRAEs (related to brigimadlin) have been reported.

Summary

Patients with BTC received brigimadlin as monotherapy in 1403–0001, or in combination with ezabenlimab (plus BI 754111 in one patient) in 1403–0002. A confirmed objective response was seen in two out of six patients in the monotherapy trial (both had *MDM2*-amplified tumors), and four out of six patients in the combination trial (all four had *MDM2*-amplified tumors; Figure 3). A further four patients achieved SD: two in the monotherapy trial, and two in the combination trial. Treatment was administered for over 4 months in four of the six patients in the monotherapy trial, and in all six patients in the combination trial; four patients were still on treatment at data cut-off (Figure 4).

In these 12 patients with BTC, the most common grade ≥ 3 TRAEs were neutropenia, thrombocytopenia, anemia, and reduced white blood cell count. TRAEs were managed by appropriate treatment delays and/or dose reductions; there were no treatment discontinuations due to TRAEs. These findings are consistent with the safety profile of brigimadlin in the overall patient populations in the 1403–0001 and 1403–0002 trials (summarized in Table 2; data cut-off December 2022). Briefly, in the 1403–0001 trial, 110 patients had been treated with brigimadlin Q3W, of whom 102 (92.7%) experienced at least one TRAE. Grade ≥ 3 TRAEs were experienced by 49 (44.5%) patients, most commonly thrombocytopenia ($n = 26$, 23.6%), neutropenia ($n = 24$, 21.8%), and leukopenia ($n = 12$, 10.9%). AEs leading to dose reduction or discontinuation occurred in 32 and 6 (29.1% and 5.5%) patients, respectively. In the 1403–0002 trial, 42 patients had been treated with brigimadlin in combination with ezabenlimab, of whom 39 (92.9%) experienced at least one TRAE. Grade ≥ 3 TRAEs were experienced by 21 (50.0%) patients, most commonly thrombocytopenia and neutropenia (both $n = 8$, 19.0%), and leukopenia ($n = 7$, 16.7%). AEs leading to dose reduction or discontinuation

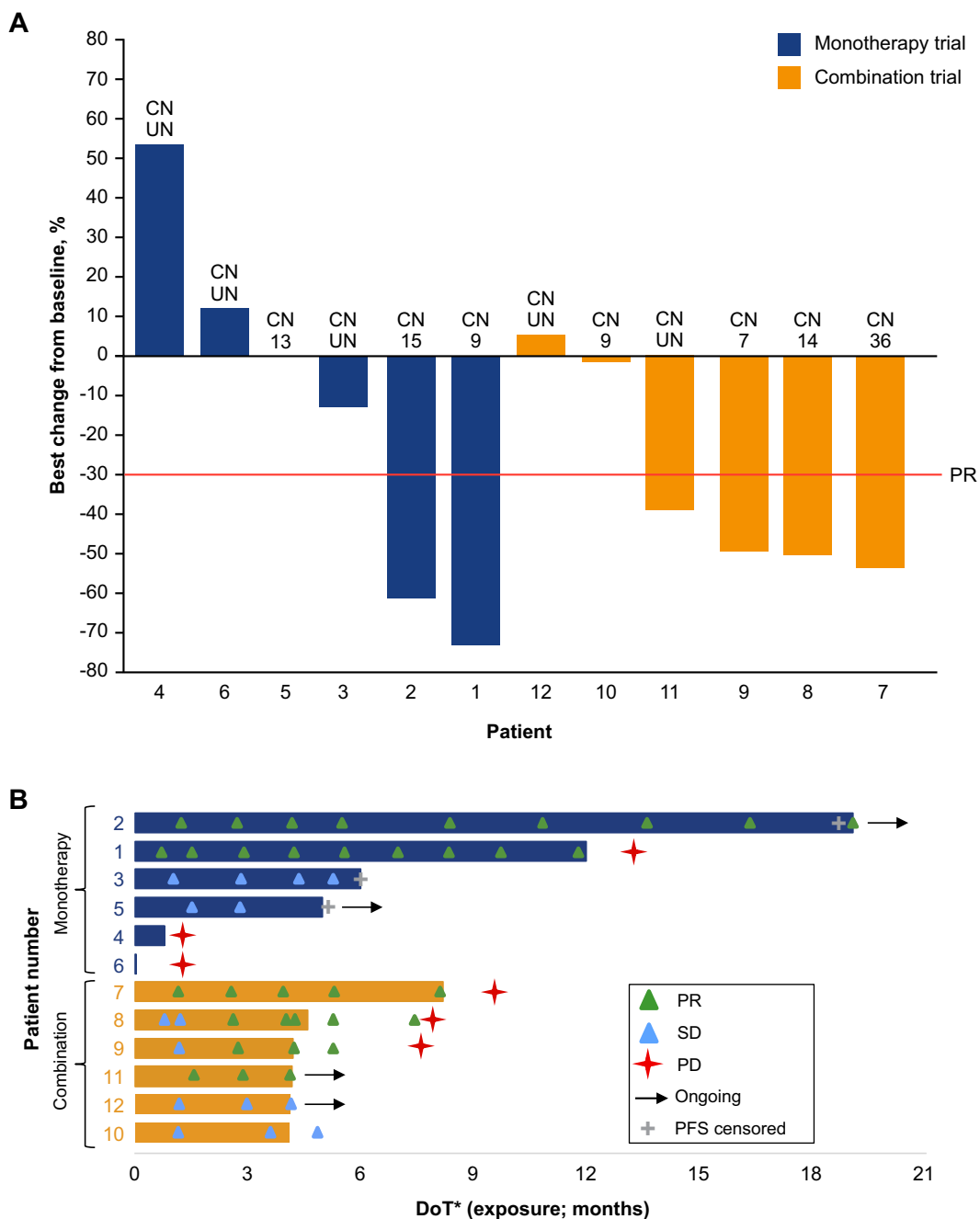


Figure 3 (A) tumor shrinkage, and (B) swimmer plot of patients with biliary tract cancer treated with brigimadlin monotherapy or in combination with ezabenlimab. **Notes:** *Time from first to last drug administration (D1 Q3W); dose could be delayed due to AE up to 63 days. Patient 10 also received BI 754111. **Abbreviations:** AE, adverse event; D1, Day 1; Q3W, every 3 weeks.

occurred in 11 and 2 (26.2% and 4.8%) patients, respectively. An infographic summary of the patient cases presented here can be found in [Supplementary Figure 1](#).

Discussion

In this sub-analysis of two Phase Ia/Ib trials, brigimadlin alone or in combination with ezabenlimab demonstrated encouraging clinical efficacy in patients with *MDM2*-amplified BTC. Responses were seen in patients treated in both trials, which were mostly durable. Overall, brigimadlin had a manageable safety profile in patients with BTC. The most common grade 3/4 TRAEs included neutropenia, thrombocytopenia, anemia, and reduced white blood cell count. Seven

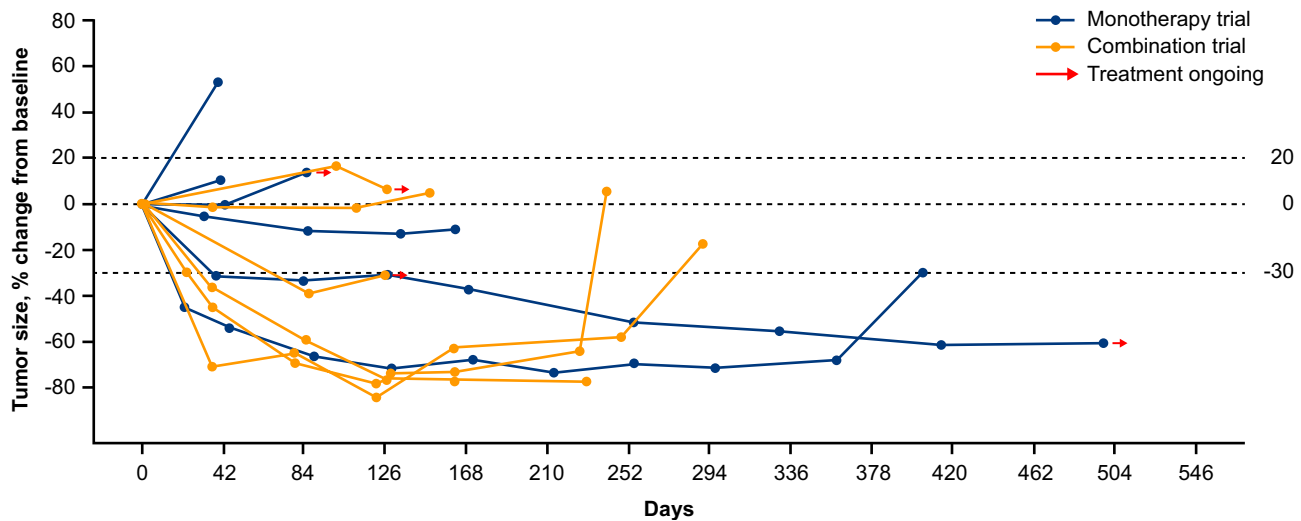


Figure 4 Tumor responses in patients with biliary tract cancer treated with brigimadlin monotherapy or in combination with ezabenlimab. Patient 10 also received BI 754111.

of 12 patients had dose reductions due to AEs, and were able to continue on treatment afterwards. No TRAEs led to treatment discontinuation. These results are similar to those observed in the overall populations of patients treated in the 1403–0001 and 1403–0002 trials. To the best of our knowledge, this is the first description of patients with BTC who

Table 2 Adverse Events in the Overall Patient Populations of Trials 1403–0001 (Brigimadlin Monotherapy) and 1403–0002 (Combination with Ezabenlimab)

	1403–0001 (N = 110)		1403–0002 (N = 42)	
n (%)	Any	Grade ≥ 3	Any	Grade ≥ 3
Any AE	107 (97.3)	65 (59.1)	41 (97.6)	27 (64.3)
Serious AEs	29 (26.4)	27 (24.5)	16 (38.1)	12 (28.6)
Any AE leading to dose reduction	32 (29.1)	21 (19.1)	11 (26.2)	9 (21.4)
Any AE leading to treatment discontinuation	6 (5.5)	4 (3.6)	2 (4.8)	1 (2.4)
Any TRAE	102 (92.7)	49 (44.5)	39 (92.9)	21 (50.0)
Most common TRAEs (> 20% of patients)				
Nausea	80 (72.7)	7 (6.4)	34 (81.0)	2 (4.8)
Fatigue	61 (55.5)	3 (2.7)	17 (40.5)	1 (2.4)
Thrombocytopenia	48 (43.6)	26 (23.6)	17 (40.5)	8 (19.0)
Vomiting	45 (40.9)	1 (0.9)	20 (47.6)	0
Decreased appetite	42 (38.2)	1 (0.9)	23 (54.8)	0
Neutropenia	40 (36.4)	24 (21.8)	14 (33.3)	8 (19.0)
Diarrhea	29 (26.4)	0	13 (31.0)	0
Anemia	29 (26.4)	11 (10.0)	12 (28.6)	5 (11.9)
Dysgeusia	23 (20.9)	0	5 (11.9)	0
Leukopenia	23 (20.9)	12 (10.9)	13 (31.0)	7 (16.7)

Notes: Adverse events reported at data cut-off of December 2022; both trials are ongoing.
Abbreviations: AE, adverse event; TRAE, treatment-related AE.

have been treated with an MDM2–p53 antagonist. These results suggest that MDM2–p53 inhibition warrants further investigation in patients with BTC with *MDM2* amplification and wild-type *TP53*.

The prevalence of *MDM2* amplification in patients with BTC is currently uncertain owing to a paucity of data. In the TOPAZ-1 trial, 8.2% of the biomarker-evaluable population had *MDM2*-amplified tumors.¹³ Importantly, *MDM2* amplification in BTC generally appears to be mutually exclusive to other targetable aberrations, such as *FGF2* and *IDH* mutations.¹⁵ Therefore, patients with *MDM2*-amplified BTC represent a subgroup of patients for whom effective treatment options are lacking.¹² Furthermore, *MDM2* amplification has been reported as a negative prognostic factor in patients with BTC.^{17,19,24–26} As MDM2 is transcriptionally transactivated and strictly regulated by p53, *MDM2* is only expected to be overexpressed in *TP53* wild-type BTC. The function of wild-type p53 may therefore be suppressed by *MDM2* overexpression, which potentially could lead to aggressive tumor behavior. *MDM2* overexpression has been significantly correlated with an increased presence of metastases, more advanced tumor stage, and lower OS.^{24,25} Given the role of MDM2 in the pathogenesis of BTC, and the emergence of potential MDM2-targeted treatment options, it is important that further studies are undertaken to establish its prevalence in BTC. In the clinic, diagnostic tests including FISH and NGS tests such as FoundationOne Cdx can be used to detect *MDM2* amplification.^{17,27,28} Analysis of *MDM2* overexpression or amplification should be included in molecular analysis of BTC tumors.

Other MDM2–p53 antagonists are currently in development for the treatment of patients with solid tumors, including alrizomadlin, ASTX295, navtemadlin, and siremadlin.^{29–32} Until recently, the most advanced MDM2–p53 antagonist in terms of clinical development was milademetan, which was being investigated versus trabectedin in patients with dedifferentiated liposarcoma in a randomized, multicenter, open-label, Phase III trial (NCT04979442; MANTRA). However, enrollment to MANTRA-2, and plans for Phase I/II combination trials, have recently been suspended (May 2023) after the primary endpoint was not met in the MANTRA trial (median PFS: 3.6 months vs 2.2 months; HR: 0.89).^{33,34} The remaining compounds are either at Phase I or Phase II stage and are predominantly being investigated in combination with other therapies. Of note, many of the TRAEs observed in this study, including thrombocytopenia, neutropenia, anemia, and nausea, have been reported in patients treated with other MDM2–p53 antagonists, suggesting that they are class-related. These AEs are manageable, and rarely lead to treatment discontinuation.²⁹

The clinical development of brigimadlin in patients with *MDM2*-amplified BTC is ongoing. Brightline-2 (NCT05512377) is a Phase IIa/IIb, open-label, single-arm, multicenter trial of brigimadlin in an estimated 100 patients for whom previous treatment was not successful, or for whom no approved treatment exists. The aims are to demonstrate the efficacy, safety, and tolerability of brigimadlin in patients with *MDM2*-amplified BTC, and other solid tumors. Patients must have locally advanced/metastatic, *MDM2*-amplified, *TP53* wild-type BTC, or pancreatic ductal adenocarcinoma. The primary endpoint is objective response, and secondary endpoints include duration of objective response, PFS, OS, and safety. Key inclusion criteria are as follows: adult patients (≥ 18 years old); *MDM2* amplification (copy number ≥ 8) and *TP53* wild-type status; ≥ 1 measurable target lesion (Response Evaluation Criteria In Solid Tumors v1.1); ECOG PS of 0/1; and adequate organ function. Key exclusion criteria are as follows: previous treatment with an MDM2/4–p53 antagonist; active bleeding; significant risk of hemorrhage or current bleeding disorder; major surgery performed ≤ 4 weeks prior to start of trial treatment or planned ≤ 6 months after screening; clinically significant previous or concomitant malignancies in the opinion of the investigator affecting the efficacy and/or outcome of the trial; and currently enrolled in another investigational device or drug trial. Recruitment is ongoing.

Conclusion

In conclusion, brigimadlin alone or in combination with ezabenlimab showed promising efficacy and a manageable safety profile in patients with BTC, including in those with *MDM2*-amplified tumors. Further assessment in this patient population is warranted, and is ongoing in trials such as Brightline-2. Given the emergence of *MDM2* amplification as a potential drug target, patients with BTC should be routinely tested for *MDM2* amplification, along with other genetic aberrations.

Data Sharing Statement

To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the ICMJE criteria, Boehringer Ingelheim grants all external authors access to clinical study data. In adherence with the

Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data, typically, one year after the approval has been granted by major Regulatory Authorities or after termination of the development program. Researchers should use the <https://vivli.org/> link to request access to study data and visit <https://www.mystudywindow.com/msw/datasharing> for further information.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Author Disclosures

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