HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TIBSOVO safely and effectively. See full prescribing information for TIBSOVO.

TIBSOVO® (ivosidenib tablets), for oral use
Initial U.S. Approval: 2018

WARNING: DIFFERENTIATION SYNDROME IN AML

See full prescribing information for complete boxed warning.

Patients treated with TIBSOVO have experienced symptoms of differentiation syndrome, which can be fatal. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution (5.1, 6.1).

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.1)	5/2022
Indications and Usage (1.3)	8/2021
Dosage and Administration (2.2)	5/2022

----------INDICATIONS AND USAGE----------

TIBSOVO is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for patients with a susceptible IDH1 mutation as detected by an FDA-approved test with:

Newly Diagnosed Acute Myeloid Leukemia (AML)

- In combination with azacitidine or as monotherapy for the treatment of newly diagnosed AML in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy (1.1).

Relapsed or refractory AML

- For the treatment of adult patients with relapsed or refractory AML (1.2).

Locally Advanced or Metastatic Cholangiocarcinoma

- For the treatment of adult patients with locally advanced or metastatic cholangiocarcinoma who have been previously treated (1.3).

----------DOSAGE AND ADMINISTRATION----------

500 mg orally once daily with or without food until disease progression or unacceptable toxicity (2.2). Avoid a high-fat meal.

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 250 mg (3).

----------CONTRAINDICATIONS----------

None (4).

----------WARNINGS AND PRECAUTIONS----------

- QTc Interval Prolongation: Monitor electrocardiograms and electrolytes. If QTc interval prolongation occurs, dose reduce or withhold, then resume dose or permanently discontinue TIBSOVO (2.3, 5.2).
- Guillain-Barré Syndrome: Monitor patients for signs and symptoms of new motor and/or sensory findings. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome (2.3, 5.3).

----------ADVERSE REACTIONS----------

The most common adverse reactions including laboratory abnormalities (≥25%) in patients with AML are leukocytes decreased, diarrhea, hemoglobin decreased, platelets decreased, glucose increased, fatigue, alkaline phosphatase increased, edema, potassium decreased, nausea, vomiting, phosphate decreased, decreased appetite, sodium decreased, leukocytosis, magnesium decreased, aspartate aminotransferase increased, arthralgia, dyspnea, uric acid increased, abdominal pain, creatinine increased, mucositis, rash, electrocardiogram QT prolonged, differentiation syndrome, calcium decreased, neutrophils decreased, and myalgia (6.1).

The most common adverse reactions (≥15%) in patients with cholangiocarcinoma are fatigue, nausea, abdominal pain, diarrhea, cough, decreased appetite, ascites, vomiting, anemia, and rash (6.1).

The most common laboratory abnormalities (≥10%) in patients with cholangiocarcinoma are hemoglobin decreased, aspartate aminotransferase increased, and bilirubin increased (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Servier Pharmaceuticals at 1-800-807-6124 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong or Moderate CYP3A4 Inhibitors: Reduce TIBSOVO dose with strong CYP3A4 inhibitors. Monitor patients for increased risk of QTc interval prolongation (2.4, 5.2, 7.1, 12.3).
- Strong CYP3A4 Inducers: Avoid concomitant use with TIBSOVO (7.1, 12.3).
- Sensitive CYP3A4 substrates: Avoid concomitant use with TIBSOVO (7.2, 12.3).
- QTc Prolonging Drugs: Avoid concomitant use with TIBSOVO. If co-administration is unavoidable, monitor patients for increased risk of QTc interval prolongation (5.2, 7.1).

----------USE IN SPECIFIC POPULATIONS----------

Lactation: Advise women not to breastfeed (8.2).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 5/2022

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: DIFFERENTIATION SYNDROME IN AML

Patients treated with TIBSOVO have experienced symptoms of differentiation syndrome, which can be fatal. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution *[see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]*.

1. INDICATIONS AND USAGE

1.1 Newly Diagnosed Acute Myeloid Leukemia

TIBSOVO is indicated in combination with azacitidine or as monotherapy for the treatment of newly diagnosed acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test in adults 75 years or older, or who have comorbidities that preclude use of intensive induction chemotherapy *[see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.1)]*.

1.2 Relapsed or Refractory Acute Myeloid Leukemia

TIBSOVO is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test *[see Dosage and Administration (2.1), Clinical Pharmacology (12.1) and Clinical Studies (14.2)]*.

1.3 Locally Advanced or Metastatic Cholangiocarcinoma

TIBSOVO is indicated for the treatment of adult patients with previously treated, locally advanced or metastatic cholangiocarcinoma with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test *[see Dosage and Administration (2.1), Clinical Pharmacology (12.1), and Clinical Studies (14.3)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Acute Myeloid Leukemia

Select patients for the treatment of AML with TIBSOVO based on the presence of IDH1 mutations in the blood or bone marrow *[see Clinical Studies (14.1)]*. Patients with AML without IDH1 mutations at diagnosis should be retested at relapse because a mutation in IDH1 may emerge during treatment and at relapse.

Locally Advanced or Metastatic Cholangiocarcinoma

Select patients for the treatment of locally advanced or metastatic cholangiocarcinoma with

TIBSOVO based on the presence of IDH1 mutations *[see Clinical Studies (14.3)]*.

Information on FDA-approved tests for the detection of IDH1 mutations in AML and cholangiocarcinoma is available at http://www.fda.gov/CompanionDiagnostics.

2.2 Recommended Dosage

Newly Diagnosed AML (Combination Regimen)

The recommended dosage of TIBSOVO is 500 mg taken orally once daily until disease progression or unacceptable toxicity. Start TIBSOVO administration on Cycle 1 Day 1 in combination with azacitidine 75 mg/m^2 subcutaneously or intravenously once daily on Days 1-7 (or Days 1-5 and 8-9) of each 28-day cycle *[see Clinical Studies (14.1)]*. Refer to the Prescribing Information for azacitidine for additional dosing information.

For patients without disease progression or unacceptable toxicity, continue TIBSOVO, in combination with azacitidine, for a minimum of 6 months to allow time for clinical response.

Newly Diagnosed AML and Relapsed or Refractory AML (Monotherapy Regimen)

The recommended dosage of TIBSOVO is 500 mg taken orally once daily until disease progression or unacceptable toxicity *[see Clinical Studies (14.1 and 14.2)]*.

For patients without disease progression or unacceptable toxicity, continue TIBSOVO for a minimum of 6 months to allow time for clinical response.

Cholangiocarcinoma

The recommended dosage of TIBSOVO is 500 mg taken orally once daily until disease progression or unacceptable toxicity [see Clinical Studies (14.3)].

Administer TIBSOVO with or without food. Do not administer TIBSOVO with a high-fat meal because of an increase in ivosidenib concentration *[see Warnings and Precautions (5.2) and Clinical Pharmacology (12.3)]*. Do not split, crush, or chew TIBSOVO tablets. Administer TIBSOVO tablets orally about the same time each day. If a dose of TIBSOVO is vomited, do not administer a replacement dose; wait until the next scheduled dose is due. If a dose of TIBSOVO is missed or not taken at the usual time, administer the dose as soon as possible and at least 12 hours prior to the next scheduled dose. Return to the normal schedule the following day. Do not administer 2 doses within 12 hours.

2.3 Monitoring and Dosage Modifications for Toxicities

Obtain an electrocardiogram (ECG) prior to treatment initiation. Monitor ECGs at least once weekly for the first 3 weeks of therapy and then at least once monthly for the duration of therapy. Manage any abnormalities promptly *[see Adverse Reactions (6.1)]*.

Interrupt dosing or reduce dose for toxicities. See Table 1 for dose modification guidelines.

Table 1: Recommended Dosage Modifications for TIBSOVO

Adverse Reactions	Recommended Action
• Differentiation syndrome	• If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a

Adverse Reactions	Recommended Action
	minimum of 3 days *[see Warnings and Precautions (5.1)]*. • Interrupt TIBSOVO if severe signs and/or symptoms persist for more than 48 hours after initiation of systemic corticosteroids *[see Warnings and Precautions (5.1)]*. • Resume TIBSOVO when signs and symptoms improve to Grade 2* or lower.
• Noninfectious leukocytosis (white blood cell [WBC] count greater than 25 x 10^9/L or an absolute increase in total WBC of greater than 15 x 10^9/L from baseline)	• Initiate treatment with hydroxyurea, as per standard institutional practices, and leukapheresis if clinically indicated. • Taper hydroxyurea only after leukocytosis improves or resolves. • Interrupt TIBSOVO if leukocytosis is not improved with hydroxyurea, and then resume TIBSOVO at 500 mg daily when leukocytosis has resolved.
• QTc interval greater than 480 msec to 500 msec	• Monitor and supplement electrolyte levels as clinically indicated *[see Warnings and Precautions (5.2)]*. • Review and adjust concomitant medications with known QTc interval-prolonging effects *[see Drug Interactions (7.1)]*. • Interrupt TIBSOVO. • Restart TIBSOVO at 500 mg once daily after the QTc interval returns to less than or equal to 480 msec. • Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation.
• QTc interval greater than 500 msec	• Monitor and supplement electrolyte levels as clinically indicated *[see Warnings and Precautions (5.2)]*. • Review and adjust concomitant medications with known QTc interval-prolonging effects *[see Drug Interactions (7.1)]*. • Interrupt TIBSOVO. • Resume TIBSOVO at a reduced dose of 250 mg once daily when QTc interval returns to within 30 msec of baseline or less than or equal to 480 msec. • Monitor ECGs at least weekly for 2 weeks following resolution of QTc prolongation. • Consider re-escalating the dose of TIBSOVO to 500 mg daily if an alternative etiology for QTc prolongation can be identified.

Adverse Reactions	Recommended Action
• QTc interval prolongation with signs/symptoms of life-threatening arrhythmia	• Discontinue TIBSOVO permanently *[see Warnings and Precautions (5.2)]*.
• Guillain-Barré syndrome	• Discontinue TIBSOVO permanently *[see Warnings and Precautions (5.3)]*.
• Other Grade 3* adverse reactions	*AML monotherapy*: • Interrupt TIBSOVO until toxicity resolves to Grade 2* or lower. • Resume TIBSOVO at 250 mg once daily; may increase to 500 mg once daily if toxicities resolve to Grade 1* or lower. • If Grade 3* or higher toxicity recurs, discontinue TIBSOVO. *AML in combination with azacitidine, Cholangiocarcinoma*: • Interrupt TIBSOVO until toxicity resolves to Grade 1* or lower, or baseline, then resume at 500 mg daily (Grade 3 toxicity) or 250 mg daily (Grade 4 toxicity). • If Grade 3 toxicity recurs (a second time), reduce TIBSOVO dose to 250 mg daily until the toxicity resolves, then resume 500 mg daily. • If Grade 3 toxicity recurs (a third time), or Grade 4 toxicity recurs, discontinue TIBSOVO.

*Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

Patients with Acute Myeloid Leukemia

Assess blood counts and blood chemistries prior to the initiation of TIBSOVO, at least once weekly for the first month, once every other week for the second month, and once monthly for the duration of therapy. Monitor blood creatine phosphokinase weekly for the first month of therapy.

2.4 Dosage Modification for Use with Strong CYP3A4 Inhibitors

If a strong CYP3A4 inhibitor must be coadministered, reduce the TIBSOVO dose to 250 mg once daily. If the strong inhibitor is discontinued, increase the TIBSOVO dose (after at least 5 half-lives of the strong CYP3A4 inhibitor) to the recommended dose of 500 mg once daily.

3 DOSAGE FORMS AND STRENGTHS

Tablets: 250 mg as a blue oval-shaped film-coated tablet debossed “IVO” on one side and “250” on the other side.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Differentiation Syndrome in AML

In the combination study AG120-C-009, 15% (11/71) patients with newly diagnosed AML treated with TIBSOVO plus azacitidine experienced differentiation syndrome *[see Adverse Reactions (6.1)]*. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal. Symptoms of differentiation syndrome in patients treated with TIBSOVO included noninfectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome and creatinine increased. Of the 11 patients with newly diagnosed AML who experienced differentiation syndrome with TIBSOVO plus azacitidine 8 (73%) recovered. Differentiation syndrome occurred as early as 3 days after start of therapy and during the first month on treatment.

In the monotherapy clinical trial AG120-C-001, 25% (7/28) of patients with newly diagnosed AML and 19% (34/179) of patients with relapsed or refractory AML treated with TIBSOVO experienced differentiation syndrome *[see Adverse Reactions (6.1)]*. Of the 7 patients with newly diagnosed AML who experienced differentiation syndrome, 6 (86%) patients recovered. Of the 34 patients with relapsed or refractory AML who experienced differentiation syndrome, 27 (79%) patients recovered after treatment or after dose interruption of TIBSOVO. Differentiation syndrome occurred as early as 1 day and up to 3 months after TIBSOVO initiation and has been observed with or without concomitant leukocytosis.

If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement *[see Dosage and Administration (2.3)]*. If concomitant noninfectious leukocytosis is observed, initiate treatment with hydroxyurea or leukapheresis, as clinically indicated. Taper corticosteroids and hydroxyurea after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxyurea treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt TIBSOVO until signs and symptoms are no longer severe *[see Dosage and Administration (2.3)]*.

5.2 QTc Interval Prolongation

Patients treated with TIBSOVO can develop QT (QTc) prolongation *[see Clinical Pharmacology (12.2)]* and ventricular arrhythmias.

Of the 71 patients with newly diagnosed AML treated with TIBSOVO in combination with azacitidine in the clinical trial (Study AG120-C-009), 10 (14%) were found to have a heart-rate corrected QT interval (using Fridericia's method) (QTcF) greater than 500 msec and 15 out of 69 (22%) had an increase from baseline QTcF greater than 60 msec *[see Adverse Reactions (6.1)]*. The clinical trial excluded patients with a QTcF $\geq$ 470 msec or other factors that increased the risk of QT prolongation or arrhythmic events (e.g. NYHA Class III or IV congestive heart failure, hypokalemia, family history of long QT interval syndrome).

Of the 258 patients with hematological malignancies treated with TIBSOVO monotherapy in the clinical trial (AG120-C-001), 9% were found to have a QTc interval greater than 500 msec and

14% of patients had an increase from baseline QTc greater than 60 msec *[see Adverse Reactions (6.1)]*. One patient developed ventricular fibrillation attributed to TIBSOVO. The clinical trial excluded patients with baseline QTc of ≥ 450 msec (unless the QTc ≥ 450 msec was due to a pre-existing bundle branch block) or with a history of long QT syndrome or uncontrolled or significant cardiovascular disease.

Of the 123 patients with cholangiocarcinoma treated with TIBSOVO in the clinical trial (Study AG120-C-005), 2% were found to have a QTc interval greater than 500 msec. and 5% of patients had an increase from baseline QTc greater than 60 msec *[see Adverse Reactions (6.1)]*. The clinical trial excluded patients with a heart-rate corrected QT interval (using Fridericia's formula) (QTcF) ≥ 450 msec or other factors that increased the risk of QT prolongation or arrhythmic events (e.g., heart failure, hypokalemia, family history of long QT interval syndrome).

Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (e.g., anti-arrhythmic medicines, fluoroquinolones, triazole anti-fungals, 5-HT_3 receptor antagonists) and CYP3A4 inhibitors may increase the risk of QTc interval prolongation *[see Drug Interactions (7.1), Clinical Pharmacology (12.2)].* Conduct monitoring of electrocardiograms (ECGs) and electrolytes *[see Dosage and Administration (2.3)]*.

In patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary.

Interrupt TIBSOVO if QTc increases to greater than 480 msec and less than 500 msec. Interrupt and reduce TIBSOVO if QTc increases to greater than 500 msec. Permanently discontinue TIBSOVO in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia *[See Dosage and Administration (2.3)]*.

5.3 Guillain-Barré Syndrome

Guillain-Barré syndrome can develop in patients treated with TIBSOVO. Guillain-Barré syndrome occurred in <1% (2/258) of patients treated with TIBSOVO in study AG120-C-001 *[see Adverse Reactions (6.1)]*.

Monitor patients taking TIBSOVO for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome *[see Dosage and Administration (2.3)].*

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Differentiation Syndrome in AML *[see Warnings and Precautions (5.1)]*
- QTc Interval Prolongation *[see Warnings and Precautions (5.2)]*
- Guillain-Barré Syndrome *[see Warnings and Precautions (5.3)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Acute Myeloid Leukemia

In AML, the safety population reflects exposure to TIBSOVO at 500 mg daily in combination with azacitidine or as monotherapy in patients in Studies AG120-C-009 (N=71) and AG120-C-001 (N=213), respectively *[see Clinical Studies (14.1 and 14.2)]*. In this safety population, the most common adverse reactions including laboratory abnormalities (≥ 25% in either trial) were leukocytes decreased, diarrhea, hemoglobin decreased, platelets decreased, glucose increased, fatigue, alkaline phosphatase increased, edema, potassium decreased, nausea, vomiting, phosphatase decreased, decreased appetite, sodium decreased, leukocytosis, magnesium decreased, aspartate aminotransferase increased, arthralgia, dyspnea, uric acid increased, abdominal pain, creatinine increased, mucositis, rash, electrocardiogram QT prolonged, differentiation syndrome, calcium decreased, neutrophils decreased, and myalgia.

Newly Diagnosed AML

TIBSOVO in Combination with Azacitidine

The safety of TIBSOVO was evaluated in AML patients treated in combination with azacitidine, in Study AG120-C-009 *[see Clinical Studies (14.1)]*. Patients received at least one dose of either TIBSOVO 500 mg daily (N=71) or placebo (N=73). Among patients who received TIBSOVO in combination with azacitidine, the median duration of exposure to TIBSOVO was 6 months (range 0 to 33 months). 34 patients (48%) were exposed to TIBSOVO for at least 6 months and 22 patients (31%) were exposed for at least 1 year.

Common (≥ 5%) serious adverse reactions in patients who received TIBSOVO in combination with azacitidine included differentiation syndrome (8%).

Fatal adverse reactions occurred in 4% of patients who received TIBSOVO in combination with azacitidine, due to differentiation syndrome (3%) and one case of cerebral ischemia.

Adverse reactions leading to discontinuation of TIBSOVO in ≥2% of patients were differentiation syndrome (3%) and pulmonary embolism (3%).

The most common (>5%) adverse reactions leading to dose interruption of TIBSOVO were neutropenia (25%), electrocardiogram QT prolonged (7%), and thrombocytopenia (7%).

Adverse reactions leading to dose reduction of TIBSOVO included electrocardiogram QT prolonged (8%), neutropenia (8%), and thrombocytopenia (1%).

The most common adverse reactions and laboratory abnormalities observed in Study AG120-C-009 are shown in Tables 2 and 3.

Table 2: Adverse Reactions (≥10%) in Patients with AML Who Received TIBSOVO + azacitidine with a Difference Between Arms of ≥ 2% Compared with Placebo + azacitidine in AG120-C-009

	TIBSOVO + Azacitidine N=71		Placebo + Azacitidine N=73	
Body System Adverse Reaction	**All Grades n (%)**	**Grade ≥3 n (%)**	**All Grades n (%)**	**Grade ≥3 n (%)**
Gastrointestinal disorders				
Nausea	30 (42)	2 (3)	28 (38)	3 (4)
Vomiting[1]	29 (41)	0	20 (27)	1 (1)
Investigations				
Electrocardiogram QT prolonged	14 (20)	7 (10)	5 (7)	2 (3)
Psychiatric Disorders				
Insomnia	13 (18)	1 (1)	9 (12)	0
Blood system and lymphatic system disorders				
Differentiation Syndrome[2]	11 (15)	7 (10)	6 (8)	6 (8)
Leukocytosis[3]	9 (13)	0	1 (1)	0
Vascular disorders				
Hematoma[4]	11 (15)	0	3 (4)	0
Hypertension[5]	9 (13)	3 (4)	6 (8)	4 (5)
Musculoskeletal and connective tissue disorders				
Arthralgia[6]	21 (30)	3 (4)	6 (8)	1 (1)
Respiratory, thoracic and mediastinal disorders				
Dyspnea[7]	14 (20)	2 (3)	11 (15)	4 (5)
Nervous system disorders				
Headache	8 (11)	0	2 (3)	0

[1] Grouped term includes vomiting and retching.
[2] Differentiation syndrome can be associated with other commonly reported events such as peripheral edema, leukocytosis, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonia, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased.
[3] Grouped term includes leukocytosis, white blood cell count increased.
[4] Grouped term includes hematoma, eye hematoma, catheter sire hematoma, oral mucosa hematoma, spontaneous hematoma, application site hematoma, injection site hematoma, periorbital hematoma.
[5] Grouped term includes blood pressure increased, essential hypertension, and hypertension.
[6] Grouped term includes pain in extremity, arthralgia, back pain, musculoskeletal stiffness, cancer pain, and neck pain.
[7] Grouped term includes dyspnea, dyspnea exertional, hypoxia, respiration failure.

Table 3: Select Laboratory Abnormalities[1, 2] (≥10%) That Worsened from Baseline in Patients with AML Who Received TIBSOVO + azacitidine in AG120-C-009

	TIBSOVO + Azacitidine N=71		Placebo + Azacitidine N=73	
Parameter	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Hematology Parameters				
Leukocytes decreased	46 (65)	39 (55)	47 (64)	42 (58)
Platelets decreased	41 (58)	30 (42)	52 (71)	42 (58)
Hemoglobin decreased	40 (56)	33 (46)	48 (66)	42 (58)
Neutrophils decreased	18 (25)	16 (23)	25 (35)	23 (32)
Lymphocytes increased	17 (24)	1 (1)	7 (10)	1 (1)

	TIBSOVO + Azacitidine N=71		Placebo + Azacitidine N=73	
Parameter	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Chemistry Parameters				
Glucose increased	40 (56)	9 (13)	34 (47)	8 (11)
Phosphate decreased	29 (41)	7 (10)	25 (34)	9 (12)
Aspartate Aminotransferase increased	26 (37)	0	17 (23)	0
Magnesium decreased	25 (35)	0	19 (26)	0
Alkaline Phosphatase increased	23 (32)	0	21 (29)	0
Potassium increased	17 (24)	2 (3)	9 (12)	1 (1)

[1] Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or if baseline is unknown.
[2] The denominator used to calculate percentages is the number of treated subjects who can be evaluated for CTCAE criteria for each parameter in each arm.

TIBSOVO Monotherapy

The safety profile of single-agent TIBSOVO was studied in 28 adults with newly diagnosed AML treated with 500 mg daily *[see Clinical Studies (14.1)]*. The median duration of exposure to TIBSOVO was 4.3 months (range 0.3 to 40.9 months). Ten patients (36%) were exposed to TIBSOVO for at least 6 months and 6 patients (21%) were exposed for at least 1 year.

Common (≥ 5%) serious adverse reactions included differentiation syndrome (18%), electrocardiogram QT prolonged (7%), and fatigue (7%). There was one case of posterior reversible encephalopathy syndrome (PRES).

Common (≥ 10%) adverse reactions leading to dose interruption included electrocardiogram QT prolonged (14%) and differentiation syndrome (11%). Two (7%) patients required a dose reduction due to electrocardiogram QT prolonged. One patient each required permanent discontinuation due to diarrhea and PRES.

The most common adverse reactions reported in the trial are shown in Table 4.

Table 4: Adverse Reactions Reported in ≥ 10% (Any Grade) or ≥ 5% (Grade ≥ 3) of Patients with Newly Diagnosed AML in AG120-C-001

	TIBSOVO (500 mg daily) N=28	
Body System Adverse Reaction	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Gastrointestinal disorders		
Diarrhea	17 (61)	2 (7)
Nausea	10 (36)	2 (7)
Abdominal pain[1]	8 (29)	1 (4)
Constipation	6 (21)	1 (4)
Vomiting	6 (21)	1 (4)
Mucositis[2]	6 (21)	0
Dyspepsia	3 (11)	0
General disorders and administration site conditions		
Fatigue[3]	14 (50)	4 (14)

	TIBSOVO (500 mg daily) N=28	
Body System Adverse Reaction	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Edema[4]	12 (43)	0
Metabolism and nutrition disorders		
Decreased appetite	11 (39)	1 (4)
Blood system and lymphatic system disorders		
Leukocytosis[5]	10 (36)	2 (7)
Differentiation Syndrome[6]	7 (25)	3 (11)
Musculoskeletal and connective tissue disorders		
Arthralgia[7]	9 (32)	1 (4)
Myalgia[8]	7 (25)	1 (4)
Respiratory, thoracic, and mediastinal disorders		
Dyspnea[9]	8 (29)	1 (4)
Cough[10]	4 (14)	0
Investigations		
Electrocardiogram QT prolonged	6 (21)	3 (11)
Weight decreased	3 (11)	0
Nervous system disorders		
Dizziness	6 (21)	0
Neuropathy[11]	4 (14)	0
Headache	3 (11)	0
Skin and subcutaneous tissue disorders		
Pruritis	4 (14)	1 (4)
Rash[12]	4 (14)	1 (4)

[1] Grouped term includes abdominal pain, upper abdominal pain, abdominal discomfort, and abdominal tenderness.
[2] Grouped term includes aphthous ulcer, esophageal pain, esophagitis, gingival pain, gingivitis, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal pain, proctalgia, and stomatitis.
[3] Grouped term includes asthenia and fatigue.
[4] Grouped term includes edema, face edema, fluid overload, fluid retention, hypervolemia, peripheral edema, and swelling face.
[5] Grouped term includes leukocytosis, hyperleukocytosis, and increased white blood cell count.
[6] Differentiation syndrome can be associated with other commonly reported events such as peripheral edema, leukocytosis, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonia, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased.
[7] Grouped term includes arthralgia, back pain, musculoskeletal stiffness, neck pain, and pain in extremity.
[8] Grouped term includes myalgia, muscular weakness, musculoskeletal pain, musculoskeletal chest pain, musculoskeletal discomfort, and myalgia intercostal.
[9] Grouped term includes dyspnea, dyspnea exertional, hypoxia, and respiratory failure.
[10] Grouped term includes cough, productive cough, and upper airway cough syndrome.
[11] Grouped term includes burning sensation, lumbosacral plexopathy, neuropathy peripheral, paresthesia, and peripheral motor neuropathy.
[12] Grouped term includes dermatitis acneiform, dermatitis, rash, rash maculo-papular, urticaria, rash erythematous, rash macular, rash pruritic, rash generalized, rash papular, skin exfoliation, and skin ulcer.

Changes in selected post-baseline laboratory values that were observed in patients with newly diagnosed AML are shown in Table 5.

Table 5: Most Common (≥ 10%) or ≥ 5% (Grade ≥ 3) New or Worsening Laboratory Abnormalities Reported in Patients with Newly Diagnosed AML[1] in AG120-C-001

	TIBSOVO (500 mg daily) N=28	
Parameter	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Hemoglobin decreased	15 (54)	12 (43)
Alkaline phosphatase increased	13 (46)	0
Potassium decreased	12 (43)	3 (11)
Sodium decreased	11 (39)	1 (4)
Uric acid increased	8 (29)	1 (4)
Aspartate aminotransferase increased	8 (29)	1 (4)
Creatinine increased	8 (29)	0
Magnesium decreased	7 (25)	0
Calcium decreased	7 (25)	1 (4)
Phosphate decreased	6 (21)	2 (7)
Alanine aminotransferase increased	4 (14)	1 (4)

[1] Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or if baseline is unknown.

Relapsed or Refractory AML

The safety profile of single-agent TIBSOVO was studied in 179 adults with relapsed or refractory AML treated with 500 mg daily *[see Clinical Studies (14.2)]*.
The median duration of exposure to TIBSOVO was 3.9 months (range 0.1 to 39.5 months). Sixty-five patients (36%) were exposed to TIBSOVO for at least 6 months and 16 patients (9%) were exposed for at least 1 year.

Serious adverse reactions (≥ 5%) were differentiation syndrome (10%), leukocytosis (10%), and electrocardiogram QT prolonged (7%). There was one case of progressive multifocal leukoencephalopathy (PML).

The most common adverse reactions leading to dose interruption were electrocardiogram QT prolonged (7%), differentiation syndrome (3%), leukocytosis (3%) and dyspnea (3%). Five out of 179 patients (3%) required a dose reduction due to an adverse reaction. Adverse reactions leading to a dose reduction included electrocardiogram QT prolonged (1%), diarrhea (1%), nausea (1%), decreased hemoglobin (1%), and increased transaminases (1%). Adverse reactions leading to permanent discontinuation included Guillain-Barré syndrome (1%), rash (1%), stomatitis (1%), and creatinine increased (1%).

The most common adverse reactions reported in the trial are shown in Table 6.

Table 6: Adverse Reactions Reported in ≥ 10% (Any Grade) or ≥ 5% (Grade ≥ 3) of Patients with Relapsed or Refractory AML

	TIBSOVO (500 mg daily) N=179	
Body System Adverse Reaction	**All Grades n (%)**	**Grade ≥ 3 n (%)**

	TIBSOVO (500 mg daily) N=179	
General disorders and administration site conditions		
Fatigue[1]	69 (39)	6 (3)
Edema[2]	57 (32)	2 (1)
Pyrexia	41 (23)	2 (1)
Chest pain[3]	29 (16)	5 (3)
Blood system and lymphatic system disorders		
Leukocytosis[4]	68 (38)	15 (8)
Differentiation Syndrome[5]	34 (19)	23 (13)
Musculoskeletal and connective tissue disorders		
Arthralgia[6]	64 (36)	8 (4)
Myalgia[7]	33 (18)	1 (1)
Gastrointestinal disorders		
Diarrhea	60 (34)	4 (2)
Nausea	56 (31)	1 (1)
Mucositis[8]	51 (28)	6 (3)
Constipation	35 (20)	1 (1)
Vomiting[9]	32 (18)	2 (1)
Abdominal pain[10]	29 (16)	2 (1)
Respiratory, thoracic, and mediastinal disorders		
Dyspnea[11]	59 (33)	16 (9)
Cough[12]	40 (22)	1 (<1)
Pleural effusion	23 (13)	5 (3)
Investigations		
Electrocardiogram QT prolonged	46 (26)	18 (10)
Skin and subcutaneous tissue disorders		
Rash[13]	46 (26)	4 (2)
Metabolism and nutrition disorders		
Decreased appetite	33 (18)	3 (2)
Tumor lysis syndrome	14 (8)	11 (6)
Nervous system disorders		
Headache	28 (16)	0
Neuropathy[14]	21 (12)	2 (1)
Vascular disorders		
Hypotension[15]	22 (12)	7 (4)

[1] Grouped term includes asthenia and fatigue.
[2] Grouped term includes peripheral edema, edema, fluid overload, fluid retention, and face edema.
[3] Grouped term includes angina pectoris, chest pain, chest discomfort, and non-cardiac chest pain.
[4] Grouped term includes leukocytosis, hyperleukocytosis, and increased white blood cell count.
[5] Differentiation syndrome can be associated with other commonly reported events such as peripheral edema, leukocytosis, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonia, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased.
[6] Grouped term includes arthralgia, back pain, musculoskeletal stiffness, neck pain, and pain in extremity.
[7] Grouped term includes myalgia, muscular weakness, musculoskeletal pain, musculoskeletal chest pain, musculoskeletal discomfort, and myalgia intercostal.
[8] Grouped term includes aphthous ulcer, esophageal pain, esophagitis, gingival pain, gingivitis, mouth ulceration, mucosal inflammation, oral pain, oropharyngeal pain, proctalgia, and stomatitis.
[9] Grouped term includes vomiting and retching.
[10] Grouped term includes abdominal pain, upper abdominal pain, abdominal discomfort, and abdominal tenderness.
[11] Grouped term includes dyspnea, respiratory failure, hypoxia, and dyspnea exertional.
[12] Grouped term includes cough, productive cough, and upper airway cough syndrome.

[13] Grouped term includes dermatitis acneiform, dermatitis, rash, rash maculo-papular, urticaria, rash erythematous, rash macular, rash pruritic, rash generalized, rash papular, skin exfoliation, and skin ulcer.
[14] Grouped term includes ataxia, burning sensation, gait disturbance, Guillain-Barré syndrome, neuropathy peripheral, paresthesia, peripheral sensory neuropathy, peripheral motor neuropathy, and sensory disturbance.
[15] Grouped term includes hypotension and orthostatic hypotension.

Changes in selected post-baseline laboratory values that were observed in patients with relapsed or refractory AML are shown in Table 7.

Table 7: Most Common (≥ 10%) or ≥ 5% (Grade ≥ 3) New or Worsening Laboratory Abnormalities Reported in Patients with Relapsed or Refractory AML[1]

	TIBSOVO (500 mg daily) N=179	
Parameter	**All Grades n (%)**	**Grade ≥ 3 n (%)**
Hemoglobin decreased	108 (60)	83 (46)
Sodium decreased	69 (39)	8 (4)
Magnesium decreased	68 (38)	0
Uric acid increased	57 (32)	11 (6)
Potassium decreased	55 (31)	11 (6)
Alkaline phosphatase increased	49 (27)	1 (1)
Aspartate aminotransferase increased	49 (27)	1 (1)
Phosphate decreased	45 (25)	15 (8)
Creatinine increased	42 (23)	2 (1)
Alanine aminotransferase increased	26 (15)	2 (1)
Bilirubin increased	28 (16)	1 (1)

[1] Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or if baseline is unknown.

Locally Advanced or Metastatic Cholangiocarcinoma

The safety of TIBSOVO was studied in patients with previously treated, locally advanced or metastatic cholangiocarcinoma in Study AG120-C-005 *[see Clinical Studies (14.3)]*. Patients received at least one dose of either TIBSOVO 500 mg daily (N=123) or placebo (N=59). The median duration of treatment was 2.8 months (range 0.1 to 34.4 months) with TIBSOVO.

Serious adverse reactions occurred in 34% of patients receiving TIBSOVO. Serious adverse reactions in ≥2% of patients in the TIBSOVO arm were pneumonia, ascites, hyperbilirubinemia, and jaundice cholestatic. Fatal adverse reactions occurred in 4.9% of patients receiving TIBSOVO, including sepsis (1.6%) and pneumonia, intestinal obstruction, pulmonary embolism, and hepatic encephalopathy (each 0.8%)

TIBSOVO was permanently discontinued in 7% of patients. The most common adverse reactions leading to permanent discontinuation was acute kidney injury (1.6%).

Dose interruptions due to adverse reactions occurred in 29% of patients treated with TIBSOVO. The most common (>2%) adverse reactions leading to dose interruption were hyperbilirubinemia, alanine aminotransferase increased, aspartate aminotransferase increased, ascites, and fatigue.

Dose reductions of TIBSOVO due to an adverse reaction occurred in 4.1% of patients. Adverse

reactions leading to dose reduction were electrocardiogram QT prolonged (3.3%) and neuropathy peripheral (0.8%).

The most common adverse reactions (≥15%) were fatigue, nausea, abdominal pain, diarrhea, cough, decreased appetite, ascites, vomiting, anemia, and rash.

Adverse reactions and laboratory abnormalities observed in Study AG120-C-005 are shown in Tables 8 and 9.

Table 8: Adverse Reactions Occurring in ≥ 10% of Patients Receiving TIBSOVO in Study AG120-C-005

	TIBSOVO (500 mg daily) N=123		**Placebo N=59**	
Body System Adverse Reaction	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
General disorders and administration site conditions				
Fatigue[1]	53 (43)	4 (3)	18 (31)	3 (5)
Gastrointestinal disorders				
Nausea	51 (41)	3 (2)	17 (29)	1 (2)
Diarrhea	43 (35)	0	10 (17)	0
Abdominal pain[2]	43 (35)	3 (2)	13 (22)	2 (3)
Ascites	28 (23)	11 (9)	9 (15)	4 (7)
Vomiting[3]	28 (23)	3 (2)	12 (20)	0
Respiratory, thoracic, and mediastinal disorders				
Cough[4]	33 (27)	0	5 (9)	0
Metabolism and nutrition disorders				
Decreased appetite	30 (24)	2 (2)	11 (19)	0
Blood and lymphatic system disorders				
Anemia	22 (18)	8 (7)	3 (5)	0
Skin and subcutaneous tissue disorders				
Rash[5]	19 (15)	1 (1)	4 (7)	0
Nervous system disorders				
Headache	16 (13)	0	4 (7)	0
Neuropathy peripheral[6]	13 (11)	0	0	0
Investigations				
Electrocardiogram QT prolonged	12 (10)	2 (2)	2 (3)	0

[1] Grouped term includes asthenia and fatigue.
[2] Grouped term includes abdominal pain, abdominal pain upper, abdominal discomfort, abdominal pain lower, epigastric discomfort, abdominal tenderness, and gastrointestinal pain.
[3] Grouped term includes vomiting and retching.
[4] Grouped term includes cough and productive cough.
[5] Grouped term includes rash, rash maculo-papular, erythema, rash macular, dermatitis exfoliative generalized, drug eruption, and drug hypersensitivity.
[6] Grouped term includes neuropathy peripheral, peripheral sensory neuropathy, and paresthesia.

Table 9: Selected Laboratory Abnormalities Occurring in ≥ 10% of Patients Receiving TIBSOVO in Study AG120-C-005[1]

	TIBSOVO (500 mg daily) N=123		Placebo N=59	
Parameter	**All Grades n (%)**	**Grade ≥ 3 n (%)**	**All Grades n (%)**	**Grade ≥ 3 n (%)**
AST increased	41 (34)	5 (4)	14 (24)	1 (2)
Bilirubin increased	36 (30)	15 (13)	11 (19)	2 (3)
Hemoglobin decreased	48 (40)	8 (7)	14 (25)	0

[1] Laboratory abnormality is defined as new or worsened by at least one grade from baseline, or baseline is unknown.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Ivosidenib

Strong or Moderate CYP3A4 Inhibitors	
Clinical Impact	• Co-administration of TIBSOVO with strong or moderate CYP3A4 inhibitors increased ivosidenib plasma concentrations *[see Clinical Pharmacology (12.3)]*. • Increased ivosidenib plasma concentrations may increase the risk of QTc interval prolongation *[see Warnings and Precautions (5.2)]*.
Prevention or Management	• Consider alternative therapies that are not strong or moderate CYP3A4 inhibitors during treatment with TIBSOVO. • If co-administration of a strong CYP3A4 inhibitor is unavoidable, reduce TIBSOVO to 250 mg once daily *[see Dosage and Administration (2.3)]*. • Monitor patients for increased risk of QTc interval prolongation *[see Warnings and Precautions (5.2)]*.
Strong CYP3A4 Inducers	
Clinical Impact	• Co-administration of TIBSOVO with strong CYP3A4 inducers decreased ivosidenib plasma concentrations *[see Clinical Pharmacology (12.3)]*.
Prevention or Management	• Avoid co-administration of strong CYP3A4 inducers with TIBSOVO.
QTc Prolonging Drugs	
Clinical Impact	• Co-administration of TIBSOVO with QTc prolonging drugs may increase the risk of QTc interval prolongation *[see Warnings and Precautions (5.2)]*.
Prevention or Management	• Avoid co-administration of QTc prolonging drugs with TIBSOVO or replace with alternative therapies.

	• If co-administration of a QTc prolonging drug is unavoidable, monitor patients for increased risk of QTc interval prolongation [*see Warnings and Precautions (5.2)]*.

7.2 Effect of Ivosidenib on Other Drugs

Ivosidenib induces CYP3A4 and may induce CYP2C9. Co-administration will decrease concentrations of drugs that are sensitive CYP3A4 substrates and may decrease concentrations of drugs that are sensitive CYP2C9 substrates *[see Clinical Pharmacology (12.3)]*. Use alternative therapies that are not sensitive substrates of CYP3A4 and CYP2C9 during TIBSOVO treatment. If co-administration of TIBSOVO with sensitive CYP3A4 substrates or CYP2C9 substrates is unavoidable, monitor patients for loss of therapeutic effect of these drugs.

Do not administer TIBSOVO with anti-fungal agents that are substrates of CYP3A4 due to expected loss of antifungal efficacy.

Co-administration of TIBSOVO may decrease the concentrations of hormonal contraceptives, consider alternative methods of contraception in patients receiving TIBSOVO.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on animal embryo-fetal toxicity studies, TIBSOVO may cause fetal harm when administered to a pregnant woman. There are no available data on TIBSOVO use in pregnant women to inform a drug-associated risk of major birth defects and miscarriage. In animal embryo-fetal toxicity studies, oral administration of ivosidenib to pregnant rats and rabbits during organogenesis was associated with embryo-fetal mortality and alterations to growth starting at 2 times the steady state clinical exposure based on the AUC at the recommended human dose *(see Data)*. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, advise the patient of the potential risk to a fetus.

The background risk of major birth defects and miscarriage for the indicated population is unknown. Adverse outcomes in pregnancy occur regardless of the health of the mother or the use of medications. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%-4% and 15%-20%, respectively.

Data

Animal Data
Ivosidenib administered to pregnant rats at a dose of 500 mg/kg/day during organogenesis (gestation days 6-17) was associated with adverse embryo-fetal effects including lower fetal weights, and skeletal variations. These effects occurred in rats at approximately 2 times the human exposure at the recommended dose of 500 mg daily.
In pregnant rabbits treated during organogenesis (gestation days 7-20), ivosidenib was maternally toxic at doses of 180 mg/kg/day (exposure approximately 3.9 times the human

exposure at the recommended dose of 500 mg daily) and caused spontaneous abortions as well as decreased fetal weights, skeletal variations, and visceral variations.

8.2 Lactation

Risk Summary

There are no data on the presence of ivosidenib or its metabolites in human milk, the effects on the breastfed child, or the effects on milk production. Because many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed children, advise women not to breastfeed during treatment with TIBSOVO and for 1 month after the last dose.

8.4 Pediatric Use

The safety and effectiveness of TIBSOVO in pediatric patients have not been established.

8.5 Geriatric Use

Of the 72 patients with newly diagnosed AML treated with TIBSOVO in combination with azacitidine, 94% were 65 years of age or older, and 54% were 75 years or older. Of the 34 patients with newly diagnosed AML treated with TIBSOVO monotherapy, 97% were 65 years of age or older, and 56% were 75 years or older. Of the 179 patients with relapsed or refractory AML treated with TIBSOVO monotherapy, 63% were 65 years of age or older and 22% were 75 years or older. Of the 124 patients with cholangiocarcinoma treated with TIBSOVO in Study AG120-C-005, 37% were 65 years of age or older and 11% were 75 years or older.

No overall differences in effectiveness or safety were observed between patients who were 65 years and older compared to younger patients.

8.6 Renal Impairment

No modification of the starting dose is recommended for patients with mild or moderate renal impairment (eGFR ≥ 30 mL/min/1.73m^2, MDRD). The pharmacokinetics and safety of ivosidenib in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2, MDRD) or renal impairment requiring dialysis are unknown *[see Clinical Pharmacology (12.3)]*. For patients with pre-existing severe renal impairment or who are requiring dialysis, consider the risks and potential benefits before initiating treatment with TIBSOVO.

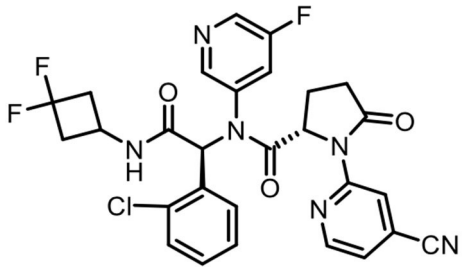
8.7 Hepatic Impairment

No modification of the starting dose is recommended for patients with mild or moderate (Child-Pugh A or B) hepatic impairment *[see Clinical Pharmacology (12.3)]*. The pharmacokinetics and safety of ivosidenib in patients with severe hepatic impairment (Child-Pugh C) are unknown. For patients with pre-existing severe hepatic impairment, consider the risks and potential benefits before initiating treatment with TIBSOVO.

11 DESCRIPTION

TIBSOVO (ivosidenib) is an inhibitor of isocitrate dehydrogenase 1 (IDH1) enzyme. The chemical name is (2*S*)-*N*-{(1*S*)-1-(2-chlorophenyl)-2-[(3,3-difluorocyclobutyl)-amino]-2-

oxoethyl}-1-(4-cyanopyridin-2-yl)-*N*-(5-fluoropyridin-3-yl)-5-oxopyrrolidine-2-carboxamide. The chemical structure is:



The molecular formula is $C_{28}H_{22}ClF_3N_6O_3$ and the molecular weight is 583.0 g/mol. Ivosidenib is practically insoluble in aqueous solutions between pH 1.2 and 7.4.

TIBSOVO (ivosidenib) is available as a film-coated 250 mg tablet for oral administration. Each tablet contains the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet coating includes FD&C blue #2, hypromellose, lactose monohydrate, titanium dioxide, and triacetin.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Ivosidenib is a small molecule inhibitor that targets the mutant isocitrate dehydrogenase 1 (IDH1) enzyme. In patients with AML, susceptible IDH1 mutations are defined as those leading to increased levels of 2-hydroxyglutarate (2-HG) in the leukemia cells and where efficacy is predicted by 1) clinically meaningful remissions with the recommended dose of ivosidenib and/or 2) inhibition of mutant IDH1 enzymatic activity at concentrations of ivosidenib sustainable at the recommended dosage according to validated methods. The most common of such mutations in patients with AML are R132H and R132C substitutions.

Ivosidenib was shown to inhibit selected IDH1 R132 mutants at much lower concentrations than wild-type IDH1 in vitro. Inhibition of the mutant IDH1 enzyme by ivosidenib led to decreased 2-HG levels and induced myeloid differentiation in vitro and in vivo in mouse xenograft models of IDH1-mutated AML. In blood samples from patients with AML with mutated IDH1, ivosidenib decreased 2-HG levels ex-vivo, reduced blast counts, and increased percentages of mature myeloid cells.

In a patient-derived xenograft intra-hepatic cholangiocarcinoma mouse model with IDH1 R132C, ivosidenib reduced 2-HG levels.

12.2 Pharmacodynamics

Multiple doses of ivosidenib 500 mg daily were observed to decrease plasma 2-HG concentrations in patients with hematological malignancies and cholangiocarcinoma to levels similar to those observed at baseline in healthy subjects. In bone marrow of patients with hematological malignancies and in tumor biopsy of patients with cholangiocarcinoma, the mean

[% coefficient of variation (%CV)] reduction in 2-HG concentrations were 93.1% (11.1%) and 82.2% (32.4%), respectively.

Cardiac Electrophysiology

The mean increase in QTc was 17 msec (UCI: 20 msec) following administration of TIBSOVO 500 mg in patients with newly diagnosed AML and patients with relapsed or refractory AML. The increase in QTc interval was concentration-dependent *[see Warnings and Precautions (5.2)]*. A similar mean increase of 17 msec following administration of TIBSOVO 500 mg daily was observed in patients with solid tumors, including patients with cholangiocarcinoma. Co-administration with moderate or strong CYP3A inhibitors is expected to further increase QTc interval prolongation from baseline.

12.3 Pharmacokinetics

The AUC and C_{max} of ivosidenib increase in a less than dose-proportional manner from 200 mg to 1,200 mg daily (0.4 to 2.4 times the approved recommended dosage). The following ivosidenib pharmacokinetic parameters (Table 10) were observed following administration of ivosidenib 500 mg as a single dose or daily dose (for steady state), unless otherwise specified. The steady-state pharmacokinetics of ivosidenib 500 mg were comparable between patients with newly diagnosed AML and relapsed or refractory AML and were lower in patients with cholangiocarcinoma.

Table 10: Pharmacokinetics of ivosidenib

	Cholangiocarcinoma treated with TIBSOVO	**Relapsed or refractory AML treated with TIBSOVO**	**Newly diagnosed AML treated with a combination of TIBSOVO and azacitidine**
PK parameters			
Single dose C_{max} (ng/mL)[a]	4,060 (45%)	4,503 (38%)	4,820 (39%)
Steady state C_{max} (ng/mL)[a]	4,799 (33%)	6,551 (44%)	6,145 (34%)
Steady state AUC (ng·hr/mL)[a]	86,382 (34%)	117,348 (50%)	106,326 (41%)
Steady state PK	Within 14 days		
Accumulation			
C_{max}	1.2	1.5	1.2
AUC	1.5	1.9	1.6
Absorption			
Median T_{max} (hr)	2	3	2
Effect of Food[b] C_{max} AUC	1.98-fold (90% CI: 1.79, 2.19) 1.24-fold (90% CI: 1.16, 1.33)		
Distribution			
In vitro protein binding	92 to 96%		
Apparent volume of distribution at steady state (L)[a]	706 (45%)	403 (35%)	504 (22%)
Elimination			
Apparent clearance at steady state (L/hr)[a]	6.1 (31%)	5.6 (35%)	4.6 (35%)
Terminal half-life at steady state (hr)[a]	129 (102%)	58 (42%)	98 (42%)
Metabolism			
Plasma[c]	>92% of total radioactivity as ivosidenib		
Metabolic pathways			
Major	CYP3A4		
Minor	N-dealkylation and hydrolytic pathways		

Excretion[c]	
Urine	17% (10% as unchanged ivosidenib)
Feces	77% (67% as unchanged ivosidenib)

[a] PK parameters expressed as mean (%CV)
[b] Following administration of a single dose in healthy subjects, a high-fat meal (approximately 900 to 1,000 calories, 500 to 600 fat calories, 250 carbohydrate calories and 150 protein calories)
[c] Data from a single radiolabeled ivosidenib dose in healthy subjects

Specific Populations

No clinically significant effects on the pharmacokinetics of ivosidenib were observed based on age (18 years to 89 years), sex, race (White, Asian, Black or African American), body weight (38 to 150 kg), ECOG performance status, mild or moderate hepatic impairment (Child-Pugh A or B) or mild or moderate renal impairment (eGFR ≥30 mL/min/1.73m^2, MDRD). The pharmacokinetics of ivosidenib in patients with severe renal impairment (eGFR <30 mL/min/1.73m^2, MDRD) or renal impairment requiring dialysis or severe hepatic impairment (Child-Pugh C) is unknown.

Drug Interaction Studies

Clinical Studies and Model-Based Approaches

Effect of Strong or Moderate CYP3A4 Inhibitors on Ivosidenib

Co-administration of 250 mg ivosidenib with a strong CYP3A4 inhibitor (200 mg itraconazole once daily for 18 days) increased ivosidenib single-dose AUC by 269% (90% CI: 245%, 295%) with no change in C_{max} in healthy subjects.

Co-administration of 500 mg ivosidenib with the moderate CYP3A4 inhibitor fluconazole (dosed to steady-state) increases ivosidenib single-dose AUC by 173% with no change in C_{max}. Co-administration of fluconazole following multiple daily ivosidenib doses is predicted to increase ivosidenib steady-state C_{max} by 152% and AUC by 190%.

Effect of Strong CYP3A4 Inducers on Ivosidenib

Co-administration of ivosidenib with a strong CYP3A4 inducer (600 mg rifampin once daily for 15 days) is predicted to decrease ivosidenib steady-state AUC by 33%.

Effect of Ivosidenib on CYP3A4 Substrates

Ivosidenib induces CYP3A4, including its own metabolism. Co-administration of ivosidenib with CYP3A4 substrates, including certain azole anti-fungal agents, is expected to decrease CYP3A4 substrate steady-state AUC.

Effect of Gastric Acid Reducing Agents on Ivosidenib

No clinically significant ivosidenib pharmacokinetic differences were observed following co-administration with gastric acid reducing agents (e.g., proton pump inhibitors, H2-receptor antagonists, antacids).

In vitro Studies

Metabolic Pathways

Ivosidenib may induce CYP2B6, CYP2C8, and CYP2C9.

Drug Transporter Systems

Ivosidenib is a substrate for P-glycoprotein (P-gp). Ivosidenib is not a substrate for BCRP or hepatic transporters OATP1B1 and OATP1B3.

Ivosidenib is an inhibitor of OAT3 and P-gp. Ivosidenib does not inhibit BCRP, OATP1B1, OATP1B3, OAT1, and OCT2.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with ivosidenib. Ivosidenib was not mutagenic in an in vitro bacterial reverse mutation (Ames) assay. Ivosidenib was not clastogenic in an in vitro human lymphocyte micronucleus assay, or in an in vivo rat bone marrow micronucleus assay. Fertility studies in animals have not been conducted with ivosidenib. In repeat-dose toxicity studies up to 90 days in duration with twice daily oral administration of ivosidenib in rats, uterine atrophy was reported in females at non-tolerated dose levels.

14 CLINICAL STUDIES

14.1 Newly Diagnosed AML

Newly Diagnosed AML in Combination with Azacitidine

The efficacy of TIBSOVO was evaluated in a randomized (1:1), multicenter, double-blind, placebo-controlled clinical trial (Study AG120-C-009, NCT03173248) of 146 adult patients with newly-diagnosed AML with an IDH1 mutation who were 75 years or older, or had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline Eastern Cooperative Oncology Group (ECOG) performance status of 2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin > 1.5 times the upper limit of normal, creatinine clearance < 45 mL/min, or other comorbidity. IDH1 mutations were confirmed centrally using the Abbott RealTime™ IDH1 Assay. Local diagnostic tests were permitted for screening and randomization provided a bone marrow or peripheral blood sample was sent for central confirmation. Gene mutation analysis to document IDH1 mutated disease from a bone marrow or peripheral blood sample was conducted for all patients. Patients were randomized to receive either TIBSOVO 500 mg or matched placebo orally once daily on Days 1-28 in combination with azacitidine 75 mg/m^2/day either subcutaneously or intravenously on Days 1-7 or Days 1-5 and 8-9 of each 28-day cycle beginning on Cycle 1 Day 1. Patients were treated for a minimum of 6 cycles unless they experienced disease progression, unacceptable toxicity or undergoing hematopoietic stem cell transplantation. Baseline demographic and disease characteristics are shown in Table 11.

Table 11: Baseline Demographic and Disease Characteristics in Patients with Newly Diagnosed AML (Study AG120-C-009)

Demographic and Disease Characteristics	TIBSOVO + azacitidine (500 mg daily) N=72	Placebo + azacitidine N=74
Demographics		
Age (Years) Median (Min, Max)	76 (58, 84)	76 (45, 94)
Age Categories, n (%)		
<65 years	4 (6)	4 (5)
≥65 years to <75 years	29 (40)	27 (36)
≥75 years	39 (54)	43 (58)
Sex, n (%)		
Male	42 (58)	38 (51)
Female	30 (42)	36 (49)
Race, n (%)		
Asian	15 (21)	19 (26)
White	12 (17)	12 (16)
Black or African American	0	2 (3)
Other	1 (1)	1 (1)
Not provided	44 (61)	40 (54)
Disease Characteristics		
ECOG PS, n (%)		
0	14 (19)	10 (14)
1	32 (44)	40 (54)
2	26 (36)	24 (32)
IDH1 Mutation, n (%)[1]		
R132C	45 (63)	51 (69)
R132H	14 (19)	12 (16)
R132G	6 (8)	4 (5)
R132L	3 (4)	0
R132S	2 (3)	6 (8)
Wild type	1 (1)	0
Missing	1 (1)	1 (1)
Cytogenetic risk status[2] n (%)		
Favorable	3 (4)	7 (9)
Intermediate	48 (67)	44 (59)
Poor	16 (22)	20 (27)
Other	3 (4)	1 (1)
Missing	2 (3)	2 (3)
Transfusion Dependent at Baseline[3], n (%)	39 (54)	40 (54)
Type of AML, n (%)		
De novo AML	54 (75)	53 (72)
Secondary AML	18 (25)	21 (28)
Therapy-related AML	2 (3)	1 (1)
MDS related	10 (14)	12 (16)
MPN related	4 (6)	8 (11)

ECOG PS: Eastern Cooperative Oncology Group Performance Status; MPN = Myeloproliferative Neoplasm; MDS = Myelodysplastic syndrome

[1] Using confirmatory Abbott RealTime IDH1 assay testing results.

[2] Cytogenetic risk status: National Comprehensive Cancer Network (NCCN) guidelines.
[3] Patients were defined as transfusion dependent at baseline if they received any red blood cell or platelet transfusion within 56 days prior to the first dose of TIBSOVO.

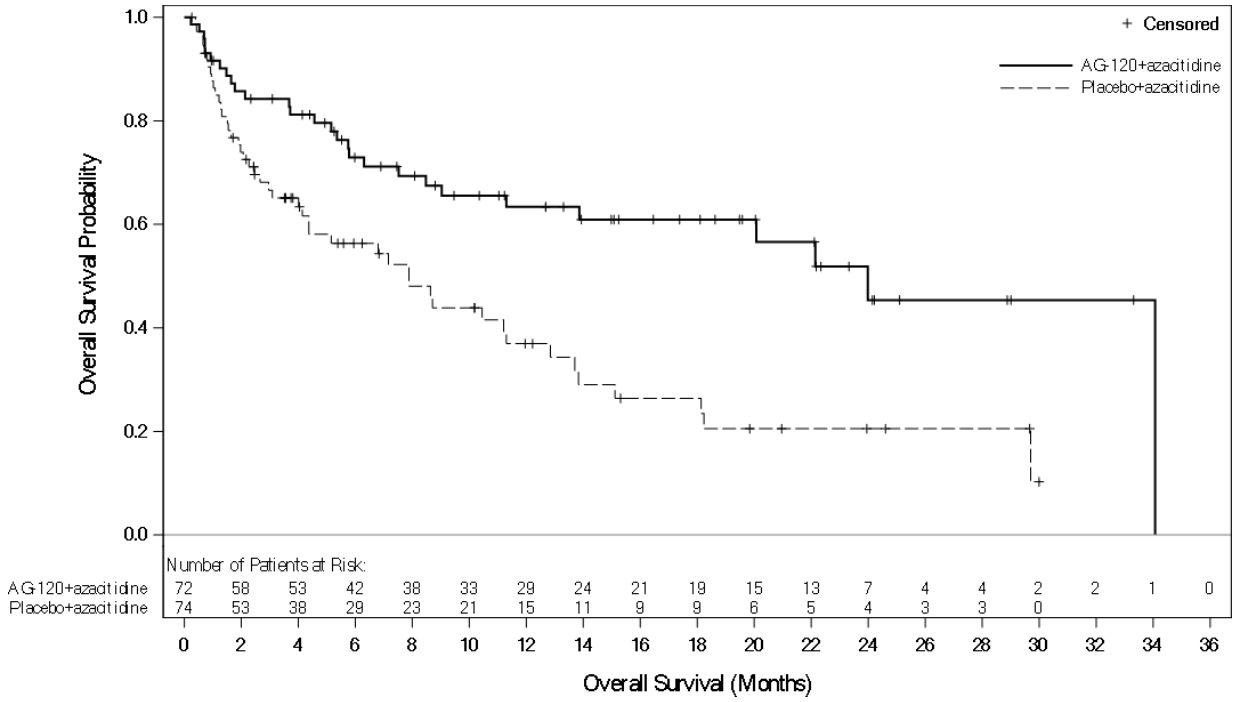
Efficacy was established on the basis of event-free survival (EFS), overall survival (OS), and rate and duration of complete remission (CR). EFS was defined as the time from randomization until treatment failure, relapse from remission, or death from any cause, whichever occurred first. Treatment failure was defined as failure to achieve CR by 24 weeks. The efficacy results are shown in Table 12 and Figure 1.

Table 12: Efficacy Results in Patients with Newly Diagnosed AML (Study AG120-C-009)

Endpoint	TIBSOVO (500 mg daily) + azacitidine N=72	Placebo + azacitidine N=74
EFS, events (%)	47 (65)	62 (84)
Treatment Failure	43 (60)	59 (80)
Relapse	3 (4)	2 (3)
Death	1 (1)	1 (1)
Hazard ratio[1] (95% CI)	0.35 (0.17, 0.72)	
p-value[2]	0.0038	
OS events (%)	28 (39)	46 (62)
Median OS (95% CI) months	24.0 (11.3, 34.1)	7.9 (4.1, 11.3)
Hazard ratio[1] (95% CI)	0.44 (0.27, 0.73)	
p-value[2]	0.0010	
CR, n (%)	34 (47)	11 (15)
95% CI[3]	(35, 59)	(8, 25)
Risk difference[4] (95% CI), (%)	31 (17, 46)	
p-value[5]	<0.0001	
Median duration of CR (95% CI), months	NE (13.0, NE)	11.2 (3.2, NE)
CR+CRh, n (%)	37 (51)	13 (18)
95% CI[3]	(39, 63)	(10, 28)
Risk difference[4] (95% CI), (%)	33 (18, 47)	
p-value[5]	<0.0001	
Median duration of CR + CRh (95% CI), months	NE (13.0, NE)	9.2 (5.8, NE)

Abbreviations: EFS = Event free survival; CI: confidence interval; OS = Overall survival; CR = Complete remission; CRh = Complete remission with partial hematologic recovery; NE = Not estimable.
The 2-sided p-value boundaries for EFS, OS, CR, and CR+CRh are 0.0095, 0.0034, 0.0174, and 0.0174, respectively.
[1] Hazard ratio is estimated using a Cox's proportional hazards model stratified by the randomization stratification factors (AML status and geographic region) with Placebo+ azacitidine as the denominator.
[2] Two-sided p-value is calculated from the log-rank test stratified by the randomization stratification factors (AML status and geographic region).
[3] CI of percentage is calculated with the Clopper and Pearson (exact Binomial) method.
[4] Mantel-Haenszel estimate of risk difference in percentage between TIBSOVO + azacitidine and Placebo+ azacitidine is calculated.
[5] Two-sided p-value is calculated from the Cochran-Mantel-Haenszel test stratified by the randomization stratification factors (AML status and geographic region).

Figure 1: Kaplan-Meier Curve for Overall Survival in AG120-C-009



The median time to first CR for TIBSOVO with azacitidine was 4 months (range, 1.7 to 11.9 months).

The median time to first CR + CRh for TIBSOVO with azacitidine was 4 months (range, 1.7 to 11.9 months).

Monotherapy in Newly Diagnosed AML

The efficacy of TIBSOVO was evaluated in an open-label, single-arm, multicenter clinical trial (Study AG120-C-001, NCT02074839) that included 28 adult patients with newly diagnosed AML with an IDH1 mutation. IDH1 mutations were identified by a local or central diagnostic test and confirmed retrospectively using the Abbott RealTi*me*™ IDH1 Assay. The cohort included patients who were age 75 years or older or who had comorbidities that precluded the use of intensive induction chemotherapy based on at least one of the following criteria: baseline ECOG performance status of ≥ 2, severe cardiac or pulmonary disease, hepatic impairment with bilirubin > 1.5 times the upper limit of normal, or creatinine clearance < 45 mL/min. TIBSOVO was given orally at a starting dose of 500 mg daily until disease progression, development of unacceptable toxicity, or undergoing hematopoietic stem cell transplantation. Two (7%) of the 28 patients went on to stem cell transplantation following TIBSOVO treatment.

The baseline demographic and disease characteristics are shown in Table 13.

Table 13: Baseline Demographic and Disease Characteristics in Patients with Newly Diagnosed AML (Study AG120-C-001)

Demographic and Disease Characteristics	TIBSOVO (500 mg daily) N=28
Demographics	
Age (Years) Median (Min, Max)	77 (64, 87)
Age Categories, n (%)	
<65 years	1 (4)
≥65 years to <75 years	8 (29)
≥75 years	19 (68)
Sex, n (%)	
Male	15 (54)
Female	13 (46)
Race, n (%)	
White	24 (86)
Black or African American	2 (7)
Asian	0
Native Hawaiian/Other Pacific Islander	0
Other/Not provided	2 (7)
Disease Characteristics	
ECOG PS, n (%)	
0	6 (21)
1	16 (57)
2	5 (18)
3	1 (4)
IDH1 Mutation, n (%)[1]	
R132C	24 (86)
R132G	1 (4)
R132H	2 (7)
R132L	1 (4)
R132S	0
ELN Risk Category, n (%)	
Favorable	0
Intermediate	9 (32)
Adverse	19 (68)
Transfusion Dependent at Baseline[2], n (%)	17 (61)
Type of AML, n (%)	
De novo AML	6 (21)
AML-MRC[3]	19 (68)
Therapy-related AML	3 (11)
Prior Hypomethylating Agent for Antecedent Hematologic Disorder	13 (46)

ECOG PS: Eastern Cooperative Oncology Group Performance Status. ELN: European Leukemia Net

[1] Using confirmatory Abbott RealTi*m*e IDH1 assay testing results.

[2] Patients were defined as transfusion dependent at baseline if they received any transfusion occurring within 56 days prior to the first dose of TIBSOVO.

[3] AML with myelodysplasia-related changes.

Efficacy was established on the basis of the rate of complete remission (CR) or complete remission with partial hematologic recovery (CRh), the duration of CR+CRh, and the rate of

conversion from transfusion dependence to transfusion independence. The efficacy results are shown in Table 14. The median follow-up was 8.1 months (range, 0.6 to 40.9 months) and median treatment duration was 4.3 months (range, 0.3 to 40.9 months).

Table 14: Efficacy Results in Patients with Newly Diagnosed AML (Study AG120-C-001)

Endpoint	TIBSOVO (500 mg daily) N=28
CR[1] n (%)	8 (28.6)
95% CI	(13.2, 48.7)
Median DOCR[2] (months)	NE[3]
95% CI	(4.2, NE)
CRh[4] n (%)	4 (14.3)
95% CI	(4.0, 32.7)
Observed DOCRh[2] (months)	2.8, 4.6, 8.3, 15.7+
CR+CRh n (%)	12 (42.9)
95% CI	(24.5, 62.8)
Median DOCR+CRh[2] (months)	NE[3]
95% CI	(4.2, NE)

CI: confidence interval, NE: not estimable

[1] CR (complete remission) was defined as <5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts [ANC] >1,000/microliter).

[2] DOCR (duration of CR), DOCRh (duration of CRh), and DOCR+CRh (duration of CR+CRh) was defined as time since first response of CR, CRh or CR/CRh, respectively, to relapse or death, whichever is earlier. + indicates censored observation.

[3] The median durations of CR and CR+CRh were not estimable, with 5 patients (41.7%) who achieved CR or CRh remaining on TIBSOVO treatment (treatment duration range: 20.3 to 40.9 months).

[4] CRh (complete remission with partial hematological recovery) was defined as <5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).

For patients who achieved a CR or CRh, the median time to CR or CRh was 2.8 months (range, 1.9 to 12.9 months). Of the 12 patients who achieved a best response of CR or CRh, 11 (92%) achieved a first response of CR or CRh within 6 months of initiating TIBSOVO.

Among the 17 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 7 (41.2%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 11 patients who were independent of both RBC and platelet transfusions at baseline, 6 (54.5%) remained transfusion independent during any 56-day post-baseline period.

14.2 Relapsed or Refractory AML

The efficacy of TIBSOVO was evaluated in an open-label, single-arm, multicenter clinical trial (Study AG120-C-001, NCT02074839) of 174 adult patients with relapsed or refractory AML with an IDH1 mutation. IDH1 mutations were identified by a local or central diagnostic test and confirmed retrospectively using the Abbott RealTi*m*e™ IDH1 Assay. TIBSOVO was given orally at a starting dose of 500 mg daily until disease progression, development of unacceptable toxicity, or undergoing hematopoietic stem cell transplantation. Twenty-one (12%) of the 174 patients went on to stem cell transplantation following TIBSOVO treatment.

The baseline demographic and disease characteristics are shown in Table 15.

Table 15: Baseline Demographic and Disease Characteristics in Patients with Relapsed or Refractory AML (Study AG120-C-001)

Demographic and Disease Characteristics	TIBSOVO (500 mg daily) N=174
Demographics	
Age (Years) Median (Min, Max)	67 (18, 87)
Age Categories, n (%)	
<65 years	63 (36)
≥65 years to <75 years	71 (41)
≥75 years	40 (23)
Sex, n (%)	
Male	88 (51)
Female	86 (49)
Race, n (%)	
White	108 (62)
Black or African American	10 (6)
Asian	6 (3)
Native Hawaiian/Other Pacific Islander	1 (1)
Other/Not provided	49 (28)
Disease Characteristics	
ECOG PS, n (%)	
0	36 (21)
1	97 (56)
2	39 (22)
3	2 (1)
IDH1 Mutation, n (%)[1]	
R132C	102 (59)
R132H	43 (25)
R132G	12 (7)
R132S	10 (6)
R132L	7 (4)
Cytogenetic Risk Status, n (%)	
Intermediate	104 (60)
Poor	47 (27)
Missing/Unknown	23 (13)
Relapse Type	
Primary refractory	64 (37)
Refractory relapse	45 (26)
Untreated relapse	65 (37)
Relapse Number	
0	64 (37)
1	83 (48)
2	21 (12)
≥3	6 (3)
Prior Stem Cell Transplantation for AML, n (%)	40 (23)
Transfusion Dependent at Baseline[2], n (%)	110 (63)
Median Number of Prior Therapies (Min, Max)	2 (1, 6)

Type of AML, n (%)	
De novo AML	116 (67)
Secondary AML	58 (33)

ECOG PS: Eastern Cooperative Oncology Group Performance Status.
[1] Using confirmatory Abbott RealTi*m*e IDH1 assay testing results.
[2] Patients were defined as transfusion dependent at baseline if they received any transfusion occurring within 56 days prior to the first dose of TIBSOVO.

Efficacy was established on the basis of the rate of complete remission (CR) plus complete remission with partial hematologic recovery (CRh), the duration of CR+CRh, and the rate of conversion from transfusion dependence to transfusion independence. The efficacy results are shown in Table 16. The median follow-up was 8.3 months (range, 0.2 to 39.5 months) and median treatment duration was 4.1 months (range, 0.1 to 39.5 months).

Table 16: Efficacy Results in Patients with Relapsed or Refractory AML (Study AG120-C-001)

Endpoint	**TIBSOVO (500 mg daily) N=174**
CR[1] n (%)	43 (24.7)
95% CI	(18.5, 31.8)
Median DOCR[2] (months)	10.1
95% CI	(6.5, 22.2)
CRh[3] n (%)	14 (8.0)
95% CI	(4.5, 13.1)
Median DOCRh[2] (months)	3.6
95% CI	(1, 5.5)
CR+CRh[4] n (%)	57 (32.8)
95% CI	(25.8, 40.3)
Median DOCR+CRh[2] (months)	8.2
95% CI	(5.6, 12)

CI: confidence interval
[1] CR (complete remission) was defined as <5% blasts in the bone marrow, no evidence of disease, and full recovery of peripheral blood counts (platelets >100,000/microliter and absolute neutrophil counts [ANC] >1,000/microliter).
[2] DOCR (duration of CR), DOCRh (duration of CRh), and DOCR+CRh (duration of CR+CRh) was defined as time since first response of CR, CRh or CR/CRh, respectively, to relapse or death, whichever is earlier.
[3] CRh (complete remission with partial hematological recovery) was defined as <5% blasts in the bone marrow, no evidence of disease, and partial recovery of peripheral blood counts (platelets >50,000/microliter and ANC >500/microliter).
[4] CR+CRh rate appeared to be consistent across all baseline demographic and baseline disease characteristics with the exception of number of prior regimens.

For patients who achieved a CR or CRh, the median time to CR or CRh was 2 months (range, 0.9 to 5.6 months). Of the 57 patients who achieved a best response of CR or CRh, all achieved a first response of CR or CRh within 6 months of initiating TIBSOVO.

Among the 110 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 41 (37.3%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. Of the 64 patients who were independent of both RBC and platelet transfusions at baseline, 38 (59.4%) remained transfusion independent during any 56-day post-baseline period.

14.3 Locally Advanced or Metastatic Cholangiocarcinoma

The efficacy of TIBSOVO was evaluated in a randomized (2:1), multicenter, double-blind, placebo-controlled clinical trial (Study AG120-C-005, NCT02989857) of 185 adult patients with locally advanced or metastatic cholangiocarcinoma with an IDH1 mutation whose disease had progressed following at least 1 but not more than 2 prior regimens, including at least one gemcitabine- or 5-FU-containing regimen. Patients were randomized to receive either TIBSOVO 500 mg orally once daily or matched placebo until disease progression or unacceptable toxicity. Randomization was stratified by number of prior therapies (1 or 2). Eligible patients who were randomized to placebo were allowed to cross over to receive TIBSOVO after documented radiographic disease progression. Patients with IDH1 mutations were selected using a central diagnostic next generation sequencing assay. Tumor imaging assessments were performed every 6 weeks for the first 8 assessments and every 8 weeks thereafter.

The major efficacy outcome measure was Progression Free Survival (PFS) as determined by independent review committee (IRC) according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

The median age was 62 years (range: 33 to 83); 63% were female; 57% were White, 12% Asian, 1.1% Black, 0.5% Native Hawaiian/Other Pacific Islander, 0.5% American Indian or Alaska Native, 28% race missing/not reported; and 37% had an ECOG performance status of 0 (37%) or 1 (62%). All patients received at least 1 prior line of systemic therapy and 47% received two prior lines. Most patients had intrahepatic cholangiocarcinoma (91%) at diagnosis and 92% had metastatic disease. Across both arms, 70% patients had an R132C mutation, 15% had an R132L mutation, 12% had an R132G mutation, 1.1% had an R132H mutation, and 1.6% had an R132S mutation.

The efficacy results are shown in Table 17 and Figure 2. The study demonstrated a statistically significant improvement in PFS.

Table 17: Efficacy Results in Patients with Locally Advanced or Metastatic Cholangiocarcinoma in AG120-C-005

Endpoint	TIBSOVO (500 mg daily)	Placebo
Progression-Free Survival by IRC Assessment	**N=124**	**N=61**
Events, n (%) Progressive Disease Death	76 (61) 64 (52) 12 (10)	50 (82) 44 (72) 6 (10)
Hazard ratio (95% CI)[1]	0.37 (0.25, 0.54)	
p-value[2]	<0.0001	
Objective Response Rate, n (%)	3 (2.4)	0
Overall Survival[3]	**N=126**	**N=61**
Deaths, n (%)	100 (79)	50 (82)
Hazard ratio (95% CI)[1]	0.79 (0.56, 1.12)	
p-value[2]	0.093	

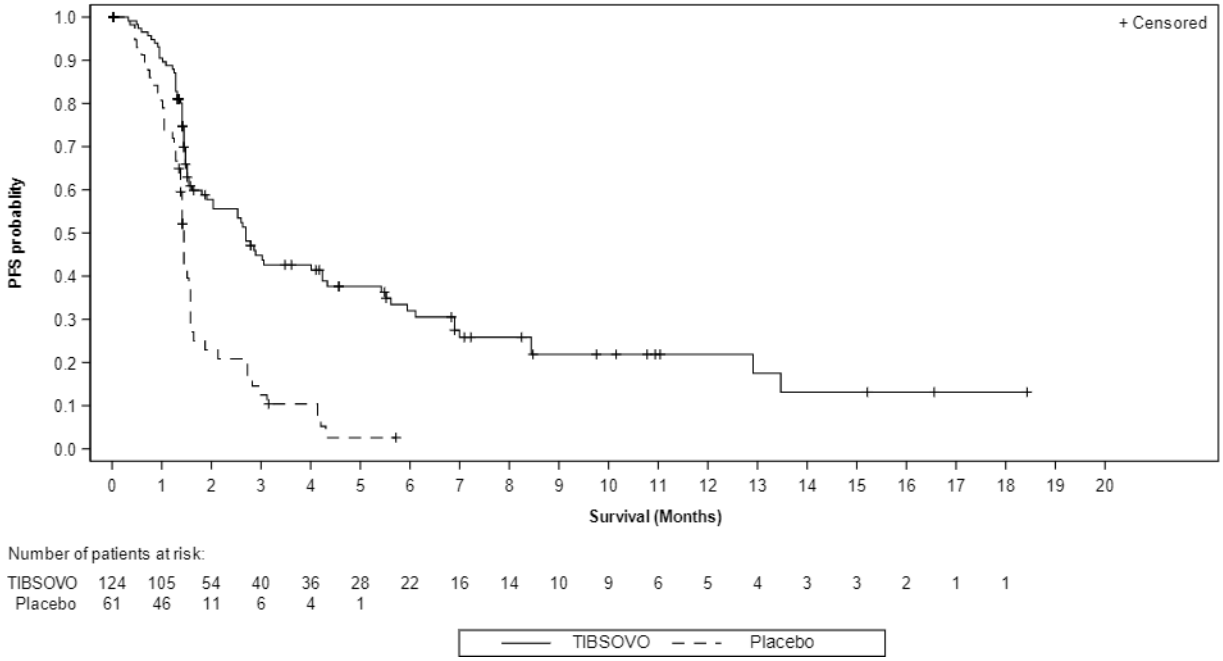
IRC: Independent Review Committee; CI: Confidence Interval

[1] Hazard ratio is calculated from stratified Cox regression model. Stratified by number of prior lines of therapy.

[2] P-value is calculated from the one-sided stratified log-rank test. Stratified by number of prior lines of therapy.

[3] OS results are based on the final analysis of OS (based on 150 deaths) which occurred 16 months after the final analysis of PFS. The median OS (95% CI) for TIBSOVO was 10.3 (7.8, 12.4) months; and placebo was 7.5 (4.8, 11.1) months without adjusting for crossover. In the analysis of OS, 70% of the patients randomized to placebo had crossed over to receive TIBSOVO after radiographic disease progression.

Figure 2: Kaplan-Meier Plot of Progression-Free Survival per Independent Review Committee - Before Crossover (ITT)



16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

250 mg tablet: Blue oval-shaped film-coated tablet debossed “IVO” on one side and “250” on the other side.

- 60-count bottles of 250 mg tablets with a desiccant canister (NDC 72694-617-60)

Storage

Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Differentiation Syndrome in AML

Advise patients with AML being treated with TIBSOVO of the risks of developing differentiation syndrome as early as 1 day after start of therapy and during the first 3 months on treatment. Ask patients to immediately report any symptoms suggestive of differentiation

syndrome, such as fever, cough or difficulty breathing, rash, decreased urinary output, low blood pressure, rapid weight gain, or swelling of their arms or legs, to their healthcare provider for further evaluation *[see Boxed Warning and Warnings and Precautions (5.1)]*.

QTc Interval Prolongation

Inform patients of symptoms that may be indicative of significant QTc interval prolongation including dizziness, lightheadedness, and fainting. Advise patients to report these symptoms and the use of all medications to their healthcare provider *[see Warnings and Precautions (5.2)]*.

Guillain-Barré Syndrome

Inform patients of symptoms that may be indicative of Guillain-Barré syndrome, including new signs or symptoms of motor and/or sensory neuropathy, such as weakness or tingling sensation in the legs, arms, or upper body, numbness and pain on one side or both sides of the body, changes to any sensory function, or burning or prickling sensation, or difficulty breathing. Advise patients to report these symptoms to their healthcare provider *[see Warnings and Precautions (5.3)]*.

Drug Interactions

Advise patients to inform their healthcare providers of all concomitant medications, including over-the-counter medications, vitamins, and herbal products *[see Drug Interactions (7)]*.

Tumor Lysis Syndrome

Advise patients on the risks of developing tumor lysis syndrome. Advise patients on the importance of maintaining high fluid intake, and the need for frequent monitoring of blood chemistry values *[see Adverse Reactions (6.1)]*.

Gastrointestinal Adverse Reactions

Advise patients on the risks of experiencing gastrointestinal reactions such as diarrhea, nausea, mucositis, constipation, vomiting, decreased appetite, ascites and abdominal pain. Ask patients to report these events to their healthcare provider and advise patients how to manage them *[see Adverse Reactions (6.1)]*.

Lactation

Advise women not to breastfeed during treatment with TIBSOVO and for 1 month after the last dose *[see Use in Specific Populations (8.2)]*.

Dosing and Storage Instructions

- Advise patients to swallow tablets whole and to not split, crush, or chew TIBSOVO tablets.
- Advise patients to avoid taking TIBSOVO with a high-fat meal.
- Instruct patients that if a dose of TIBSOVO is vomited, not to take an additional dose, and wait until the next scheduled dose is due. If a dose of TIBSOVO is missed or not taken at the usual time, instruct patients to take the dose as soon as possible unless the next dose is due within 12 hours. Patients can return to the normal schedule the following day.
- Store TIBSOVO at room temperature from 20°C to 25°C (68°F to 77°F).

Manufactured for Servier Pharmaceuticals LLC, Boston, MA 02210

MEDICATION GUIDE

TIBSOVO® (tib-SOH-voh)
(ivosidenib tablets)

What is the most important information I should know about TIBSOVO?

TIBSOVO may cause serious side effects, including:

- **Differentiation Syndrome.** Differentiation syndrome is a serious condition that affects your blood cells and may be life-threatening or lead to death. Differentiation syndrome in adults with acute myeloid leukemia (AML) has happened as early as 1 day and up to 3 months after starting TIBSOVO. Call your healthcare provider or go to the nearest hospital emergency room right away if you develop any of the following symptoms of differentiation syndrome during treatment with TIBSOVO:
  - fever
  - cough
  - trouble breathing
  - rash
  - decreased urination
  - dizziness or lightheadedness
  - rapid weight gain
  - swelling of your arms or legs

If you develop signs and symptoms of differentiation syndrome, your healthcare provider may treat you with a corticosteroid medicine or a medicine called hydroxyurea and may monitor you in the hospital.

See **"What are the possible side effects of TIBSOVO?"** for more information about side effects.

What is TIBSOVO?

TIBSOVO is a prescription medicine used to treat:

- acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation in:
  - adults with newly diagnosed AML treated in combination with TIBSOVO and azacitidine who are 75 years or older or who have health problems that prevent the use of certain chemotherapy treatments.
  - adults with newly diagnosed AML who are 75 years or older or who have health problems that prevent the use of certain chemotherapy treatments.
  - adults with AML when the disease has come back or has not improved after previous treatment(s).
- adults with bile duct cancer (cholangiocarcinoma) that has spread:
  - who have already received previous treatment(s) and
  - whose tumor has a certain type of abnormal IDH1 mutation

Your healthcare provider will perform a test to make sure that TIBSOVO is right for you.
It is not known if TIBSOVO is safe and effective in children.

Before taking TIBSOVO, tell your healthcare provider about all of your medical conditions, including if you:

- have any heart problems, including a condition called long QT syndrome.
- have problems with abnormal electrolytes, such as sodium, potassium, calcium or magnesium levels.
- have nervous system problems.
- have problems with your kidneys or are on dialysis.
- have any liver disorders, including cirrhosis.
- are pregnant or plan to become pregnant. TIBSOVO may cause harm to your unborn baby. You should avoid becoming pregnant during treatment with TIBSOVO. Tell your healthcare provider right away if you become pregnant or think you might be pregnant during treatment with TIBSOVO.
- are breastfeeding or plan to breastfeed. It is not known if TIBSOVO passes into your breast milk. Do not breastfeed during your treatment with TIBSOVO and for 1 month after your last dose of TIBSOVO.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.

Especially tell your healthcare provider if you take hormonal contraceptives. TIBSOVO may affect how hormonal contraceptives work and may cause them to not work as well.

How should I take TIBSOVO?

- Take TIBSOVO exactly as your healthcare provider tells you to.
- Do not change your dose or stop taking TIBSOVO without talking to your healthcare provider.
- Take TIBSOVO 1 time a day about the same time each day.
- Swallow TIBSOVO tablets whole. Do not split, crush, or chew the tablet.
- TIBSOVO can be taken with or without food.
- Do not take TIBSOVO with a high-fat meal. An example of a high-fat meal includes 2 eggs fried in butter, 2 strips of bacon, 2 slices of white bread with butter, 1 croissant with 1 slice of cheese, and 8 ounces of whole milk (approximately 1,000 calories and 58 grams of fat).
- If you vomit after taking a dose of TIBSOVO, do not take an additional dose. Take your next dose at your usual time.
- If you miss a dose of TIBSOVO or did not take it at the usual time, take your dose as soon as possible and at least 12 hours before your next dose. Return to your normal schedule the following day. **Do not** take 2 doses of TIBSOVO within 12 hours.

What are the possible side effects of TIBSOVO?

TIBSOVO may cause serious side effects, including:

- See **"What is the most important information I should know about TIBSOVO?"**
- **Changes in the electrical activity of your heart called QTc prolongation. QTc prolongation can cause irregular heartbeats that can be life-threatening.** Your healthcare provider will check the electrical activity of your heart with a test called an electrocardiogram (ECG) during treatment with TIBSOVO. Tell your healthcare provider right away if you feel dizzy, lightheaded, or faint.
- **Guillain-Barré syndrome** has happened in people treated with TIBSOVO. Your healthcare provider will monitor you for nervous system problems and will permanently stop your treatment with TIBSOVO if you develop Guillain-Barré syndrome. Tell your healthcare provider right away if you develop any signs or symptoms of Guillain-Barré syndrome, including:
    - weakness or tingling feeling in your legs, arms, or upper body
    - numbness and pain on one side or both sides of your body
    - any changes in your ability to see, touch, hear, or taste
    - burning or prickling sensation
    - difficulty breathing

The most common side effects of TIBSOVO when used in combination with azacitidine or alone in adults with AML include:

- changes in certain blood cell counts
- diarrhea
- increased blood sugar
- fatigue
- changes in certain liver function tests
- swelling of arms or legs
- decreased levels of electrolytes in the blood
- nausea
- vomiting
- decreased appetite
- joint pain
- shortness of breath
- uric acid increased
- stomach (abdominal) pain
- changes in certain kidney function tests
- pain or sores in your mouth or throat
- rash
- irregular heart rhythm or heartbeat (QTc prolongation)
- differentiation syndrome
- muscle pain

The most common side effects of TIBSOVO in adults with Cholangiocarcinoma include:

- fatigue
- nausea
- abdominal pain
- diarrhea
- cough
- decreased appetite
- fluid and swelling in your stomach area
- vomiting
- hemoglobin decreased (anemia)
- rash
- changes in liver function tests

Your healthcare provider will do blood tests before you start and during treatment with TIBSOVO. Your healthcare provider may decrease, temporarily hold, or permanently stop your treatment with TIBSOVO if you develop certain side effects.

TIBSOVO may cause fertility problems in females and males, which may affect your ability to have children. Talk to your healthcare provider if you have concerns about fertility.

These are not all of the possible side effects of TIBSOVO.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store TIBSOVO?

- Store TIBSOVO at room temperature between 68°F to 77°F (20°C to 25°C).

Keep TIBSOVO and all medicines out of the reach of children.

General information about the safe and effective use of TIBSOVO

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not take TIBSOVO for conditions for which it was not prescribed. Do not give TIBSOVO to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about TIBSOVO that is written for healthcare professionals.

What are the ingredients in TIBSOVO?

Active ingredient: ivosidenib

Inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, hypromellose acetate succinate, magnesium stearate, microcrystalline cellulose, and sodium lauryl sulfate. The tablet coating includes FD&C blue #2, hypromellose, lactose monohydrate, titanium dioxide, and triacetin.

Manufactured for Servier Pharmaceuticals LLC, Boston, MA 02210

For more information go to www.TIBSOVO.com or call 1-800-807-6124.

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: May 2022