PRODUCT MONOGRAPH

Pr CYRAMZA®

ramucirumab

intravenous injection, 10 mg ramucirumab / mL

10 mL and 50 mL vials

Antineoplastic

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RECENT MAJOR LABEL CHANGES

Warnings and Precautions	January, 2020
Dosage and Administration, Recommended Dose and Dosage Adjustment	January, 2020

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Pr CYRAMZA®

ramucirumab

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous infusion	Solution / 10 mg/mL	None *For a complete listing see DOSAGE FORMS, COMPOSITION AND PACKAGING section.*

DESCRIPTION

CYRAMZA® (ramucirumab) is a recombinant human IgG1 monoclonal antibody that specifically binds to vascular endothelial growth factor (VEGF) Receptor 2.

INDICATIONS AND CLINICAL USE

Gastric Cancer
CYRAMZA (ramucirumab) as a single agent or in combination with paclitaxel is indicated for the treatment of patients with advanced or metastatic gastric cancer or gastro-esophageal junction adenocarcinoma, with disease progression on or after prior platinum and fluoropyrimidine chemotherapy.

Geriatrics (≥ 65 years of age)
No overall differences in safety or effectiveness have been observed between the elderly and younger patients, but greater safety sensitivity of some older individuals cannot be ruled out.

Pediatrics (< 18 years of age)
The safety and effectiveness of CYRAMZA in children and adolescents have not been established.

CONTRAINDICATIONS

CYRAMZA (ramucirumab) is contraindicated in patients with a known hypersensitivity to ramucirumab or to any other ingredient used in the formulation. For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- Increases risk of hemorrhage, including gastrointestinal hemorrhage (see Hematologic, Hemorrhage below and DOSAGE AND ADMINISTRATION)
- Increases risk of gastrointestinal perforations, including fatal events, (see Gastrointestinal, Gastrointestinal Perforations below and DOSAGE AND ADMINISTRATION)
- Impaired wound healing. Withhold prior to scheduled surgery and discontinue if there are wound healing complications (see Impaired Wound Healing below and DOSAGE AND ADMINISTRATION)

Cardiovascular

Arterial Thromboembolic Events

Serious, sometimes fatal, arterial thromboembolic events (ATEs) including myocardial infarction, cardiac arrest, cerebrovascular accident, and cerebral ischemia have been reported in clinical trials. Permanently discontinue CYRAMZA in patients who experience a severe ATE (see DOSAGE AND ADMINISTRATION).

Hypertension

An increased incidence of severe hypertension was reported in patients receiving CYRAMZA as compared to placebo. In most cases hypertension was managed using standard antihypertensive treatment.

Pre-existing hypertension should be controlled before starting CYRAMZA treatment. Monitoring of blood pressure is recommended during therapy.

Temporarily suspend CYRAMZA for severe hypertension until controlled with medical management. Permanently discontinue CYRAMZA if medically significant hypertension cannot be controlled with antihypertensive therapy (see DOSAGE AND ADMINISTRATION).

Congestive Heart Failure

CYRAMZA belongs to the class of antiangiogenic drugs which are known to increase the risk of congestive heart failure (CHF). Events consistent with CHF have been reported in patients receiving CYRAMZA therapy in clinical trials. Patients with known or increased risk of coronary artery disease should be treated with caution. CYRAMZA may enhance cardiotoxicity of chemotherapeutic cardiotoxic drugs.

Gastrointestinal

Gastrointestinal Perforations

CYRAMZA increases the risk of gastrointestinal perforations. Permanently discontinue CYRAMZA in patients who experience gastrointestinal perforations (see DOSAGE AND ADMINISTRATION).

Severe gastrointestinal perforations, including fatal events, were reported in patients with gastric cancer treated with CYRAMZA alone and in combination with paclitaxel. The typical presentation may include severe abdominal pain. Risk factors for gastrointestinal perforations can include intra-abdominal malignancy and metastases, inflammatory bowel disease, diverticulitis, ischemic bowel, peptic ulcers, obstruction and injury from an endoscopy, colonoscopy, laparoscopy, and surgery.

Fistula
CYRAMZA may increase the risk for development of fistulas. Permanently discontinue CYRAMZA in patients who experience fistula formation.

Hematologic
Hemorrhage
CYRAMZA increases the risk of hemorrhage, including gastrointestinal hemorrhage. Permanently discontinue CYRAMZA in patients who experience Grade 3 or 4 bleeding (see DOSAGE AND ADMINISTRATION).

Severe gastrointestinal hemorrhage, including fatal events, was reported in patients with gastric cancer treated with CYRAMZA in combination with paclitaxel, and also in clinical trials of patients with other types of cancers treated with CYRAMZA alone or in combination therapy.

Neutropenia
Increased rates of severe neutropenia have been observed in patients treated with CYRAMZA in combination with paclitaxel compared to paclitaxel alone. Patients should be closely monitored and treated according to established oncologic standards.

Thrombocytopenia
The incidence of thrombocytopenia was higher in patients receiving CYRAMZA in combination with paclitaxel compared to paclitaxel alone and the majority of these events were Grade 1-2. Given the increased incidence of gastrointestinal hemorrhage, patients found to have high grade thrombocytopenia should be closely monitored and treated according to established oncologic standards.

Hepatic
Hepatic Impairment
CYRAMZA can cause clinical deterioration in patients with cirrhosis. New onset or worsening encephalopathy, ascites, or hepatorenal syndrome can occur in patients with Child-Pugh B or C cirrhosis. Use only if the potential benefits of treatment are judged to outweigh the risk of clinical deterioration in these patients (see DOSAGE AND ADMINISTRATION).

Infusion-Related Reactions
Infusion-related reactions (IRRs) were reported in clinical trials with CYRAMZA. The majority of events occurred during or following a first or second CYRAMZA infusion. Monitor patients during the infusion for signs of hypersensitivity reactions with resuscitation equipment readily available. Symptoms included rigors/tremors, back pain/spasms, chest pain and/or tightness,

chills, flushing, dyspnea, wheezing, hypoxia, and paresthesia. In severe cases symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Premedicate all patients with a histamine H1 antagonist (e.g., diphenhydramine) intravenously prior to administration of CYRAMZA (see DOSAGE AND ADMINISTRATION).

Immediately and permanently discontinue CYRAMZA for Grade 3 or 4 IRRs (see DOSAGE AND ADMINISTRATION).

Impaired Wound Healing

CYRAMZA treatment should be withheld prior to scheduled surgery and discontinued if there are wound healing complications. The impact of CYRAMZA has not been evaluated in patients with serious or non-healing wounds. CYRAMZA is known to have the potential to adversely affect wound healing. The decision to resume CYRAMZA following surgical intervention should be based on clinical judgment of adequate wound healing.

If a patient develops wound healing complications during therapy, discontinue CYRAMZA until the wound is fully healed (see DOSAGE AND ADMINISTRATION).

Renal

Proteinuria

An increased incidence of proteinuria was reported in patients treated with CYRAMZA plus paclitaxel compared to patients treated with paclitaxel alone. Patients should be monitored for the development or worsening of proteinuria during therapy. Based on urine protein levels, suspension of treatment, or dosage adjustment may be necessary (see DOSAGE AND ADMINISTRATION).

Nephrotic syndrome has been observed in patients treated with CYRAMZA in combination therapy for metastatic colorectal carcinoma (3 cases). CYRAMZA should be permanently discontinued in patients who develop nephrotic syndrome (see DOSAGE AND ADMINISTRATION).

Posterior Reversible Encephalopathy Syndrome

Posterior Reversible Encephalopathy Syndrome (PRES) (also known as Reversible Posterior Leukoencephalopathy Syndrome [RPLS]) has been reported with a rate of < 0.1% in clinical studies with CYRAMZA. Symptoms of PRES include seizure, headache, nausea/vomiting, blindness, or altered consciousness, with or without associated hypertension. A diagnosis of PRES can be confirmed by brain imaging (e.g., magnetic resonance imaging). Permanently discontinue CYRAMZA in patients who develop PRES (see ADVERSE REACTIONS, Post-Market Adverse Reactions and DOSAGE AND ADMINISTRATION). Symptoms may resolve or improve within days, although some patients with PRES can experience ongoing neurologic sequelae or death.

Thyroid Dysfunction

CYRAMZA may increase thyroid stimulating hormone (TSH) levels and the incidence of hypothyroidism. Monitor TSH levels and thyroid function during treatment with CYRAMZA.

Some of these patients may need to be followed for evidence of persistent thyroid dysfunction after CYRAMZA therapy.

Special Populations

Pregnant Women: Based on CYRAMZA's mechanism of action, CYRAMZA can cause fetal harm when administered to pregnant women. Animal models link angiogenesis, VEGF, and VEGF Receptor 2 to critical aspects of female reproduction, embryofetal development, and postnatal development.

CYRAMZA is not recommended during pregnancy and in women of childbearing potential not using contraception. Advise women of child bearing potential to use effective contraception during treatment with CYRAMZA. Patients should avoid getting pregnant while receiving CYRAMZA and for at least 3 months after the last dose of CYRAMZA.

Fertility in Females and Males of Reproductive Potential: There are no data on the effect of CYRAMZA on human fertility. Female fertility is likely to be compromised during treatment with ramucirumab based on studies in animals.

Nursing Women: No studies have been conducted to assess CYRAMZA's impact on milk production, its presence in breast milk, or its effects on the nursing child.

It is not known whether CYRAMZA is excreted in human milk. Human IgG is excreted in human milk and due to potential risks to the nursing infant, it is recommended to discontinue nursing or discontinue CYRAMZA.

Pediatrics: The safety and effectiveness of CYRAMZA in pediatric patients have not been established. In animal studies, effects on epiphyseal growth plates were identified (see TOXICOLOGY).

Geriatrics: Of the 563 CYRAMZA-treated patients in two Phase 3 gastric cancer clinical studies, 36% were 65 and over, while 7% were 75 and over. No overall differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

Renal Impairment: No dedicated clinical studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of CYRAMZA.

Hepatic Impairment: No dedicated clinical studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of CYRAMZA (see WARNINGS AND PRECAUTIONS).

Race-Asian Patients: A higher incidence of Grade 3 proteinuria and nephrotic syndrome was reported in Asian patients living in East Asia compared to Caucasian patients receiving CYRAMZA in studies involving patients with various types of cancer.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The most common adverse reactions observed in CYRAMZA (ramucirumab) treated patients are: fatigue/asthenia, neutropenia, leukopenia, diarrhea, epistaxis, hypertension, edema peripheral, and stomatitis.

Clinically relevant reactions (including Grade ≥ 3) associated with antiangiogenic therapy observed in CYRAMZA-treated patients across clinical trials were proteinuria, infusion-related reactions, and gastrointestinal perforations (see DOSAGE AND ADMINISTRATION and WARNINGS AND PRECAUTIONS).

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Gastric Cancer

The safety of CYRAMZA has been evaluated as a single agent and in combination with paclitaxel.

Gastric Cancer - Single Agent

REGARD was a Phase 3, placebo-controlled study of CYRAMZA as a single agent. Patients with locally advanced or metastatic gastric cancer (including adenocarcinoma of the gastro-esophageal junction [GEJ]) following platinum- or fluoropyrimidine-containing chemotherapy received best supportive care (BSC) plus an intravenous infusion of CYRAMZA 8 mg/kg or placebo solution every 2 weeks.

Table 1 provides the frequency and severity of adverse drug reactions (ADRs) reported in ≥ 5% of CYRAMZA-treated patients in REGARD.

Table 1: ADRs Reported in ≥ 5% of CYRAMZA-Treated Patients in REGARD

System Organ Class	Frequency	Event[a,b]	CYRAMZA + BSC (N=236)		Placebo + BSC (N=115)	
			All Grades[c] Toxicity (%)	Grade 3-4 Toxicity (%)	All Grades Toxicity (%)	Grade 3-4 Toxicity (%)
Gastrointestinal Disorders	Very Common (≥ 10%)	Abdominal Pain[d]	28.8	5.9	27.8	2.6

	Very Common (≥ 10%)	Diarrhea	14.4	0.8	8.7	1.7
Metabolism and Nutrition Disorders	Common (< 10% and ≥ 1%)	Hypokalemia[e]	5.9	2.1	5.2	0.9
	Common (< 10% and ≥ 1%)	Hyponatremia	5.5	3.4	1.7	0.9
Nervous System Disorders	Common (< 10% and ≥ 1%)	Headache	9.3	0	3.5	0
Vascular Disorders	Very Common (≥ 10%)	Hypertension[f]	16.1	7.6	7.8	2.6

[a] MedDRA preferred term (Version 15.0)

[b] There were no Grade 5 ADRs for CYRAMZA. There was one Grade 4 ADR of hypokalemia and one of hyponatraemia.

[c] Refer to NCI CTCAE Criteria (Version 4.0) for each Grade of toxicity.

[d] MedDRA preferred terms included are: abdominal pain, abdominal pain lower, abdominal pain upper, and hepatic pain.

[e] MedDRA preferred terms included are: blood potassium decreased and hypokalemia.

[f] MedDRA preferred terms included are: blood pressure increased and hypertension.

Clinically relevant ADRs reported in ≥ 1% and < 5% of the CYRAMZA-treated patients in REGARD were: neutropenia (3.8% CYRAMZA versus 0.9% placebo), arterial thromboembolic events (1.7% versus 0%), intestinal obstruction (2.1% versus 0%), proteinuria (3.0% versus 2.6%), epistaxis (4.7% versus 0.9%), and rash (3.8% versus 0.9%).

Table 2 lists treatment-emergent adverse events (TEAEs) reported in the REGARD study, regardless of causality assessment.

Table 2: Treatment-Emergent Adverse Events Occurring in ≥ 1% of Patients in REGARD Study (Safety Population)

System Organ Class Preferred Term	Number Of Patients (%)			
	CYRAMZA + BSC N=236		Placebo + BSC N=115	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Blood And Lymphatic System Disorders				
Anemia	35 (14.8)	15 (6.4)	17 (14.8)	9 (7.8)
Leukopenia	0	0	2 (1.7)	0
Neutropenia	9 (3.8)	2 (0.8)	1 (0.9)	0
Pancytopenia	0	0	2 (1.7)	1 (0.9)
Thrombocytopenia	10 (4.2)	1 (0.4)	3 (2.6)	3 (2.6)
Cardiac Disorders				
Tachycardia	3 (1.3)	0	4 (3.5)	0
Endocrine Disorders				
Hypothyroidism	3 (1.3)	0	0	0
Gastrointestinal Disorders				
Abdominal discomfort	3 (1.3)	0	0	0
Abdominal distension	9 (3.8)	1 (0.4)	4 (3.5)	1 (0.9)
Abdominal pain	45 (19.1)	12 (5.1)	29 (25.2)	3 (2.6)

System Organ Class Preferred Term	Number Of Patients (%)			
	CYRAMZA + BSC N=236		Placebo + BSC N=115	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Abdominal pain upper	27 (11.4)	3 (1.3)	5 (4.3)	0
Ascites	23 (9.7)	10 (4.2)	11 (9.6)	5 (4.3)
Constipation	36 (15.3)	1 (0.4)	26 (22.6)	3 (2.6)
Diarrhea	34 (14.4)	2 (0.8)	10 (8.7)	2 (1.7)
Dry mouth	4 (1.7)	0	1 (0.9)	0
Dyspepsia	6 (2.5)	1 (0.4)	7 (6.1)	0
Dysphagia	25 (10.6)	5 (2.1)	12 (10.4)	5 (4.3)
Eructation	0	0	2 (1.7)	0
Flatulence	2 (0.8)	0	3 (2.6)	0
Gastrointestinal hemorrhage	3 (1.3)	3 (1.3)	2 (1.7)	1 (0.9)
Hematemesis	9 (3.8)	2 (0.8)	3 (2.6)	0
Intestinal obstruction	5 (2.1)	4 (1.7)	0	0
Nausea	45 (19.1)	3 (1.3)	30 (26.1)	0
Small intestinal obstruction	3 (1.3)	1 (0.4)	0	0
Vomiting	47 (19.9)	6 (2.5)	29 (25.2)	5 (4.3)
General Disorders And Administration Site Conditions				
Asthenia	28 (11.9)	5 (2.1)	19 (16.5)	8 (7.0)
Chills	4 (1.7)	0	2 (1.7)	0
Death	4 (1.7)	4 (1.7)	0	0
Disease progression	11 (4.7)	11 (4.7)	7 (6.1)	6 (5.2)
Fatigue	58 (24.6)	10 (4.2)	28 (24.3)	4 (3.5)
Feeling cold	3 (1.3)	0	0	0
General physical health deterioration	5 (2.1)	4 (1.7)	1 (0.9)	1 (0.9)
Generalised edema	3 (1.3)	1 (0.4)	0	0
Mucosal inflammation	9 (3.8)	0	1 (0.9)	0
Multi-organ failure	6 (2.5)	6 (2.5)	1 (0.9)	1 (0.9)
Non-cardiac chest pain	3 (1.3)	0	2 (1.7)	0
Edema peripheral	20 (8.5)	1 (0.4)	10 (8.7)	2 (1.7)
Pain	10 (4.2)	4 (1.7)	1 (0.9)	0
Pyrexia	10 (4.2)	0	5 (4.3)	1 (0.9)
Hepatobiliary Disorders				
Hyperbilirubinemia	3 (1.3)	1 (0.4)	3 (2.6)	3 (2.6)
Jaundice	4 (1.7)	1 (0.4)	1 (0.9)	0
Infections And Infestations				
Nasopharyngitis	6 (2.5)	0	0	0
Oral candidiasis	4 (1.7)	0	1 (0.9)	0
Pneumonia	5 (2.1)	4 (1.7)	3 (2.6)	2 (1.7)
Sepsis	3 (1.3)	3 (1.3)	2 (1.7)	2 (1.7)
Upper respiratory tract infection	3 (1.3)	0	1 (0.9)	0

System Organ Class Preferred Term	Number Of Patients (%)			
	CYRAMZA + BSC N=236		Placebo + BSC N=115	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Urinary tract infection	2 (0.8)	0	5 (4.3)	3 (2.6)
Injury, Poisoning And Procedural Complications				
Fall	4 (1.7)	0	2 (1.7)	1 (0.9)
Medication error	7 (3.0)	0	1 (0.9)	0
Procedural pain	3 (1.3)	0	0	0
Underdose	4 (1.7)	0	1 (0.9)	0
Investigations				
Alanine aminotransferase increased	9 (3.8)	3 (1.3)	2 (1.7)	1 (0.9)
Aspartate aminotransferase increased	9 (3.8)	3 (1.3)	2 (1.7)	2 (1.7)
Blood alkaline phosphatase increased	8 (3.4)	4 (1.7)	2 (1.7)	1 (0.9)
Blood bilirubin increased	6 (2.5)	3 (1.3)	1 (0.9)	1 (0.9)
Blood creatinine increased	4 (1.7)	1 (0.4)	0	0
Blood pressure increased	3 (1.3)	1 (0.4)	0	0
Eastern Cooperative Oncology Group performance status worsened	3 (1.3)	1 (0.4)	1 (0.9)	0
Hemoglobin decreased	3 (1.3)	1 (0.4)	1 (0.9)	1 (0.9)
Neutrophil count decreased	3 (1.3)	3 (1.3)	0	0
Weight decreased	27 (11.4)	3 (1.3)	11 (9.6)	1 (0.9)
Weight increased	5 (2.1)	0	0	0
Metabolism And Nutrition Disorders				
Decreased appetite	57 (24.2)	8 (3.4)	26 (22.6)	4 (3.5)
Dehydration	12 (5.1)	5 (2.1)	4 (3.5)	4 (3.5)
Hyperkalemia	4 (1.7)	3 (1.3)	2 (1.7)	2 (1.7)
Hyperuricemia	3 (1.3)	0	0	0
Hypoalbuminemia	12 (5.1)	1 (0.4)	6 (5.2)	1 (0.9)
Hypocalcemia	7 (3.0)	1 (0.4)	3 (2.6)	1 (0.9)
Hypoglycemia	3 (1.3)	2 (0.8)	2 (1.7)	2 (1.7)
Hypokalemia	13 (5.5)	5 (2.1)	6 (5.2)	1 (0.9)
Hypomagnesemia	2 (0.8)	0	2 (1.7)	0
Hyponatremia	13 (5.5)	8 (3.4)	2 (1.7)	1 (0.9)
Hypophosphatemia	5 (2.1)	2 (0.8)	0	0
Hypoproteinemia	3 (1.3)	1 (0.4)	0	0
Musculoskeletal And Connective Tissue Disorders				
Arthralgia	8 (3.4)	0	4 (3.5)	0
Back pain	18 (7.6)	3 (1.3)	11 (9.6)	3 (2.6)
Bone pain	3 (1.3)	0	0	0
Flank pain	1 (0.4)	0	3 (2.6)	1 (0.9)
Joint swelling	2 (0.8)	0	2 (1.7)	0
Musculoskeletal chest pain	7 (3.0)	0	1 (0.9)	0

System Organ Class Preferred Term	Number Of Patients (%)			
	CYRAMZA + BSC N=236		Placebo + BSC N=115	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Musculoskeletal pain	7 (3.0)	0	3 (2.6)	0
Myalgia	2 (0.8)	0	4 (3.5)	0
Neck pain	3 (1.3)	0	1 (0.9)	0
Pain in extremity	8 (3.4)	0	6 (5.2)	1 (0.9)
Neoplasms Benign, Malignant And Unspecified (Incl Cysts And Polyps)				
Neoplasm malignant	0	0	2 (1.7)	2 (1.7)
Nervous System Disorders				
Dizziness	4 (1.7)	1 (0.4)	6 (5.2)	0
Dizziness postural	0	0	2 (1.7)	0
Dysgeusia	7 (3.0)	0	6 (5.2)	0
Headache	22 (9.3)	0	4 (3.5)	0
Lethargy	4 (1.7)	2 (0.8)	1 (0.9)	0
Neuropathy peripheral	6 (2.5)	0	3 (2.6)	0
Paresthesia	1 (0.4)	0	2 (1.7)	0
Peripheral sensory neuropathy	1 (0.4)	0	2 (1.7)	1 (0.9)
Psychiatric Disorders				
Anxiety	7 (3.0)	1 (0.4)	3 (2.6)	0
Confusional state	3 (1.3)	1 (0.4)	0	0
Depression	6 (2.5)	0	3 (2.6)	0
Insomnia	13 (5.5)	1 (0.4)	8 (7.0)	0
Mental status changes	0	0	2 (1.7)	2 (1.7)
Renal And Urinary Disorders				
Dysuria	2 (0.8)	0	2 (1.7)	0
Hematuria	3 (1.3)	1 (0.4)	2 (1.7)	0
Proteinuria	7 (3.0)	1 (0.4)	3 (2.6)	0
Renal failure acute	6 (2.5)	2 (0.8)	4 (3.5)	2 (1.7)
Urinary retention	2 (0.8)	1 (0.4)	3 (2.6)	0
Respiratory, Thoracic And Mediastinal Disorders				
Cough	19 (8.1)	0	9 (7.8)	0
Dysphonia	3 (1.3)	0	1 (0.9)	0
Dyspnea	22 (9.3)	4 (1.7)	15 (13.0)	7 (6.1)
Epistaxis	11 (4.7)	0	1 (0.9)	0
Hiccups	6 (2.5)	2 (0.8)	3 (2.6)	1 (0.9)
Pleural effusion	5 (2.1)	3 (1.3)	2 (1.7)	0
Productive cough	4 (1.7)	0	2 (1.7)	0
Pulmonary embolism	4 (1.7)	3 (1.3)	3 (2.6)	3 (2.6)
Respiratory failure	1 (0.4)	0	3 (2.6)	2 (1.7)
Skin And Subcutaneous Tissue Disorders				
Decubitus ulcer	3 (1.3)	1 (0.4)	0	0

System Organ Class Preferred Term	Number Of Patients (%)			
	CYRAMZA + BSC N=236		Placebo + BSC N=115	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Dry skin	5 (2.1)	0	1 (0.9)	0
Night sweats	0	0	2 (1.7)	0
Pruritus	4 (1.7)	0	1 (0.9)	0
Rash	9 (3.8)	0	1 (0.9)	0
Vascular Disorders				
Deep vein thrombosis	3 (1.3)	0	3 (2.6)	2 (1.7)
Embolism	0	0	2 (1.7)	0
Hypertension	36 (15.3)	17 (7.2)	9 (7.8)	3 (2.6)
Hypotension	5 (2.1)	1 (0.4)	6 (5.2)	1 (0.9)

Abbreviations: BSC = best supportive care
Note: A patient was only counted once for each category.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

The following clinically important adverse drug reactions were reported in < 1% of patients treated with CYRAMZA in the REGARD study.

Gastrointestinal perforation (0.8% CYRAMZA versus 0.9% placebo)
Infusion related reaction (0.4% CYRAMZA versus 1.7% placebo)

Gastric Cancer – Combination with Paclitaxel

RAINBOW was a Phase 3, placebo-controlled study of CYRAMZA in combination with paclitaxel. Patients with locally advanced or metastatic gastric cancer (including adenocarcinoma of the GEJ) following platinum- and fluoropyrimidine-containing chemotherapy, with or without anthracycline, received CYRAMZA plus paclitaxel or placebo plus paclitaxel. CYRAMZA at 8 mg/kg or placebo was administered by intravenous infusion every 2 weeks (on days 1 and 15) of a 28-day cycle. Paclitaxel at 80 mg/m^2 was administered by intravenous infusion on days 1, 8, and 15 of each 28-day cycle.

Table 3 provides the frequency and severity of ADRs reported in ≥ 5% of CYRAMZA-treated patients in RAINBOW.

Table 3: ADRs Reported in ≥ 5% of CYRAMZA-Treated Patients in RAINBOW

System Organ Class	Frequency	Event	CYRAMZA + Paclitaxel (N=327)		Placebo + Paclitaxel (N=329)	
			All Grades Toxicity (%)	Grade ≥ 3 Toxicity (%)	All Grades Toxicity (%)	Grade ≥ 3 Toxicity (%)
Blood and Lymphatic	Very Common (≥ 10%)	Leukopenia	33.9	17.4	21.0	6.7
	Very Common	Neutropenia	54.4	40.7	31.0	18.8

System Disorders	(≥ 10%)					
	Very Common (≥ 10%)	Thrombocytopenia	13.1	1.5	6.1	1.8
Gastrointestinal Disorders	Very Common (≥ 10%)	Diarrhea	32.4	3.7	23.1	1.5
	Very Common (≥ 10%)	Gastrointestinal hemorrhage events[a]	10.1	3.7	6.1	1.5
	Very Common (≥ 10%)	Stomatitis	19.6	0.6	7.3	0.6
General Disorders and Administration Site Disorders	Very Common (≥ 10%)	Fatigue/Asthenia	56.9	11.9	43.8	5.5
	Very Common (≥ 10%)	Edema Peripheral	25.1	1.5	13.7	0.6
Metabolism and Nutrition Disorders	Very Common (≥ 10%)	Hypoalbuminemia	11.0	1.2	4.9	0.9
Renal and Urinary Disorders	Very Common (≥ 10%)	Proteinuria	16.8	1.2	6.1	0.0
Respiratory, Thoracic, and Mediastinal Disorders	Very Common (≥ 10%)	Epistaxis	30.6	0.0	7.0	0.0
Vascular Disorder	Very Common (≥ 10%)	Hypertension[b]	25.1	14.7	5.8	2.7

[a] MedDRA preferred terms included anal hemorrhage, diarrhea hemorrhage, gastric hemorrhage, gastrointestinal hemorrhage, hematemesis, hematochezia, hemorrhoidal hemorrhage, Mallory-Weiss syndrome, melena, esophageal hemorrhage, rectal hemorrhage, and upper gastrointestinal hemorrhage.

[b] Includes hypertensive cardiomyopathy.

The RAINBOW safety population consisted of 402 (61.3%) White and 228 (34.8%) Asian patients, 96.5% of the Asian patients came from East Asia.

In the CYRAMZA plus paclitaxel arm, the incidence of any-grade proteinuria was higher in Asian patients (CYRAMZA plus paclitaxel versus placebo plus paclitaxel [26.6% versus 6.7%]) than in White patients (CYRAMZA plus paclitaxel versus placebo plus paclitaxel [12.1% versus 5.1%]). The majority of proteinuria events reported in Asian and White patients in the CYRAMZA plus paclitaxel arm were Grade 1 or Grade 2.

Independent of treatment arm, a higher incidence of neutropenia of any grade was observed in Asian patients (CYRAMZA plus paclitaxel versus placebo plus paclitaxel [77.1% versus 44.5%]) versus White patients (CYRAMZA plus paclitaxel versus placebo plus paclitaxel [43.7% versus 23.5%]). In the CYRAMZA plus paclitaxel arm the incidence of Grade 4 neutropenia was higher in Asian (CYRAMZA plus paclitaxel versus placebo plus paclitaxel [37.6% versus 4.2%]) than in White patients (CYRAMZA plus paclitaxel versus placebo plus paclitaxel [9.7% versus 3.1%]) although the incidences of neutropenic infectious complications and febrile neutropenia were similar between Asian and White patients.

Clinically relevant ADRs reported in ≥ 1% and < 5% of the CYRAMZA plus paclitaxel versus placebo plus paclitaxel-treated patients in RAINBOW were gastrointestinal perforation (1.2% versus 0.3%) and sepsis (3.1% versus 1.8%).

A higher incidence of events associated with congestive heart failure was observed in the CYRAMZA plus paclitaxel arm versus the placebo plus paclitaxel arm (2.4% versus 1.2%).

Table 4 lists TEAEs reported in the RAINBOW study, regardless of causality assessment.

Table 4: Treatment-Emergent Adverse Events Occurring in ≥ 1% of Patients in RAINBOW Study (Safety Population)

System Organ Class Preferred Term	Number of Patients (%)			
	CYRAMZA + Paclitaxel N=327		Placebo + Paclitaxel N=329	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Blood and Lymphatic System Disorders				
Anemia	111 (33.9)	30 (9.2)	117 (35.6)	34 (10.3)
Febrile neutropenia	10 (3.1)	10 (3.1)	8 (2.4)	8 (2.4)
Iron deficiency anemia	4 (1.2)	0	2 (0.6)	0
Leukocytosis	9 (2.8)	1 (0.3)	6 (1.8)	2 (0.6)
Leukopenia	111 (33.9)	57 (17.4)	69 (21.0)	22 (6.7)
Lymphopenia	5 (1.5)	2 (0.6)	5 (1.5)	2 (0.6)
Neutropenia	178 (54.4)	133 (40.7)	102 (31.0)	62 (18.8)
Neutrophilia	5 (1.5)	0	1 (0.3)	0
Thrombocytopenia	43 (13.1)	5 (1.5)	20 (6.1)	6 (1.8)
Cardiac Disorders				
Atrial fibrillation	4 (1.2)	3 (0.9)	2 (0.6)	0
Tachycardia	7 (2.1)	0	2 (0.6)	0
Ear and Labyrinth Disorders				
Vertigo	3 (0.9)	0	5 (1.5)	1 (0.3)
Eye Disorders				
Conjunctival hemorrhage	4 (1.2)	0	2 (0.6)	0
Conjunctivitis	4 (1.2)	1 (0.3)	3 (0.9)	0
Eyelid edema	7 (2.1)	0	1 (0.3)	0
Lacrimation increased	3 (0.9)	1 (0.3)	4 (1.2)	0
Vision blurred	9 (2.8)	0	1 (0.3)	0
Gastrointestinal Disorders				
Abdominal discomfort	7 (2.1)	0	9 (2.7)	0
Abdominal distension	21 (6.4)	2 (0.6)	20 (6.1)	4 (1.2)
Abdominal pain	101 (30.9)	18 (5.5)	67 (20.4)	11 (3.3)
Abdominal pain lower	1 (0.3)	0	5 (1.5)	0
Abdominal pain upper	32 (9.8)	3 (0.9)	35 (10.6)	1 (0.3)
Anal hemorrhage	5 (1.5)	0	3 (0.9)	0
Ascites	33 (10.1)	12 (3.7)	27 (8.2)	13 (4.0)

System Organ Class Preferred Term	Number of Patients (%)			
	CYRAMZA + Paclitaxel N=327		Placebo + Paclitaxel N=329	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Constipation	70 (21.4)	0	71 (21.6)	2 (0.6)
Dental caries	4 (1.2)	0	1 (0.3)	0
Diarrhea	106 (32.4)	12 (3.7)	76 (23.1)	5 (1.5)
Dry mouth	9 (2.8)	0	7 (2.1)	0
Dyspepsia	17 (5.2)	0	16 (4.9)	0
Dysphagia	16 (4.9)	4 (1.2)	19 (5.8)	7 (2.1)
Esophageal pain	4 (1.2)	0	0	0
Esophagitis	4 (1.2)	3 (0.9)	1 (0.3)	0
Flatulence	4 (1.2)	0	3 (0.9)	0
Gastric hemorrhage	5 (1.5)	4 (1.2)	5 (1.5)	2 (0.6)
Gastrointestinal hemorrhage	5 (1.5)	4 (1.2)	4 (1.2)	2 (0.6)
Gastroesophageal reflux disease	11 (3.4)	0	9 (2.7)	0
Gingival bleeding	9 (2.8)	0	0	0
Gingival pain	5 (1.5)	0	0	0
Hematemesis	4 (1.2)	2 (0.6)	1 (0.3)	0
Hemorrhoidal hemorrhage	5 (1.5)	0	3 (0.9)	0
Hemorrhoids	7 (2.1)	0	2 (0.6)	0
Ileus	2 (0.6)	1 (0.3)	4 (1.2)	1 (0.3)
Intestinal obstruction	6 (1.8)	5 (1.5)	5 (1.5)	3 (0.9)
Melena	6 (1.8)	2 (0.6)	3 (0.9)	0
Mouth ulceration	7 (2.1)	1 (0.3)	2 (0.6)	0
Nausea	115 (35.2)	6 (1.8)	108 (32.8)	8 (2.4)
Odynophagia	5 (1.5)	0	0	0
Oral pain	5 (1.5)	0	0	0
Periodontal disease	4 (1.2)	0	0	0
Proctalgia	4 (1.2)	0	2 (0.6)	0
Rectal hemorrhage	4 (1.2)	0	1 (0.3)	0
Small intestinal obstruction	3 (0.9)	3 (0.9)	4 (1.2)	3 (0.9)
Stomatitis	64 (19.6)	2 (0.6)	24 (7.3)	2 (0.6)
Toothache	8 (2.4)	0	1 (0.3)	0
Vomiting	88 (26.9)	10 (3.1)	68 (20.7)	12 (3.6)
General Disorders and Administration Site Conditions				
Asthenia	69 (21.1)	18 (5.5)	45 (13.7)	6 (1.8)
Chest pain	3 (0.9)	2 (0.6)	4 (1.2)	0
Chills	10 (3.1)	0	3 (0.9)	0
Face edema	5 (1.5)	0	0	0
Fatigue	130 (39.8)	23 (7.0)	106 (32.2)	13 (4.0)
Feeling cold	1 (0.3)	0	4 (1.2)	0
General physical health deterioration	17 (5.2)	11 (3.4)	18 (5.5)	11 (3.3)

System Organ Class Preferred Term	Number of Patients (%)			
	CYRAMZA + Paclitaxel N=327		Placebo + Paclitaxel N=329	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Influenza like illness	9 (2.8)	0	5 (1.5)	0
Malaise	16 (4.9)	0	13 (4.0)	0
Mucosal inflammation	10 (3.1)	2 (0.6)	6 (1.8)	0
Non-cardiac chest pain	6 (1.8)	0	4 (1.2)	0
Edema	4 (1.2)	0	3 (0.9)	0
Edema peripheral	82 (25.1)	5 (1.5)	45 (13.7)	2 (0.6)
Pain	10 (3.1)	3 (0.9)	4 (1.2)	1 (0.3)
Performance status decreased	4 (1.2)	1 (0.3)	1 (0.3)	0
Pyrexia	59 (18.0)	3 (0.9)	37 (11.2)	1 (0.3)
Spinal pain	0	0	4 (1.2)	1 (0.3)
Hepatobiliary Disorders				
Hyperbilirubinemia	7 (2.1)	1 (0.3)	7 (2.1)	2 (0.6)
Immune System Disorders				
Drug hypersensitivity	4 (1.2)	1 (0.3)	3 (0.9)	0
Infections and Infestations				
Bronchitis	3 (0.9)	0	5 (1.5)	0
Cystitis	4 (1.2)	0	1 (0.3)	0
Device related infection	5 (1.5)	2 (0.6)	7 (2.1)	4 (1.2)
Gingivitis	5 (1.5)	0	2 (0.6)	0
Influenza	7 (2.1)	0	3 (0.9)	0
Lung infection	6 (1.8)	2 (0.6)	1 (0.3)	0
Nasopharyngitis	23 (7.0)	0	19 (5.8)	0
Oral candidiasis	6 (1.8)	1 (0.3)	3 (0.9)	0
Paronychia	4 (1.2)	0	2 (0.6)	0
Peritonitis	7 (2.1)	6 (1.8)	0	0
Pharyngitis	4 (1.2)	0	2 (0.6)	0
Pneumonia	10 (3.1)	5 (1.5)	7 (2.1)	5 (1.5)
Rhinitis	4 (1.2)	0	1 (0.3)	0
Sepsis	5 (1.5)	5 (1.5)	2 (0.6)	2 (0.6)
Upper respiratory tract infection	15 (4.6)	1 (0.3)	10 (3.0)	0
Urinary tract infection	19 (5.8)	1 (0.3)	12 (3.6)	2 (0.6)
Injury, Poisoning and Procedural Complications				
Infusion related reaction	14 (4.3)	1 (0.3)	8 (2.4)	0
Investigations				
Alanine aminotransferase increased	20 (6.1)	4 (1.2)	18 (5.5)	3 (0.9)
Aspartate aminotransferase increased	27 (8.3)	6 (1.8)	17 (5.2)	5 (1.5)
Blood albumin decreased	5 (1.5)	0	3 (0.9)	1 (0.3)
Blood alkaline phosphatase increased	15 (4.6)	4 (1.2)	15 (4.6)	6 (1.8)
Blood bilirubin increased	16 (4.9)	3 (0.9)	11 (3.3)	5 (1.5)

System Organ Class Preferred Term	Number of Patients (%)			
	CYRAMZA + Paclitaxel N=327		Placebo + Paclitaxel N=329	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Blood creatinine increased	14 (4.3)	2 (0.6)	8 (2.4)	2 (0.6)
Blood lactate dehydrogenase increased	6 (1.8)	1 (0.3)	7 (2.1)	1 (0.3)
Blood potassium increased	4 (1.2)	0	1 (0.3)	0
Blood pressure increased	5 (1.5)	2 (0.6)	2 (0.6)	0
C-reactive protein increased	10 (3.1)	2 (0.6)	6 (1.8)	1 (0.3)
Eastern Cooperative Oncology Group performance status worsened	7 (2.1)	3 (0.9)	4 (1.2)	3 (0.9)
Ejection fraction decreased	5 (1.5)	2 (0.6)	3 (0.9)	1 (0.3)
Electrocardiogram QT prolonged	4 (1.2)	0	2 (0.6)	0
Gamma-glutamyltransferase increased	11 (3.4)	3 (0.9)	6 (1.8)	3 (0.9)
Protein total decreased	7 (2.1)	0	1 (0.3)	0
Weight decreased	45 (13.8)	6 (1.8)	49 (14.9)	4 (1.2)
Weight increased	13 (4.0)	2 (0.6)	11 (3.3)	2 (0.6)
Metabolism and Nutrition Disorders				
Cachexia	3 (0.9)	2 (0.6)	12 (3.6)	5 (1.5)
Decreased appetite	131 (40.1)	10 (3.1)	105 (31.9)	13 (4.0)
Dehydration	15 (4.6)	9 (2.8)	13 (4.0)	8 (2.4)
Hyperglycemia	8 (2.4)	3 (0.9)	10 (3.0)	5 (1.5)
Hyperkalemia	10 (3.1)	5 (1.5)	11 (3.3)	2 (0.6)
Hyperuricemia	5 (1.5)	1 (0.3)	5 (1.5)	0
Hypoalbuminemia	31 (9.5)	4 (1.2)	13 (4.0)	2 (0.6)
Hypocalcemia	11 (3.4)	0	5 (1.5)	1 (0.3)
Hypoglycemia	4 (1.2)	0	2 (0.6)	1 (0.3)
Hypokalemia	14 (4.3)	6 (1.8)	15 (4.6)	5 (1.5)
Hypomagnesemia	10 (3.1)	1 (0.3)	6 (1.8)	0
Hyponatremia	19 (5.8)	11 (3.4)	9 (2.7)	4 (1.2)
Hypophosphatemia	8 (2.4)	4 (1.2)	7 (2.1)	4 (1.2)
Hypoproteinemia	5 (1.5)	0	3 (0.9)	0
Musculoskeletal and Connective Tissue Disorders				
Arthralgia	29 (8.9)	1 (0.3)	20 (6.1)	1 (0.3)
Back pain	39 (11.9)	4 (1.2)	40 (12.2)	5 (1.5)
Bone pain	4 (1.2)	0	7 (2.1)	0
Flank pain	4 (1.2)	0	4 (1.2)	1 (0.3)
Joint swelling	4 (1.2)	0	2 (0.6)	0
Muscle spasms	5 (1.5)	0	5 (1.5)	0
Muscular weakness	5 (1.5)	1 (0.3)	5 (1.5)	3 (0.9)
Musculoskeletal chest pain	11 (3.4)	0	4 (1.2)	0
Musculoskeletal pain	5 (1.5)	1 (0.3)	6 (1.8)	1 (0.3)
Myalgia	34 (10.4)	0	33 (10.0)	1 (0.3)

System Organ Class Preferred Term	Number of Patients (%)			
	CYRAMZA + Paclitaxel N=327		Placebo + Paclitaxel N=329	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Neck pain	5 (1.5)	0	3 (0.9)	0
Pain in extremity	19 (5.8)	0	10 (3.0)	0
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)				
Cancer pain	7 (2.1)	1 (0.3)	7 (2.1)	2 (0.6)
Malignant neoplasm progression	52 (15.9)	47 (14.4)	60 (18.2)	59 (17.9)
Tumour pain	4 (1.2)	0	4 (1.2)	1 (0.3)
Nervous System Disorders				
Dizziness	19 (5.8)	1 (0.3)	13 (4.0)	0
Dysgeusia	29 (8.9)	0	21 (6.4)	0
Headache	32 (9.8)	0	22 (6.7)	1 (0.3)
Hypoesthesia	10 (3.1)	1 (0.3)	8 (2.4)	0
Lethargy	5 (1.5)	1 (0.3)	5 (1.5)	0
Neuropathy peripheral	47 (14.4)	10 (3.1)	30 (9.1)	7 (2.1)
Neurotoxicity	9 (2.8)	3 (0.9)	3 (0.9)	0
Paresthesia	24 (7.3)	6 (1.8)	25 (7.6)	1 (0.3)
Peripheral sensory neuropathy	57 (17.4)	6 (1.8)	36 (10.9)	3 (0.9)
Polyneuropathy	18 (5.5)	4 (1.2)	22 (6.7)	4 (1.2)
Somnolence	4 (1.2)	0	2 (0.6)	0
Psychiatric Disorders				
Anxiety	7 (2.1)	0	9 (2.7)	0
Depression	8 (2.4)	1 (0.3)	7 (2.1)	0
Insomnia	30 (9.2)	0	26 (7.9)	0
Renal and Urinary Disorders				
Dysuria	3 (0.9)	0	4 (1.2)	0
Hematuria	16 (4.9)	0	11 (3.3)	0
Hydronephrosis	6 (1.8)	1 (0.3)	3 (0.9)	1 (0.3)
Proteinuria	54 (16.5)	4 (1.2)	20 (6.1)	0
Renal failure acute	1 (0.3)	1 (0.3)	5 (1.5)	3 (0.9)
Respiratory, Thoracic and Mediastinal Disorders				
Cough	40 (12.2)	0	25 (7.6)	0
Dysphonia	17 (5.2)	1 (0.3)	9 (2.7)	0
Dyspnea	42 (12.8)	8 (2.4)	31 (9.4)	2 (0.6)
Epistaxis	100 (30.6)	0	23 (7.0)	0
Hemoptysis	7 (2.1)	1 (0.3)	3 (0.9)	0
Hiccups	9 (2.8)	0	11 (3.3)	0
Interstitial lung disease	0	0	4 (1.2)	2 (0.6)
Oropharyngeal pain	15 (4.6)	0	10 (3.0)	0
Pleural effusion	13 (4.0)	4 (1.2)	6 (1.8)	4 (1.2)
Pneumonitis	4 (1.2)	1 (0.3)	2 (0.6)	0

System Organ Class Preferred Term	Number of Patients (%)			
	CYRAMZA + Paclitaxel N=327		Placebo + Paclitaxel N=329	
	Any Grade	Grade ≥ 3	Any Grade	Grade ≥ 3
Productive cough	13 (4.0)	0	9 (2.7)	0
Pulmonary embolism	4 (1.2)	4 (1.2)	11 (3.3)	10 (3.0)
Rhinorrhea	13 (4.0)	0	9 (2.7)	0
Skin and Subcutaneous Tissue Disorders				
Acne	6 (1.8)	0	2 (0.6)	0
Alopecia	107 (32.7)	0	127 (38.6)	1 (0.3)
Dermatitis acneiform	10 (3.1)	0	7 (2.1)	0
Dry skin	25 (7.6)	0	10 (3.0)	1 (0.3)
Erythema	7 (2.1)	1 (0.3)	4 (1.2)	0
Nail discolouration	6 (1.8)	0	2 (0.6)	0
Nail disorder	13 (4.0)	0	5 (1.5)	0
Night sweats	4 (1.2)	0	3 (0.9)	0
Onychomadesis	5 (1.5)	0	1 (0.3)	0
Palmar-plantar erythrodysesthesia syndrome	4 (1.2)	1 (0.3)	2 (0.6)	1 (0.3)
Pruritus	21 (6.4)	1 (0.3)	11 (3.3)	0
Rash	35 (10.7)	0	26 (7.9)	0
Rash maculo-papular	8 (2.4)	0	1 (0.3)	0
Vascular Disorders				
Deep vein thrombosis	5 (1.5)	3 (0.9)	3 (0.9)	1 (0.3)
Flushing	8 (2.4)	0	3 (0.9)	0
Hemorrhage	4 (1.2)	0	0	0
Hot flush	3 (0.9)	0	10 (3.0)	0
Hypertension	78 (23.9)	46 (14.1)	16 (4.9)	8 (2.4)
Hypotension	10 (3.1)	4 (1.2)	8 (2.4)	2 (0.6)

Note: A patient was only counted once for each category.
Missing grades are included in Any Grade.
Adverse events were coded using MedDRA version 16.0.

Less Common Clinical Trial Adverse Drug Reactions (< 1%)

There were no clinically important adverse drug reactions reported in < 1% of patients treated with CYRAMZA plus paclitaxel in the RAINBOW study.

Immunogenicity

In 23 clinical trials, 86/2890 (3.0%) of the CYRAMZA-treated patients tested positive for treatment-emergent anti-ramucirumab antibodies by an enzyme-linked immunosorbent assay (ELISA). Neutralizing antibodies were detected in 14 of the 86 patients who tested positive for treatment-emergent anti-ramucirumab antibodies.

Post-Market Adverse Reactions

The following adverse reactions have been identified during post-approval use of CYRAMZA. Because these reactions are reported voluntarily from a population of uncertain size, it is

generally not possible to reliably estimate their frequency.

Blood and lymphatic system
Thrombotic microangiopathy

Neoplasms benign, malignant and unspecified
Hemangioma

Nervous system
Posterior Reversible Encephalopathy Syndrome (see WARNINGS AND PRECAUTIONS and DOSAGE AND ADMINISTRATION)

DRUG INTERACTIONS

Drug-Drug Interactions

Paclitaxel: No pharmacokinetic drug-drug interactions were observed between CYRAMZA and paclitaxel. The pharmacokinetics (PK) of paclitaxel was not affected when coadministered with CYRAMZA and the PK of CYRAMZA was not affected when coadministered with paclitaxel.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Laboratory Interactions

Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION

Dosing Considerations

It is recommended that treatment be continued until progression of the underlying disease or until unacceptable toxicity.

Recommended Dose and Dosage Adjustment

Gastric Cancer
CYRAMZA single agent:
The recommended dose of CYRAMZA as a single agent is 8 mg/kg every 2 weeks administered as an intravenous infusion over approximately 60 minutes (maximum infusion rate 25 mg/min).

CYRAMZA in combination with paclitaxel:
The recommended dose of CYRAMZA is 8 mg/kg administered by intravenous infusion over approximately 60 minutes on days 1 and 15 of a 28-day cycle prior to paclitaxel infusion.

Administer paclitaxel at 80 mg/m^2 by intravenous infusion over approximately 60 minutes on days 1, 8 and 15 of a 28-day cycle. Criteria to be met prior to each paclitaxel administration are provided in Table 5.

Table 5: Criteria to be Met Prior to Each Paclitaxel Administration

	Criteria
Neutrophils	**Day 1:** ≥ 1.5 x 10^9/L **Days 8 and 15:** ≥ 1.0 x 10^9/L
Platelets	**Day 1:** ≥ 100 x 10^9/L **Days 8 and 15:** ≥ 75 x 10^9/L
Bilirubin	≤ 1.5 x upper limit of normal value (ULN)
AST/ALT	**No liver metastases:** ALT/AST ≤ 3 x ULN **Liver metastases:** ALT/AST ≤ 5 x ULN

Premedication

Premedicate all patients with a histamine H1 antagonist (e.g., diphenhydramine) intravenously prior to administration of CYRAMZA.

If a patient experiences a Grade 1 or 2 infusion-related reaction (IRR), besides the histamine H1 antagonist, also administer dexamethasone (or equivalent) and acetaminophen prior to each CYRAMZA infusion (see *Dose Adjustments* below).

See paclitaxel prescribing information for paclitaxel premedication requirements.

Dose Adjustments

Infusion-Related Reactions

Reduce the CYRAMZA infusion rate by 50% for the duration of the infusion and all subsequent infusions if the patient experiences a Grade 1 or 2 IRR [per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)] (see *Premedication* subsection above). Immediately and permanently discontinue CYRAMZA for Grade 3 or 4 IRRs (see WARNINGS AND PRECAUTIONS).

Hypertension

Monitor blood pressure during treatment with CYRAMZA and treat as clinically indicated. Temporarily suspend CYRAMZA for severe hypertension until controlled with medical management and permanently discontinue CYRAMZA for severe hypertension that cannot be controlled with antihypertensive therapy (see WARNINGS AND PRECAUTIONS).

Posterior Reversible Encephalopathy Syndrome

Permanently discontinue CYRAMZA for patients who experience Posterior Reversible Encephalopathy Syndrome (PRES) (see WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS, Post-Market Adverse Reactions).

Proteinuria

Monitor for the development or worsening of proteinuria during CYRAMZA therapy. If the urine protein level is ≥ 2+, perform a 24-hour urine collection. Temporarily discontinue CYRAMZA administration if the urine protein level is ≥ 2 g/24 hours. Resume treatment at a

reduced dose level (to 6 mg/kg every 2 weeks) once the urine protein level returns to < 2 g/24 hours. A second dose reduction (to 5 mg/kg every 2 weeks) is recommended if a urine protein level ≥ 2 g/24 hours reoccurs.

Permanently discontinue CYRAMZA therapy if the urine protein level is > 3 g/24 hours or in the setting of nephrotic syndrome.

Wound Healing Complications
Interrupt CYRAMZA prior to scheduled surgery until the wound is fully healed (see WARNINGS AND PRECAUTIONS).

Arterial Thromboembolic Events, Gastrointestinal Perforations, or Grade 3 or 4 Bleeding
Permanently discontinue CYRAMZA in patients who experience a severe arterial thromboembolic event, gastrointestinal perforations, or Grade 3 or 4 bleeding (see WARNINGS AND PRECAUTIONS).

Paclitaxel
Paclitaxel dose reductions may be applied based upon the grade of toxicity experienced by the patient. For NCI-CTCAE Grade 4 hematological toxicity or Grade 3 paclitaxel-related nonhematological toxicity, it is recommended to reduce the paclitaxel dose by 10 mg/m^2 for all following cycles. A second reduction of 10 mg/m^2 is recommended if these toxicities persist or reoccur. See paclitaxel prescribing information for additional dosage and administration recommendations.

Administration
Administer CYRAMZA as an intravenous infusion only. **Do not administer CYRAMZA as an intravenous push or bolus.**

Only use sterile sodium chloride (0.9%) solution for injection as a diluent. Do not use dextrose as a diluent.

Instructions for Use/Handling

1. Prepare the infusion solution using aseptic technique to ensure the sterility of the prepared solution.

2. Each vial is intended for single use only. Inspect the content of the vials for particulate matter and discolouration (material should be clear to slightly opalescent and colourless to slightly yellow) prior to dilution. If particulate matter or discolourations are identified, discard the vial.

3. Calculate the dose and volume of CYRAMZA needed to prepare the infusion solution. Vials contain either 100 mg or 500 mg as a 10 mg/mL solution of ramucirumab. Only use sterile sodium chloride (0.9%) solution for injection as a diluent.

   In case of prefilled intravenous infusion container usage:

Based on the calculated volume of CYRAMZA, remove the corresponding volume of sterile sodium chloride (0.9%) solution for injection from the prefilled 250 mL intravenous container. Aseptically transfer the calculated volume of CYRAMZA to the intravenous container. The final total volume in the container should be 250 mL. The container should be gently inverted to ensure adequate mixing. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medications.

In case of empty intravenous infusion container usage:
Aseptically transfer the calculated volume of CYRAMZA into an empty intravenous container. Add a sufficient quantity of sterile sodium chloride (0.9%) solution for injection to the container to make the total volume 250 mL. The container should be gently inverted to ensure adequate mixing. DO NOT FREEZE OR SHAKE the infusion solution. DO NOT dilute with other solutions or co-infuse with other electrolytes or medications.

4. Parenteral drug products should be inspected visually for particulate matter prior to administration. If particulate matter is identified, discard the infusion solution.

5. Discard any unused portion of CYRAMZA left in a vial, as the product contains no preservatives.

6. Administer via infusion pump. A separate infusion line with a protein sparing 0.22 micron filter must be used for the infusion and the line must be flushed with sterile sodium chloride (0.9%) solution for injection at the end of the infusion.

OVERDOSAGE

In case of overdose, use supportive therapy. There is no known antidote to ramucirumab overdose.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

VEGF Receptor 2 (VEGFR-2) is the key mediator of VEGF induced angiogenesis. CYRAMZA (ramucirumab) is a human receptor-targeted antibody that specifically binds VEGFR-2 and blocks binding of VEGF-A, VEGF-C, and VEGF-D. As a result, CYRAMZA inhibits ligand stimulated activation of VEGFR-2 and its downstream signaling components, including p44/p42 mitogen-activated protein kinases, neutralizing ligand-induced proliferation and migration of human endothelial cells. Ramucirumab inhibited angiogenesis in an *in vivo* animal model.

Pharmacodynamics

Ramucirumab does not cross-react with murine VEGFR-2. Consequently, ramucirumab cannot be tested in mouse tumour models in which the host vasculature must be targeted. Therefore, in vivo studies were conducted using a "proof-of-principle" surrogate antibody for ramucirumab, designated DC101 that is an antagonist rat anti-mouse VEGFR-2. These preclinical studies were critical for modeling potential efficacy of ramucirumab in several tumour types (including gastric, hepatic, colorectal, lung, and breast cancer), characterizing its potential to combine with chemotherapy, and demonstrating its likely antiangiogenic mechanism of action in vivo.

Pharmacokinetics

The pharmacokinetics of ramucirumab were evaluated in a Phase 1 study in patients with advanced gastric adenocarcinomas. The pharmacokinetic parameters of ramucirumab following a single dose of 8 mg/kg ramucirumab IV infusion is summarized in Table 6.

Table 6: Summary of Ramucirumab's Pharmacokinetic Parameters in Patients with Gastric Cancer

N=6	C_{max} (µg/mL)	$t_{½}$ (day)	$AUC_{0-\infty}$ (µg•day/mL)	Clearance (L/h)	Volume of distribution (L)
Single dose Geometric Mean (CV%)[a]	171 (26)	7.56[b] (5.74-9.36)	1420[c]	0.0166[c]	3.27[c]

Abbreviations: AUC = area under the concentration-time curve; $AUC_{(0-\infty)}$ = AUC from time 0 extrapolated to infinity; C_{max} = maximum observed serum concentration; $t_{1/2}$ = apparent elimination half-life.
N_{PK} = number of patients with valid PK parameter.

[a] Geometric mean (range) reported for $t_{1/2}$.

[b] where N_{PK}=4.

[c] NPK = 1.

Following the dose regimen of 8 mg/kg ramucirumab (single agent) every 2 weeks, the geometric means of ramucirumab C_{min} were 49.5 µg/mL (range of 6.3-228 µg/mL) and 74.4 µg/mL (range of 13.8-234 µg/mL) prior to administration of the fourth and seventh dose, respectively, in serum from patients with advanced gastric cancer.

Absorption: CYRAMZA is for intravenous use only.

Distribution: Based on population pharmacokinetic approach (PopPK), the mean volume of distribution at steady state for ramucirumab was 5.5 L.

Elimination: Based on PopPK, the mean clearance of ramucirumab was 0.014 L/hr and the mean half-life was 15 days.

Special Populations and Conditions

PopPK analysis suggested age, gender, body weight, and race had no detectable, clinically meaningful effect on the PK of ramucirumab.

Geriatrics: Based on the results of the PopPK analysis, there was no difference in ramucirumab

exposure in patients ≥ 65 years of age compared to patients < 65 years old.

Hepatic Impairment: No formal studies have been conducted to evaluate the effect of hepatic impairment on the PK of ramucirumab.

Renal Impairment: No formal studies have been conducted to evaluate the effect of renal impairment on the PK of ramucirumab. Based on the results of the PopPK analysis, ramucirumab exposure was similar in patients with mild renal impairment (calculated creatinine clearance [CrCl] ≥ 60 to < 90 mL/min) and moderate renal impairment (CrCl ≥ 30 to < 60 mL/min) as to patients with normal renal function (CrCl ≥ 90 mL/min). No data were available from patients with severe renal impairment (CrCl < 30 mL/min).

STORAGE AND STABILITY

Vials should be stored in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton in order to protect from light. DO NOT FREEZE OR SHAKE the vial. The shelf life is 24 months when vials are stored at 2°C to 8°C (36°F to 46°F) in the original carton protected from light.

The chemical and physical stability for the CYRAMZA (ramucirumab) infusion solution was demonstrated for up to 24 hours at 2°C to 8°C (36°F to 46°F) or for 4 hours at room temperature (below 30°C [86°F]). DO NOT FREEZE OR SHAKE the CYRAMZA infusion solution.

DOSAGE FORMS, COMPOSITION AND PACKAGING

CYRAMZA (ramucirumab) is supplied as a sterile, preservative-free solution for intravenous infusion in 10 mL or 50 mL single-use vials. Each vial contains either 100 mg ramucirumab in 10 mL (10 mg/mL) or 500 mg ramucirumab in 50 mL (10 mg/mL). Non-medicinal ingredients are: L-histidine, L-histidine monohydrochloride, sodium chloride, glycine, polysorbate 80, and water for injection. Vials are individually packaged in a carton.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Ramucirumab

Chemical name: Immunoglobulin G1, anti-(human vascular endothelial growth factor receptor VEGFR-2 extracellular domain) (human monoclonal IMC-1121B γ-chain), disulfide with human monoclonal IMC-1121B κ-chain, dimer

Immunoglobulin G1, anti-(human vascular endothelial growth factor receptor 2 (kinase insert domain receptor (KDR), human monoclonal IMC-1121B [125-leucine($CH1^{9}$-F>L)]γ1 heavy chain (219-214')-disulfide with human monoclonal IMC-1121B κ light chain dimer (225-225":228-228")-bisdisulfide

Structure: Ramucirumab is a human monoclonal antibody composed of 2 heavy chain (γ1-chain) molecules consisting of 446 amino acid residues each and 2 light chain (κ-chain) molecules consisting of 214 amino acid residues each. The antibody contains one conserved N-linked glycosylation site at each heavy chain, in the Fc region.

Molecular mass: The average molecular mass of ramucirumab with the predominant form of N-linked glycosylation is 147 kDa.

Physicochemical properties: Clear to slightly opalescent and colourless to slightly yellow liquid. The solution pH is 5.7 to 6.3. The osmolality is 250 to 320 mOsm/kg.

Product Characteristics

Ramucirumab is produced in genetically engineered mammalian NS0 cells.

Ramucirumab drug product is a sterile, preservative-free solution for infusion of ramucirumab formulated in an aqueous solution at a concentration of 10 mg/mL. The buffer contains 10 mM histidine, 75 mM sodium chloride, 133 mM glycine, and 0.01% polysorbate 80.

All excipients used for the manufacture of ramucirumab drug product are of pharmacopeial grade.

The excipients used in the ramucirumab drug product are not of human or animal origin.

CLINICAL TRIALS

Gastric Cancer - Single Agent

The safety and efficacy of CYRAMZA (ramucirumab) were evaluated in patients with advanced gastric cancer or gastro-esophageal junction (GEJ) adenocarcinoma after disease progression during or following first-line platinum- or fluoropyrimidine-containing therapy (REGARD study)[1].

Study Demographics and Trial Design

Table 7: Patient Demographics – REGARD

Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Median age (range)	Gender (number)
Global, randomized (2:1), double-blind, placebo-controlled, multi-centre	CYRAMZA 8 mg/kg or placebo solution by intravenous infusion every 2 weeks	CYRAMZA (N=238) Placebo (N=117)	CYRAMZA arm Median age = 60 (30-86) years Placebo arm Median age = 60 (24-87) years	CYRAMZA arm Male (169) Female (69) Placebo arm Male (79) Female (38)

Randomized Trial

REGARD was a global, Phase 3, multi-centre, randomized, double-blind study of CYRAMZA plus best supportive care (BSC) versus placebo plus BSC that randomized (2:1) 355 patients with locally advanced or metastatic gastric cancer (including adenocarcinoma of the GEJ) who previously received platinum- or fluoropyrimidine-containing chemotherapy. The primary endpoint was overall survival and secondary endpoints included progression-free survival (PFS) and 12-week PFS rate. Patients were required to have experienced disease progression either within 4 months after the last dose of first-line therapy for locally advanced or metastatic disease or within 6 months after the last dose of adjuvant therapy. Patients were also required to have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients received either an intravenous infusion of CYRAMZA 8 mg/kg (n=238) or placebo solution (n=117) every 2 weeks. Randomization was stratified by weight loss over the prior 3 months (≥ 10% versus < 10%), geographic region, and location of the primary tumour (gastric versus GEJ).

Demographic and baseline characteristics were similar between treatment arms (Table 8). Patients had experienced disease progression during or following first-line therapy (85.1%), adjuvant therapy only (14.4%), or neoadjuvant therapy only (0.6%). Prior chemotherapy for gastric cancer consisted of platinum/fluoropyrimidine combination therapy (81.1%), fluoropyrimidine containing regimens without platinum (14.9%), or platinum-containing regimens without fluoropyrimidine (3.7%).

Table 8: Demographic, Baseline, and Pre-Treatment Disease Characteristics ITT Population; REGARD

	Variable	CYRAMZA + BSC N = 238	Placebo + BSC N = 117	Total N = 355
Demographic and Baseline Characteristics				
Sex n (%)	Male	169 (71.0)	79 (67.5)	248 (69.9)
	Female	69 (29.0)	38 (32.5)	107 (30.1)
Age (years)	Median age (range)	60.0 (30-86)	60.0 (24-87)	60.0 (24-87)
Age group n (%)	Age < 65 years	156 (65.5)	71 (60.7)	227 (63.9)
	Age ≥ 65 years	82 (34.5)	46 (39.3)	128 (36.1)
Race n (%)	White	181 (76.1)	91 (77.8)	272 (76.6)
	Asian	39 (16.4)	17 (14.5)	56 (15.8)
	Black	4 (1.7)	2 (1.7)	6 (1.7)
	Other	14 (5.9)	7 (6.0)	21 (5.9)
ECOG PS n (%)	0	67 (28.2)	31 (26.5)	98 (27.6)
	1	171 (71.8)	85 (72.6)	256 (72.1)
	2	0 (0.0)	1 (0.9)[a]	1 (0.3)[a]
Pre-Treatment Disease Characteristics				
Measurable disease n (%)	Yes	218 (91.6)	106 (90.6)	324 (91.3)
	No	20 (8.4)	11 (9.4)	31 (8.7)
Histology n (%)	Intestinal	52 (21.8)	35 (29.9)	87 (24.5)
	Diffuse	96 (40.3)	44 (37.6)	140 (39.4)
	Undetermined/Not available	90 (37.8)	38 (32.5)	128 (36.1)
Primary tumour present n (%)	Yes	174 (73.1)	86 (73.5)	260 (73.2)
	No	64 (26.9)	31 (26.5)	95 (26.8)
Site of metastasis n (%)	Peritoneal	64 (26.9)	45 (38.5)	109 (30.7)
	Liver	104 (43.7)	56 (47.9)	160 (45.1)
Number of metastatic sites	0	4 (1.7)	2 (1.7)	6 (1.7)
	1	72 (30.3)	24 (20.5)	96 (27.0)
	2	87 (36.6)	45 (38.5)	132 (37.2)
	≥ 3	75 (31.5)	46 (39.3)	121 (34.1)
Progression-free interval on prior therapy n (%)	< 6 months	154 (64.7)	83 (70.9)	237 (66.8)
	≥ 6 months	81 (34.0)	34 (29.1)	115 (32.4)
	Missing	3 (1.3)	0 (0.0)	3 (0.8)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category.

[a] Patient randomized in violation of Inclusion Criterion 9.

Patients received a median of 4 doses (range 1-34) of CYRAMZA or 3 doses (range 1-30) of placebo, with the median duration of therapy being 8 weeks or 6 weeks, respectively. The

median relative dose intensity of CYRAMZA was 99.6%. Eleven percent of patients treated with CYRAMZA and 6% of patients on placebo discontinued therapy due to adverse events.

Study Results

Overall survival was statistically significantly improved in patients receiving CYRAMZA compared with patients receiving placebo (hazard ratio [HR] 0.776; 95%CI: 0.603 to 0.998; p=0.0473), corresponding to a 22% reduction in the risk of death and an increase in median survival to 5.2 months for CYRAMZA from 3.8 months for placebo.

Progression-free survival was statistically significantly improved in patients receiving CYRAMZA compared with patients receiving placebo (HR 0.483; 95%CI: 0.376 to 0.620; p < 0.0001), corresponding to a 52% reduction in the risk of progression or death and an increase in median PFS to 2.1 months for CYRAMZA from 1.3 months for placebo. Efficacy results are shown in Table 9.

Table 9: Summary of Efficacy Data – Intent to Treat (ITT) Population

	CYRAMZA + BSC N=238	**Placebo + BSC N=117**
Overall Survival		
Median – months (95% CI)	5.2 (4.4, 5.7)	3.8 (2.8, 4.7)
Hazard Ratio (95% CI)	0.776 (0.603, 0.998)	
Stratified Log-rank p-value	0.0473	
Progression-free Survival		
Median – months (95% CI)	2.1 (1.5, 2.7)	1.3 (1.3, 1.4)
Hazard Ratio (95% CI)	0.483 (0.376, 0.620)	
Stratified Log-rank p-value	<0.0001	
12-week PFS rate, %	40.1	15.8
Objective Response Rate (CR + PR)*		
Rate – percent	3.4	2.6

Abbreviations: CI = confidence interval, PFS = progression-free survival

Primary analysis of OS and PFS were stratified by the randomization strata (weight loss over the prior 3 months, location of primary tumour and geographical region).

A gate-keeping strategy was utilized to control the overall type I error at 0.05 (2-sided) for the analysis of the primary OS endpoint and secondary PFS endpoint. Only if the primary OS test was significant would the analysis of PFS be considered inferential.

* based on tumour assessments by investigator

Figures 1 and 2 display the Kaplan-Meier curves for overall survival and progression-free survival, respectively, in the ITT population.

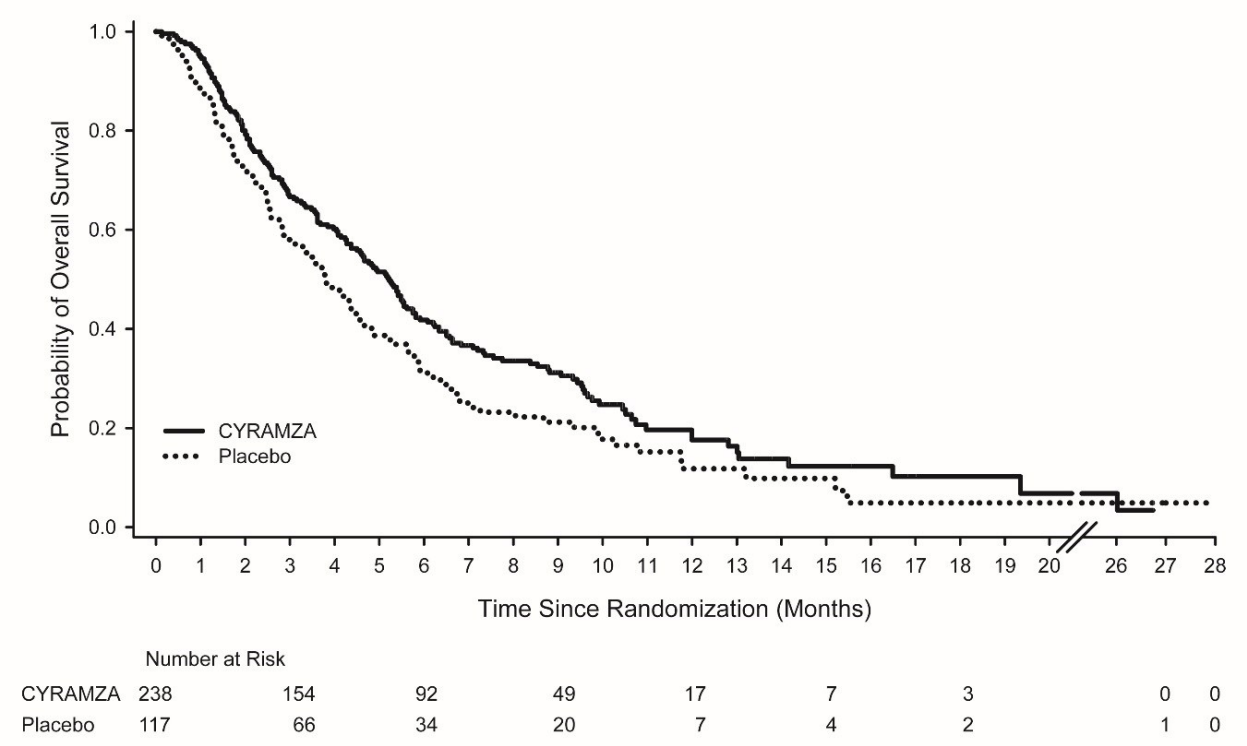

Figure 1: Kaplan-Meier curves of overall survival for CYRAMZA versus placebo in REGARD.

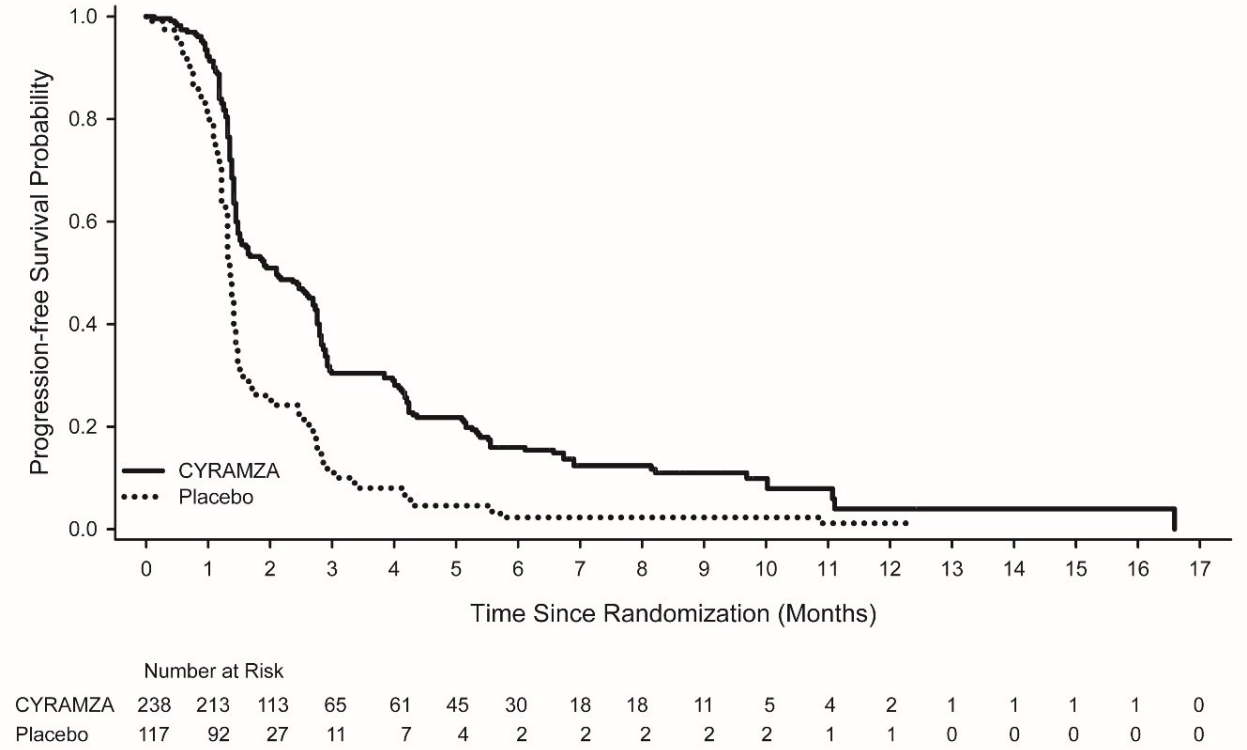

Figure 2: Kaplan-Meier curves of progression-free survival for CYRAMZA versus placebo in REGARD.

Gastric Cancer – Combination with Paclitaxel

The safety and efficacy of CYRAMZA in combination with paclitaxel were evaluated in patients with locally advanced or metastatic gastric cancer (including adenocarcinoma of the GEJ) following platinum- and fluoropyrimidine-containing chemotherapy, with or without anthracycline (RAINBOW study)[2].

Study Demographics and Trial Design

Table 10: Patient Demographics – RAINBOW

Trial design	Dosage, route of administration and duration	Study subjects (N=number)	Median age (range)	Gender (number)
Global, randomized (1:1), double-blind, placebo-controlled, multi-centre	CYRAMZA 8 mg/kg or placebo solution by intravenous infusion every 2 weeks (days 1 and 15) plus paclitaxel 80 mg/m^2 by intravenous infusion on days 1, 8, and 15 of each 28-day cycle	CYRAMZA + Paclitaxel (N=330) Placebo + Paclitaxel (N=335)	CYRAMZA + Paclitaxel arm Median age = 61 (25-83) years Placebo + Paclitaxel arm Median age = 61 (24-84) years	CYRAMZA + Paclitaxel arm Male (229) Female (101) Placebo + Paclitaxel arm Male (243) Female (92)

Randomized Trial

RAINBOW was a global, Phase 3, multi-centre, randomized, double-blind study of CYRAMZA plus paclitaxel versus placebo plus paclitaxel that randomized (1:1) 665 patients with locally advanced or metastatic gastric cancer (including adenocarcinoma of the GEJ) who previously received platinum- and fluoropyrimidine-containing chemotherapy, with or without anthracycline. The primary endpoint was overall survival and the secondary endpoints included progression free survival and overall response rate. Patients were required to have experienced disease progression during, or within 4 months after the last dose of, first-line therapy. Patients were also required to have ECOG performance status of 0 or 1. Patients received either an intravenous infusion of CYRAMZA at 8 mg/kg (n=330) or placebo (n=335) every 2 weeks (on days 1 and 15) of a 28-day cycle. Paclitaxel at 80 mg/m^2 was administered by intravenous infusion on days 1, 8, and 15 of each 28-day cycle. Randomization was stratified by geographic region, time to progression from the start of first-line therapy (< 6 months versus ≥6 months) and disease measurability.

Demographics and baseline characteristics were similar between treatment arms (Table 11). Two-thirds of the patients experienced disease progression while on first-line therapy (66.8%). The majority of patients (76.1%) experienced disease progression within 6 months from the start of first-line therapy. Prior chemotherapy for gastric cancer consisted of platinum/fluoropyrimidine combination therapy without anthracycline (75.0%) or platinum/fluoropyrimidine combination therapy with anthracycline (24.5%).

Table 11: Demographic, Baseline, and Pre-Treatment Disease Characteristics ITT Population; RAINBOW

	Variable	CYRAMZA + Paclitaxel N = 330 n (%)	Placebo + Paclitaxel N = 335 n (%)	Total N = 665 n (%)
Demographic and Baseline Characteristics				
Sex n (%)	Male	229 (69.4)	243 (72.5)	472 (71.0)
	Female	101 (30.6)	92 (27.5)	193 (29.0)
Age (years)	Median age (range)	61 (25-83)	61 (24-84)	61 (24-84)
Age group n (%)	Age < 65 years	204 (61.8)	212 (63.3)	416 (62.6)
	Age ≥ 65 years	126 (38.2)	123 (36.7)	249 (37.4)
Race n (%)	White	208 (63.0)	199 (59.4)	407 (61.2)
	Asian	110 (33.3)	121 (36.1)	231 (34.7)
	Black	6 (1.8)	6 (1.8)	12 (1.8)
	Other	6 (1.8)	9 (2.7)	15 (2.4)
ECOG PS n (%)	0	117 (35.5)	144 (43.0)	261 (39.2)
	1	213 (64.5)	191 (57.0)	404 (60.8)
Pre-Treatment Disease Characteristics				
Histological subtype	Intestinal Type	145 (43.9)	135 (40.3)	280 (42.1)
	Diffuse Type	115 (34.8)	133 (39.7)	248 (37.3)
	Mixed	21 (6.4)	14 (4.2)	35 (5.3)
	Unknown/Missing	49 (14.8)	53 (15.8)	102 (15.3)
Grade	Well differentiated	28 (8.5)	22 (6.6)	50 (7.5)
	Moderately differentiated	96 (29.1)	106 (31.6)	202 (30.4)
	Poorly differentiated	186 (56.4)	186 (55.5)	372 (55.9)
	Unknown/Missing	20 (6.1)	21 (6.3)	41 (6.2)
Primary tumour location	Gastric	264 (80.0)	264 (78.8)	528 (79.4)
	GEJ	66 (20.0)	71 (21.2)	137 (20.6)
Primary tumour present	Yes	209 (63.3)	209 (62.4)	418 (62.9)
	No	121 (36.7)	126 (37.6)	247 (37.1)
Extent of disease	Metastatic	324 (98.2)	324 (96.7)	648 (97.4)
	Locally Advanced	6 (1.8)	10 (3.0)	16 (2.4)
Most common sites of metastasis[a]	Lymph Nodes	215 (65.2)	205 (61.2)	420 (63.2)
	Peritoneal	163 (49.4)	152 (45.4)	315 (47.4)
	Liver	150 (45.5)	138 (41.2)	288 (43.3)
	Lung	77 (23.3)	70 (20.9)	147 (22.1)
Number of metastatic sites[b]	0 - 2	209 (63.3)	232 (70.3)	441 (66.3)
	≥ 3	121 (36.7)	103 (30.7)	224 (33.7)

	Variable	CYRAMZA + Paclitaxel N = 330 n (%)	Placebo + Paclitaxel N = 335 n (%)	Total N = 665 n (%)
Weight loss over prior 3 months	≥ 10%	53 (16.1)	47 (14.0)	100 (15.0)
	< 10%	277 (83.9)	286 (85.4)	563 (84.7)
	Missing	0	2 (0.6)	2 (0.3)
Presence of ascites	Yes	130 (39.4)	107 (31.9)	237 (35.6)
	No	200 (60.6)	228 (68.1)	428 (64.4)

Abbreviations: ECOG PS = Eastern Cooperative Oncology Group performance status; GEJ = gastro-esophageal junction; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; NOS = not otherwise specified.

[a] Sites of metastasis occurring in ≥ 20% of patients. Patients may record multiple sites of metastatic disease.

[b] Derived from the sites of metastatic disease case report form pages. Unknown and missing categories were counted as not involved.

Patients treated with CYRAMZA plus paclitaxel received a median of 9 doses (range 1-53) of CYRAMZA, with the median duration of therapy being 19 weeks. Patients treated with placebo plus paclitaxel received a median of 6 doses (range of 1-46) of placebo, with the median duration of therapy being 12 weeks. The median relative dose intensity of CYRAMZA was 98.6% and of placebo was 99.6%. The median relative dose intensity of paclitaxel was 87.7% for the CYRAMZA plus paclitaxel arm and 93.2% for the placebo plus paclitaxel arm. Post discontinuation systemic anticancer therapy was given to 47.9% of patients receiving CYRAMZA plus paclitaxel and 46.0% of patients receiving placebo plus paclitaxel.

Study Results

Overall survival was statistically significantly improved in patients receiving CYRAMZA plus paclitaxel compared with patients receiving placebo plus paclitaxel (HR 0.807; 95%CI: 0.678 to 0.962; p=0.0169), corresponding to a 19% reduction in the risk of death and an increase in median survival to 9.63 months for CYRAMZA plus paclitaxel from 7.36 months for placebo plus paclitaxel.

Progression-free survival was statistically significantly improved in patients receiving CYRAMZA plus paclitaxel compared with patients receiving placebo plus paclitaxel (HR 0.635; 95%CI: 0.536 to 0.752; p < 0.0001), corresponding to a 37% reduction in the risk of progression or death and an increase in median PFS to 4.4 months for CYRAMZA plus paclitaxel from 2.9 months for placebo plus paclitaxel. Efficacy results are shown in Table 12.

Table 12: Summary of Efficacy Data – Intent to Treat (ITT) Population

	CYRAMZA + Paclitaxel N=330	Placebo + Paclitaxel N=335
Overall Survival		
Median – months (95% CI)	9.6 (8.5, 10.8)	7.4 (6.3, 8.4)
Hazard Ratio (95% CI)	0.807 (0.678, 0.962)	
Stratified Log-rank p-value	0.0169	
Progression-free Survival		
Median – months (95% CI)	4.4 (4.2, 5.3)	2.9 (2.8, 3.0)

	CYRAMZA + Paclitaxel N=330	Placebo + Paclitaxel N=335
Hazard Ratio (95% CI)	0.635 (0.536, 0.752)	
Stratified Log-rank p-value	<0.0001	
Objective Response Rate (CR + PR)*		
Rate – percent	27.9	16.1

Abbreviations: CI = confidence interval

Primary analysis of OS and PFS were stratified by the randomization strata (geographic region, time-to-progression from the start of first-line therapy and disease measurability).

A gate-keeping strategy was utilized to control the overall type I error at 0.05 (2-sided) for the analysis of the primary OS endpoint and secondary PFS endpoint. Only if the primary OS test was significant would the analysis of PFS be considered inferential.

* based on tumour assessments by investigator

Figures 3 and 4 display the Kaplan-Meier curves for overall survival and progression-free survival, respectively, in the ITT population.

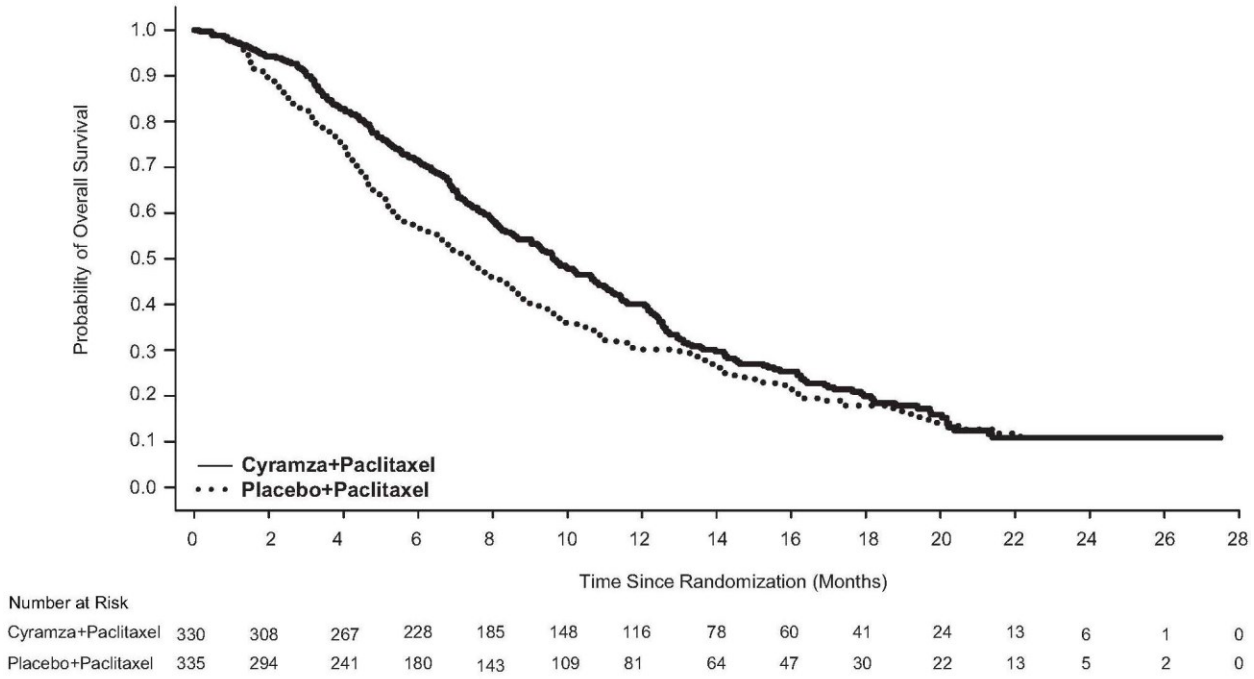

Figure 3: Kaplan-Meier curves of overall survival for CYRAMZA plus paclitaxel versus placebo plus paclitaxel in RAINBOW.

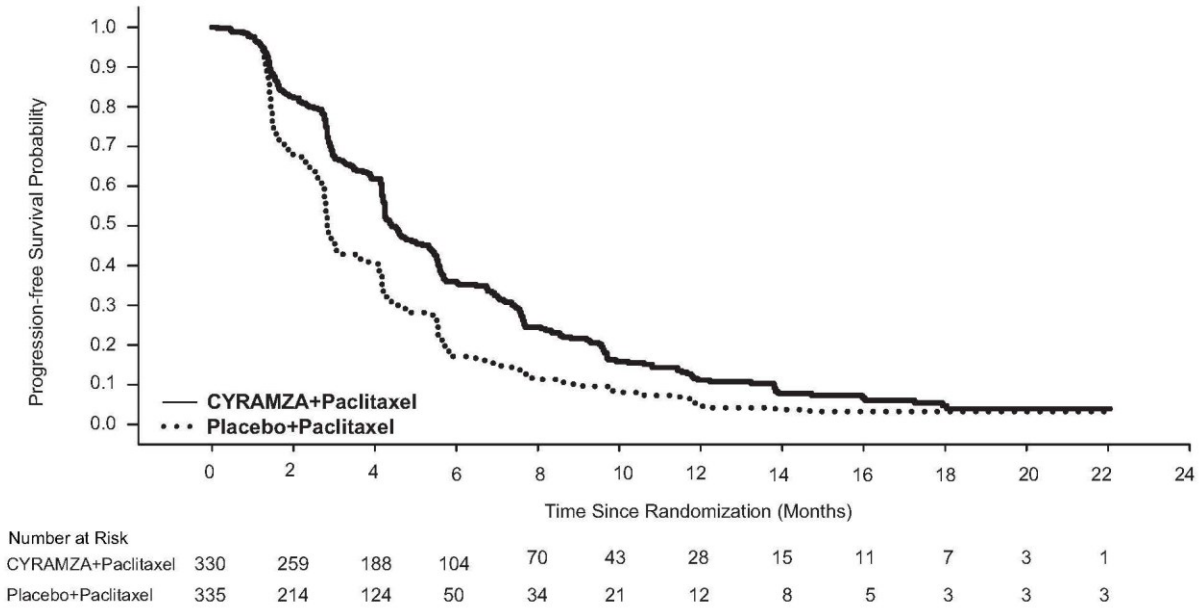

Figure 4: Kaplan-Meier curves of progression-free survival for CYRAMZA plus paclitaxel versus placebo plus paclitaxel in RAINBOW.

DETAILED PHARMACOLOGY

Nonclinical Pharmacodynamics

In vitro

The biochemical and pharmacodynamic data demonstrate that ramucirumab binds specifically and with high affinity to human VEGFR-2, and potently inhibits VEGFR-2 activation and downstream cellular events critical for normal and pathological angiogenesis. Ramucirumab binds with high affinity to human VEGFR-2 ($K_d \sim 5 \times 10^{-11}$ M) and inhibits of binding of VEGF-A to VEGFR-2 (IC_{50} ~0.8 nM). Ramucirumab blocks VEGF-A-stimulated activation of VEGFR-2, and inhibits VEGF-A-induced migration of endothelial cells. In addition, ramucirumab blocks the binding of two alternative VEGFR-2 ligands, VEGF-C and VEGF-D. Ramucirumab is highly specific for VEGFR-2 and does not cross-react with the related receptors VEGFR-1 and VEGFR-3. Ramucirumab recognizes human and cynomolgus monkey VEGFR-2, but does not recognize mouse VEGFR-2 (Flk1).

In vivo

Ramucirumab does not cross-react with murine VEGFR-2 and cannot be tested in mouse tumour models in which the host vasculature must be targeted. Therefore, in vivo studies were conducted using a “proof-of-principle” surrogate antibody for ramucirumab, designated DC101. DC101 is an antagonist rat anti-mouse VEGFR-2 specific monoclonal antibody whose biochemical and pharmacodynamic properties closely approximate those of ramucirumab.

These preclinical studies were critical for identifying potential clinical indications in which ramucirumab may be effective, for characterizing its potential to combine with various chemotherapies, and to demonstrate its mechanism of action in vivo. The efficacy of DC101

monotherapy in mouse studies of gastric cancer was investigated using Patient Derived Xenograft (PDX) models that use tumour fragments from individual patients and retain stromal and histologic features more reflective of human tumours as compared to conventional xenografts. The genetic heterogeneity of the tumours in PDX models often leads to a range of responses to tumour therapies. Inhibition of tumour growth varied widely among the different tumour lines with greater than 50% inhibition of tumour growth compared to vehicle control was achieved in seven of seventeen models. Non-clinical attempts at establishing an additive effect of DC101 and paclitaxel in xenograft studies using the gastric cancer cell line MKN-45 were unsuccessful. However, DC101 has shown combinatorial anti-tumour effects with chemotherapy in various models of other types of human cancer.

Nonclinical Pharmacokinetics
The nonclinical pharmacokinetic characterization of ramucirumab was conducted in cynomolgus monkeys since this was the species used for toxicology studies. Both single dose and multiple dose studies for up to 39-weeks were conducted. Ramucirumab was found to be cleared slowly, have a long terminal elimination half-life and a small volume of distribution when administered intravenously, once weekly. The volume of distribution was approximately equal to the plasma volume in monkeys indicating that ramucirumab did not distribute beyond the vasculature. Greater than dose-proportional increases in exposure were observed in monkey studies and were attributed to a dose-dependent reduction in clearance. The presence of anti-ramucirumab antibodies mainly at the low and mid-doses may have contributed to the nonlinear clearance. The presence of anti-ramucirumab antibodies did not interfere with the monkey toxicology assessment of ramucirumab as the serum concentrations achieved in monkeys at the highest test dose appreciably exceed the concentrations associated with the therapeutic dose of ramucirumab.

Clinical Pharmacokinetics
The geometric mean of population PK model-derived estimates of ramucirumab clearance (CL), volume of distribution at steady state (Vss) and terminal half-life (t1/2) were 0.0140 L/h, 5.5 L, and 15 days, respectively. Results from the PopPK analyses also indicate that the pharmacokinetics of ramucirumab following 8- to10-mg/kg dose administrations were linear.

No clinically meaningful changes in the exposure of either ramucirumab or paclitaxel were observed in patients with solid tumours when co-administered. Ramucirumab had no effect on dose-normalized AUC(0-∞) and Cmax of paclitaxel, with ratios (ramucirumab plus paclitaxel vs. paclitaxel) of geometric least squares (LS) means at 1.09 (90% CI; 0.93, 1.29) for AUC(0-∞) and 0.97 (90% CI; 0.83, 1.13) for Cmax. In addition, similar ramucirumab PK parameters were also observed with and without coadministration with paclitaxel. The ratios of geometric LS means of AUC(0-∞) and Cmax of ramucirumab (ramucirumab plus paclitaxel vs. ramucirumab) were 1.00 (90% CI; 0.84, 1.19) for AUC(0-∞) and 1.07 (90% CI; 0.93, 1.24) for Cmax.

TOXICOLOGY

The nonclinical safety assessment of ramucirumab was conducted in the cynomolgus monkey, which was established as an appropriate species for toxicity testing based on conservation of the binding epitope between human and monkey, affinity binding of ramucirumab to VEGFR-2,

similar patterns of tissue binding in a broad panel of human and cynomolgus monkey tissues in a GLP-compliant tissue cross-reactivity study and because ramucirumab does not cross-react with murine VEGFR-2.

An overview of the nonclinical toxicology program is provided in Table 13.

Table 13: Toxicology Study Overview

Study Type	Species	Route of Administration	Duration of Dosing	Doses (mg/kg)
Repeat-dose toxicity	Cynomolgus monkey	IV (bolus)	5 weeks (with a 6 week recovery phase)	0, 4, 12, 40[a]
Repeat-dose toxicity	Cynomolgus monkey	IV (infusion)	Once per week for 12 weeks (interim sacrifice) or 39 weeks	0, 5, 16, 50
Wound Healing	Cynomolgus monkey	IV (infusion)	Single-dose (21-day observation period)	5, 15, 50[a]
Tissue Cross-Reactivity	Human and Cynomolgus Monkey tissue	In vitro binding	1 hour incubation at room temperature	Conc. 5 and 0.5 µg/mL

Abbreviation: IV = intravenous.

[a] Highest No Observed Adverse Effects Level (NOAEL).

Single-Dose Toxicity

No dedicated single-dose toxicity studies were conducted with ramucirumab. However, no signs of acute toxicity were evident after administration of the highest single ramucirumab test dose of 50 mg/kg in the 39-week and wound healing studies.

Repeat-Dose Toxicity

Repeated intravenous dosing of ramucirumab to monkeys for up to 5 and 39 weeks was well-tolerated. No treatment-related mortalities, adverse clinical observations, or effects on body weight and food consumption occurred in either study.

Ramucirumab was well tolerated in the 5-week repeat-dose toxicity study at dose levels from 4 to 40 mg/kg for 4 doses. The no-observable-adverse-effect level (NOAEL) in this study was 40 mg/kg, the highest dose administered.

No treatment-related adverse effects were observed after 11 weekly administrations of ramucirumab at dose levels of 5, 16, and 50 mg/kg to female cynomolgus monkeys in the 39-week study.

No adverse effects on any of the toxicological parameters evaluated, including clinical, anatomic, and microscopic pathology were attributed to ramucirumab after 11 weeks of dosing in the 39-week study.

Ramucirumab had no effect on any in-life clinical observations, including blood pressure, electrocardiographic or ophthalmological examinations, or immunophenotype profile.

Several adverse clinical pathology changes were evident in animals treated with 16 and 50 mg/kg of ramucirumab at both Study Day 183 and 273. Higher blood urea nitrogen, creatinine, or cholesterol concentrations; lower albumin concentrations; and urinary protein loss were observed that were considered to be secondary to adverse microscopic changes in the kidney noted at the terminal evaluation (Study Day 274). Gross anatomic observations at terminal necropsy revealed pale kidneys (one 16 mg/kg female; one 50 mg/kg male), and increases in kidney weights at 16 and 50 mg/kg. These changes correlated microscopically with glomerulonephritis in all monkeys treated intravenously with 16 or 50 mg/kg of ramucirumab for 39 weeks. The severity and distribution of the glomerulonephritis ranged from moderate, multifocal to marked, diffuse. Grading of glomerulonephritis was based on the severity and extent of the primary glomerular lesion. Changes observed in the tubules, collecting ducts, and interstitium were considered secondary to the glomerular damage and as such were included in the glomerulonephritis diagnosis.

Because of the importance of VEGF in normal bone growth, adverse effects on this parameter were anticipated from treatment with the anti-VEGFR-2 antibody. Therefore, a bone growth evaluation was performed on the femurs and stifle joints (with synovial tissue) of animals after 39 weeks of ramucirumab treatment. As expected, monkeys treated with 5, 16, or 50 mg/kg of ramucirumab exhibited thickening and osteochondropathy of the epiphyseal growth plate in the femurs at all dose levels. The lowest weekly dose tested in the cynomolgus monkey is 1.2 times the recommended dose of ramucirumab as a single agent (8 mg/kg every 2 weeks). There were no changes noted microscopically that were considered pathological involving the stifle joint with synovial tissue.

No treatment-related adverse effects were observed on male or female reproductive tissues in either the 5-week or 39-week study.

The bone growth plate and kidney were identified as target organs of ramucirumab toxicity after weekly intravenous administration to monkeys for 39 weeks. No treatment-related adverse effects were evident in animals after 11 doses (12 weeks) of up to 50 mg/kg of ramucirumab indicating that chronic exposures are necessary to induce the changes. The kidney changes were monitorable by standard clinical pathology evaluations. Reversibility was not assessed in this study. Although the bone growth plate pathology evident at the lowest test dose level (5 mg/kg) was an anticipated mechanism-related effect, the findings were considered adverse. Thus, a NOAEL for 39-week exposure to ramucirumab was not established.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No animal studies have been performed to test ramucirumab for potential carcinogenicity, genotoxicity, or fertility impairment.

Reproductive and Developmental Toxicity
Reproductive and developmental toxicity testing of ramucirumab has not been conducted. A scientific assessment on the developmental and reproductive toxicity potential has been evaluated. In summary, VEGF is a critical mediator of angiogenesis that occurs across several stages of the female reproductive cycle, pregnancy, and embryo-fetal development. Interference with VEGF signaling through the use of transgenic models (for example, knockout mice),

nonproprietary antibodies against VEGF, or its receptors, or proprietary antibodies against VEGFR-2 have been shown to block angiogenesis and functioning or development of tissues critical for mammalian reproduction and development. Therefore, administration of ramucirumab to patients poses a potential risk to establishing and maintaining pregnancy and to the embryo-fetal development. The potential risks of ramucirumab to reproduction and development in humans can be communicated appropriately to patients and prescribers in the product information based on existing scientific information.

Local Tolerance
Local tolerance was investigated in the two repeat-dose toxicity evaluations in cynomolgus monkeys by clinical observations, and as part of the histopathological evaluations. Intravenous administration of ramucirumab was well-tolerated and no treatment-related adverse reactions at the injection site were observed in either study.

Tissue Binding Study of IMC-1121B-FITC with Normal Human and Cynomolgus Monkey Tissues
To characterize the tissue-binding profile of ramucirumab with particular focus on unexpected cell and tissue binding, and to confirm the relevance of the animal model (based on target distribution) used for the ramucirumab safety assessment, a comprehensive tissue cross-reactivity study was conducted in cryosections of normal human and cynomolgus monkey tissues. The tissue reactivity of ramucirumab observed in human tissues in this study was similar to that seen in the cynomolgus monkey tissues, indicating that the cynomolgus monkey is an appropriate animal model for toxicity of ramucirumab. Further, these data do not raise significant concerns as a consequence of human-specific binding of ramucirumab that would not have been evaluated in the monkey toxicology studies. The key finding in this study was the observation of IMC-1121B-FITC staining in vascular endothelium in both human and cynomolgus monkey tissues. This staining pattern is consistent with the distribution of the molecular target of ramucirumab, VEGFR-2, which is expressed predominantly on endothelial and hematopoietic cells, and overexpressed in the vasculature of the majority of human tumours.

Wound-Healing
Based on an anticipated mechanism-based impairment of wound-healing by an antagonist of the VEGFR-2, the effect of ramucirumab was assessed in an incisional model of wound healing after administration of a single intravenous dose (0, 5, 15, or 50 mg/kg) in cynomolgus monkeys. Serum concentrations of ramucirumab were determined to characterize the exposure:response relationship for wound-healing impairment. This study did not identify a clinical or histological impairment of wound-healing by ramucirumab in this model.

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READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

Pr CYRAMZA®
ramucirumab

Read this carefully before you receive **CYRAMZA** (pronounced "si – ram - ze")**.** This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **CYRAMZA**.

Serious Warnings and Precautions

- Increases risk of severe bleeding, including severe bleeding in your stomach or bowel.
- Increases risk of developing a hole in your stomach or bowel. In some cases this could result in death.
- Talk to your healthcare professional before you plan to have surgery and treatment should be stopped if you have a wound that is not healing properly.

What is CYRAMZA used for?

- CYRAMZA is a targeted cancer medicine used to treat advanced stomach cancer (also known as gastric cancer) and cancer of the gastro-esophageal junction (part of the food tube just as it joins the stomach), either by itself or in combination with paclitaxel (another anticancer medicine), in adults whose disease has progressed despite prior treatment with chemotherapy.

How does CYRAMZA work?

CYRAMZA is a vascular endothelial growth factor (VEGF) Receptor 2 antagonist that belongs to a group of biologic substances called monoclonal antibodies. In order to grow, tumours require oxygen and nutrients which are delivered through the blood. As tumours grow, they require larger amounts of oxygen and nutrients. Tumours get this supply by inducing the growth of new blood vessels. This process is called angiogenesis (an´-gee-o-jen´-i-sis). CYRAMZA works by blocking angiogenesis and helps starve the tumour of oxygen and other nutrients. CYRAMZA is not chemotherapy; it is considered a biologic antiangiogenic therapy.

What are the ingredients in CYRAMZA?

Medicinal ingredient: ramucirumab
Non-medicinal ingredients: glycine (E640), histidine, histidine monohydrochloride, polysorbate 80 (E433), sodium chloride and water for injection

CYRAMZA comes in the following dosage forms:

CYRAMZA is available as a solution in 10 mL or 50 mL single-use vials. Each vial contains either 100 mg ramucirumab in 10 mL (10 mg/mL) or 500 mg ramucirumab in 50 mL (10 mg/mL). After dilution and preparation, CYRAMZA is administered as an intravenous

infusion.

Do not use CYRAMZA if:
- you are allergic to this drug or to any ingredient in the formulation

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take CYRAMZA. Talk about any health conditions or problems you may have, including if you:
- have any condition which increases the risk of bleeding;
- have high blood pressure;
- are going to have planned surgery, had recent surgery or have a poorly healing wound after surgery;
- have severe liver disease ('cirrhosis') and associated conditions, such as excessive accumulation of fluid in your abdomen ('ascites');
- have had blood clots in your arteries ('arterial thromboembolic events');
- have ever had a heart attack or stroke;
- have had a hole in your stomach or bowel ('gastrointestinal perforation');
- have had an allergic reaction to the infusion;
- are pregnant or plan to become pregnant;
- are breastfeeding;
- have any allergies to this drug or its ingredients

Other warnings you should know about:

Pregnancy, breast-feeding and fertility

Avoid getting pregnant while receiving this medicine and for at least 3 months after the last dose of CYRAMZA as this medicine may potentially cause harm to your unborn child. Discontinue nursing or discontinue CYRAMZA. As CYRAMZA inhibits the development of new blood vessels, it may decrease the likelihood of you becoming pregnant or maintaining a pregnancy. Talk to your doctor about the best contraception for you.

Do not breast-feed your baby during treatment with CYRAMZA and for at least 3 months after you receive the last dose, as this medicine may have harmful effects on the growth and development of your baby.

Children and adolescents

CYRAMZA should not be given to patients under the age of 18 years because there is no information about the safety nor how it works in this age group.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take CYRAMZA:

CYRAMZA is given by intravenous infusion (through a needle placed in a vein in the arm, hand, or through a central line). The infusion lasts about 60 minutes. You will receive an infusion once every 2 weeks.

You may receive CYRAMZA alone or in combination with paclitaxel, another anticancer agent. Your doctor will determine your treatment plan. If you receive CYRAMZA in combination with paclitaxel, you should read the patient information for paclitaxel as well. Ask your doctor or health care team if you have any questions.

Usual dose:
The recommended dose of CYRAMZA for the treatment of gastric cancer is 8 mg per kg of your body weight once every 2 weeks.

If your doctor has prescribed paclitaxel, you will receive it once every week for 3 weeks followed by 1 week without treatment. It will be given by intravenous infusion for about 60 minutes. If you receive paclitaxel on the same day as CYRAMZA, it will be given after the CYRAMZA infusion has finished.

The number of infusions you will receive depends on how you are responding to treatment. Your doctor will discuss this with you.

Premedication:
You may be given medication to reduce the risk of an infusion-related reaction to the infusion before you receive CYRAMZA. If you experience an infusion-related reaction during CYRAMZA therapy, you will be given premedication for all future infusions. Symptoms of infusion-related reactions may include increased muscle tension, back pain, chest pain and/or tightness, chills, flushing, difficulty in breathing, wheezing, and feeling of tingling or numbness in hands or feet. In severe cases, symptoms may include breathing distress caused by narrowing of the airways, faster heartbeat, and feeling weak.

Dose adjustments:
During each infusion, your doctor or nurse will check for side effects. The time over which your infusion is given may lengthen if you experience an infusion-related reaction during treatment.

The amount of protein in your urine will be checked regularly during treatment. Depending on the protein level measured, CYRAMZA may be temporarily discontinued. Once the urine protein level has decreased to a certain level, treatment may be restarted with a lower dose.

CYRAMZA treatment will be temporarily stopped if you:
- develop high blood pressure, until it is controlled with antihypertensive medication
- develop wound healing problems, until the wound is healed or prior to planned surgery
- have significantly increased protein in your urine

CYRAMZA treatment will be permanently stopped if you:
- develop a blood clot in your arteries (‘arterial thromboembolic events’)
- develop a hole in your stomach or bowel (‘gastrointestinal perforation’)
- experience severe bleeding
- experience a severe infusion-related reaction
- develop high blood pressure that cannot be controlled with medication
- are passing more than a certain amount of protein with your urine or if you develop a severe

kidney disease ('nephrotic syndrome')

Overdose:

If you think you have received too much **CYRAMZA**, contact your healthcare professional, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

Missed Dose:
If you miss an infusion, contact your doctor immediately for further instructions.

What are possible side effects from using CYRAMZA?
Tell your doctor **immediately** if you experience any of the following **serious side effects** during CYRAMZA treatment:

- **vomit bright red blood or coffee ground material, blood in the stool or black, tarry stools, pain, severe fatigue, shortness of breath or a sense you may pass out when you get up from lying or sitting** which could be due to bleeding from your stomach or bowel
- **chest pain (may or may not feel like pressure or tightness in your chest) or loss of strength in an arm or leg, change in speech or change in vision** which could be due to blood clots in the arteries (can lead to a heart attack or stroke)
- **sudden onset of severe abdominal pain** which could be a symptom of a hole in the stomach or bowel
- **sudden onset of shivers and shakes often with a fever** which could be the result of a serious infection (sepsis)

Tell your doctor if you experience any of the following other side effects:

Very common: may affect more than 1 in 10 people
- high blood pressure
- protein in the urine
- feeling tired or weak
- low white blood cell count (may increase risk of infection) which on its own may not cause any symptoms and is commonly only discovered as a result of routine blood tests
- diarrhea
- nose bleed
- abdominal pain
- swelling of hands, feet and legs due to fluid retention
- inflammation of the mouth
- low platelet count (cells that help the blood to clot). This does not usually cause any problems and is commonly found in routine blood tests.
- low blood levels of albumin

Common: may affect up to 1 in 10 people
- intestinal blockage; symptoms may include constipation and abdominal pain
- rash

- headache
- low blood levels of potassium (hypokalemia) which can cause muscle weakness, twitching or abnormal heart rhythm
- low blood levels of sodium (hyponatremia) which can cause tiredness and confusion or muscle twitching
- thyroid dysfunction
- abnormal growth of blood vessels usually on the surface of the skin; this may appear as a red, raised lesion and may grow larger and/or bleed (hemangioma)

Uncommon: may affect up to 1 in 100 people
- fistula (an abnormal tube like connection between internal parts of the body that are not normally connected)

Rare: may affect up to 1 in 1000 people
- A brain condition called Posterior Reversible Encephalopathy Syndrome (PRES). Symptoms may include seizure, headache, nausea/vomiting, blindness, or loss of alertness.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Holes in the gut wall (gastrointestinal perforation): a hole in the stomach, gut or bowel [symptoms include severe stomach pain, vomiting, fever or chills]		✓	
Severe bleeding in your gut [symptoms may include extreme tiredness, weakness, dizziness or change in the colour of your stools]		✓	
Blood clots in the arteries: can lead to a heart attack or stroke [symptoms of a heart attack may include chest pain or heaviness in the chest; symptoms of a stroke may include sudden numbness or weakness of the arm, leg and face, feeling confused, difficulty speaking or understanding others, sudden difficulty in walking or loss of		✓	

balance or coordination or sudden dizziness]			
RARE			
Damage to small blood vessels in various organs of the body. This occurs most commonly in the kidney. Red blood cells and platelets may be destroyed because of this blood vessel damage (thrombotic microangiopathy). Red blood cells carry oxygen and platelet are cells that help the blood to clot. Blood flow to organs may be reduced. [Symptoms include bruising/bleeding, tiredness, shortness of breath, decreased urine output, swollen legs, headache, confusion, and symptoms of stroke. Protein in the urine and high blood pressure may occur.]		✓	
A brain condition called Posterior Reversible Encephalopathy Syndrome (PRES). [Symptoms may include seizure, headache, nausea/vomiting, blindness, or loss of alertness.]		✓	✓

Tell your doctor if you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities. These are not all the possible side effects you may feel when taking CYRAMZA. If you experience any side effects not listed here, contact your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:

- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 1908C
    Ottawa, ON
    K1A 0K9

    Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store CYRAMZA in a refrigerator at 2°C to 8°C (36°F to 46°F) until time of use. Keep the vial in the outer carton in order to protect from light.

Do not freeze or shake the vial.

Keep out of reach and sight of children.

If you want more information about CYRAMZA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website http://www.lilly.ca, or by calling 1-888-545-5972.

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