1. NAME OF THE MEDICINAL PRODUCT

Cyramza Concentrate for Solution for Infusion 100mg/ 10ml

Cyramza Concentrate for Solution for Infusion 500mg/ 50ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of concentrate for solution for infusion contains 10 mg ramucirumab.

Each 10 ml vial contains 100 mg of ramucirumab.

Each 50 ml vial contains 500 mg of ramucirumab.

Cyramza is a human IgG1 monoclonal antibody produced in murine (NS0) cells by recombinant DNA technology.

Excipient with known effect:

Each 10 ml vial contains approximately 17 mg sodium.

Each 50 ml vial contains approximately 85 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate).

The concentrate is a clear to slightly opalescent and colourless to slightly yellow solution, pH 6.0.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Gastric cancer

Cyramza as a single agent or in combination with paclitaxel, is indicated for the treatment of adult patients with advanced or metastatic, gastric or gastro-oesophageal junction adenocarcinoma, with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.

Non-small cell lung cancer (NSCLC)

Cyramza in combination with erlotinib is indicated for the first-line treatment of adult patients with metastatic non-small cell lung cancer with activating epidermal growth factor receptor (EGFR) mutations (see section 5.1).

Cyramza in combination with docetaxel, is indicated for the treatment of adult patients with locally advanced or metastatic NSCLC with disease progression on or after platinum based chemotherapy.

Colorectal cancer

Cyramza in combination with FOLFIRI (irinotecan, folinic acid, and 5-fluorouracil), is indicated for the treatment of adult patients with metastatic colorectal cancer (mCRC) with disease progression on or after prior therapy with bevacizumab, oxaliplatin and a fluoropyrimidine.

Hepatocellular carcinoma (HCC)

Cyramza monotherapy is indicated for the treatment of adult patients with advanced or unresectable HCC who have a serum alpha fetoprotein (AFP) of ≥ 400 ng/ml and who have been previously treated with sorafenib.

4.2 Posology and method of administration

Cyramza therapy must be initiated and supervised by physicians experienced in oncology.

Posology

Gastric cancer and gastro-oesophageal junction (GEJ) adenocarcinoma

Cyramza in combination with paclitaxel

The recommended dose of Cyramza is 8 mg/kg on days 1 and 15 of a 28 day cycle, prior to paclitaxel infusion. The recommended dose of paclitaxel is 80 mg/m^2 administered by intravenous infusion over approximately 60 minutes on days 1, 8 and 15 of a 28 day cycle. Prior to each paclitaxel infusion, patients should have a complete blood count and blood chemistry performed to evaluate hepatic function. Criteria to be met prior to each paclitaxel infusion are provided in Table 1.

Table 1: 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)
Aspartate aminotransferase (AST) /Alanine aminotransferase (ALT)	**No liver metastases:** ALT/AST ≤ 3 x ULN **Liver metastases:** ALT/AST ≤ 5 x ULN

Cyramza as a single agent

The recommended dose of Cyramza as a single agent is 8 mg/kg every 2 weeks.

Non-Small Cell Lung Cancer (NSCLC)

Cyramza in combination with erlotinib for the treatment of NSCLC with activating EGFR mutations

The recommended dose of Cyramza in combination with erlotinib is 10 mg/kg every two weeks.

EGFR mutation status should be determined prior to initiation of treatment with Cyramza and erlotinib using a validated test method. See erlotinib prescribing information for the posology and method of administration of erlotinib.

Cyramza in combination with docetaxel for the treatment of NSCLC after platinum-based chemotherapy

The recommended dose of Cyramza is 10 mg/kg on day 1 of a 21 day cycle, prior to docetaxel infusion. The recommended dose of docetaxel is 75 mg/m^2 administered by intravenous infusion over approximately 60 minutes on day 1 of a 21 day cycle. See docetaxel prescribing information for specific dosing advice.

Colorectal cancer

The recommended dose of Cyramza is 8 mg/kg every 2 weeks administered by intravenous infusion, prior to FOLFIRI administration. Prior to chemotherapy, patients should have a complete blood count.

Criteria to be met prior to FOLFIRI are provided in Table 2.

Table 2: Criteria to be met prior to FOLFIRI administration

	Criteria
Neutrophils	≥1.5 x 10^9/L
Platelets	≥100 x 10^9/L
Chemotherapy-related gastro- intestinal toxicity	≤Grade 1 (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE])

Hepatocellular carcinoma (HCC)

The recommended dose of Cyramza as a single agent is 8 mg/kg every 2 weeks.

Alpha fetoprotein (AFP) testing in HCC

Patients with HCC should be selected based on a serum AFP concentration of ≥ 400 ng/ml with a validated AFP test prior to Cyramza treatment (see section 5.1).

Duration of treatment

It is recommended that treatment be continued until disease progression or until unacceptable toxicity has occurred.

Premedication

Premedication is recommended with a histamine H1 antagonist (for example diphenhydramine) prior to infusion of Cyramza. If a patient experiences a Grade 1 or 2 infusion-related reaction premedication must be given for all subsequent infusions. If a patient experiences a second Grade 1 or 2 infusion-related reaction (IRR) administer dexamethasone (or equivalent); then, for subsequent infusions, premedicate with the following or equivalent medicinal products: an intravenous histamine H1 antagonist (for example diphenhydramine hydrochloride), paracetamol and dexamethasone.

See prescribing information for paclitaxel, for components of FOLFIRI and for docetaxel, as applicable, for premedication requirements and additional information.

Posology adjustments for Cyramza

Infusion-related reactions

The infusion rate of Cyramza should be reduced by 50% for the duration of the infusion and all subsequent infusions if the patient experiences a grade 1 or 2 IRR. Cyramza should be immediately and permanently discontinued in the event of a grade 3 or 4 IRR (see section 4.4).

Hypertension

The blood pressure of patients should be monitored prior to each Cyramza administration and treated as clinically indicated. Cyramza therapy should be temporarily discontinued in the event of severe hypertension, until controlled with medical management. If there is medically significant hypertension that cannot be controlled safely with antihypertensive therapy, Cyramza therapy should be permanently discontinued (see section 4.4).

Proteinuria

Patients should be monitored for the development, or worsening of proteinuria during Cyramza therapy. If the urine protein is ≥ 2+ on a dipstick, a 24 hour urine collection should be performed. Cyramza therapy should be temporarily discontinued if the urine protein level is ≥ 2 g/24 hours. Once the urine protein level returns to < 2 g/24 hours, treatment should be resumed at a reduced dose level (see Table 3). A second dose reduction (see Table 3) is recommended if a urine protein level ≥ 2 g/24 hours reoccurs.

Cyramza therapy should be permanently discontinued if the urine protein level is > 3g/ 24 hours or in the event of nephrotic syndrome.

Table 3: Cyramza dose reductions for proteinuria

Initial Cyramza dose:	First dose reduction to:	Second dose reduction to:
8 mg/kg	6 mg/kg	5 mg/kg
10 mg/kg	8 mg/kg	6 mg/kg

Elective surgery or impaired wound healing

Cyramza therapy should be temporarily discontinued for at least 4 weeks prior to elective surgery. Cyramza therapy should be temporarily discontinued if there are wound healing complications, until the wound is fully healed (see section 4.4).

Permanent discontinuation

Cyramza therapy should be permanently discontinued in the event of:

- Severe arterial thromboembolic events (see section 4.4).
- Gastrointestinal perforations (see section 4.4).
- Severe bleeding: NCI CTCAE Grade 3 or 4 bleeding (see section 4.4).
- Spontaneous development of fistula (see section 4.4).
- Hepatic encephalopathy or hepatorenal syndrome (see section 4.4).

Paclitaxel dose adjustments

Paclitaxel dose reductions may be applied based upon the grade of toxicity experienced by the patient. For NCI CTCAE Grade 4 haematological toxicity or Grade 3 paclitaxel-related non-haematological 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.

FOLFIRI dose adjustments

Dose reductions for individual components of FOLFIRI may be made for specific toxicities. Dose modifications of each component of FOLFIRI should be made independently and are provided in Table 4. Table 5 provides details of dose delays or dose reductions of components of FOLFIRI at the next cycle based on maximum grade of specific adverse drug reactions.

Table 4: FOLFIRI dose reductions

FOLFIRI Component[a]	Dose level			
	Initial dose	-1	-2	-3
Irinotecan	180 mg/m^2	150 mg/m^2	120 mg/m^2	100 mg/m^2
5-FU bolus	400 mg/m^2	200 mg/m^2	0 mg/m^2	0 mg/m^2
5-FU infusion	2,400 mg/m^2 over 46-48 hours	2,000 mg/m^2 over 46-48 hours	1,600 mg/m^2 over 46-48 hours	1,200 mg/m^2 over 46-48 hours

[a] 5-FU = 5-fluorouracil.

Table 5: Dose modification of FOLFIRI components due to specific ADRs

ADR	NCI CTCAE	Dose modification at day 1 of cycle subsequent to ADR
Diarrhoea	2	If diarrhoea has recovered to Grade ≤1, reduce by 1 dose level for 5-FU. For recurrent Grade 2 diarrhoea, reduce by 1 dose level for 5-FU **and** irinotecan.
	3	If diarrhoea has recovered to Grade ≤1, reduce by 1 dose level for 5-FU **and** irinotecan.
	4	If diarrhoea has recovered to Grade ≤1, reduce by 2 dose levels for 5-FU **and** irinotecan. If Grade 4 diarrhoea does not resolve to Grade ≤1, withhold 5-FU **and** irinotecan for a maximum of 28* days until resolution to Grade ≤1.

Neutropenia or Thrombocytopenia		Haematological criteria in Table 2 are met	Haematological criteria in Table 2 are **not** met
	2	No dose modification.	Reduce by 1 dose level for 5-FU **and** irinotecan.
	3	Reduce by 1 dose level for 5-FU **and** irinotecan.	Delay 5-FU **and** irinotecan for a maximum of 28* days until resolution to Grade ≤1, then dose reduce by 1 level for 5-FU **and** irinotecan.
	4	Reduce by 2 dose levels for 5-FU **and** irinotecan.	Delay 5-FU **and** irinotecan for a maximum of 28* days until resolution to Grade ≤1, then dose reduce by 2 levels for 5-FU **and** irinotecan.
Stomatitis/Mucositis	2	If stomatitis/mucositis has recovered to Grade ≤1, reduce by 1 dose level for 5-FU. For recurrent Grade 2 stomatitis, reduce by 2 dose levels for 5-FU.	
	3	If stomatitis/mucositis has recovered to Grade ≤1, reduce by 1 dose level for 5-FU. If Grade 3 mucositis/stomatitis does not resolve to Grade ≤1, delay 5-FU for a maximum of 28* days until resolution to Grade ≤1, then dose reduce by 2 levels for 5-FU.	
	4	Withhold 5-FU for a maximum of 28* days until resolution to Grade ≤1, then dose reduce by 2 doselevels for 5-FU.	

Febrile neutropenia		Haematological criteria in Table 2 are met and fever resolved	Haematological criteria in Table 2 are **not** met and fever resolved
		Reduce by 2 dose levelsfor 5-FU **and** irinotecan.	Delay 5-FU **and** irinotecan for a maximum of 28* days until resolution to Grade ≤1, then dose reduce by 2 levels for 5-FU **and** irinotecan. Consider use of colony-stimulating factor prior to next cycle.

*The 28 day time period begins on day 1 of the cycle subsequent to the ADR.

Docetaxel dose adjustments

Docetaxel dose reductions may be applied based upon the grade of toxicity experienced by the patient. Patients who experience either febrile neutropenia, neutrophils < 500 cells/mm^3 for more than 1 week, severe or cumulative cutaneous reactions, or other Grade 3 or 4 non-haematological toxicities during docetaxel treatment should have treatment withheld until resolution of the toxicity. It is recommended to reduce the docetaxel dose by 10 mg/m^2 for all following cycles. A second reduction of 15 mg/m^2 is recommended if these toxicities persist or reoccur.

Special populations

Elderly

In the pivotal studies there is limited evidence that patients 65 years of age or older are at increased risk of adverse events compared to patients younger than 65 years old. No dose reductions are recommended (see sections 4.4 and 5.1).

Renal impairment

There have been no formal studies with Cyramza in patients with renal impairment. Clinical data suggest that no dose adjustments are required in patients with mild, moderate or severe renal impairment (see sections 4.4 and 5.2). No dose reductions are recommended.

Hepatic impairment

There have been no formal studies with Cyramza in patients with hepatic impairment. Clinical data suggest that no dose adjustments are required in patients with mild or moderate hepatic impairment. There are no data regarding Cyramza administration in patients with severe hepatic impairment (see sections 4.4 and 5.2). No dose reductions are recommended.

Paediatric population

The safety and efficacy of Cyramza in children and adolescents (< 18 years) has not been established. Currently available data are described in section 4.8, 5.1 and 5.2. Due to limited data no recommendation on posology can be made.

There is no relevant use of Cyramza in the paediatric population for the indications of advanced gastric cancer or gastro-oesophageal adenocarcinoma, adenocarcinoma of the colon and rectum, lung carcinoma and hepatocellular carcinoma.

Method of administration

Cyramza is for intravenous use. After dilution, Cyramza is administered as an intravenous infusion over approximately 60 minutes. It should not be administered as an intravenous bolus or push. To achieve the required infusion duration of approximately 60 minutes, the maximum infusion rate of 25 mg/minute should not be exceeded, instead the infusion duration should be increased. The patient should be monitored during infusion for signs of infusion-related reactions (see section 4.4) and the availability of appropriate resuscitation equipment should be ensured.
For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

For patients with NSCLC, Cyramza is contraindicated where there is tumour cavitation or tumour involvement of major vessels (see section 4.4).

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

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 studies. Cyramza should be permanently discontinued in patients who experience a severe ATE (see section 4.2).

Gastrointestinal perforations

Cyramza is an antiangiogenic therapy and may increase the risk of gastrointestinal perforations. Cases of gastrointestinal perforation have been reported in patients treated with Cyramza. Cyramza should be permanently discontinued in patients who experience gastrointestinal perforations (see section 4.2).

Severe bleeding

Cyramza is an antiangiogenic therapy and may increase the risk of severe bleeding. Cyramza should be permanently discontinued in patients who experience Grade 3 or 4 bleeding (see section 4.2). Blood counts and coagulation parameters should be monitored in patients with conditions predisposing to bleeding, and in those treated with anticoagulants or other concomitant medicinal products that increase the risk of bleeding. For HCC patients with evidence of portal hypertension or prior history of oesophageal variceal bleeding, screening for and treatment of oesophageal varices should be performed as per standard of care before starting Cyramza treatment.

Severe gastrointestinal haemorrhage, including fatal events were reported in patients with gastric cancer treated with Cyramza in combination with paclitaxel and in patients with mCRC treated with Cyramza in combination with FOLFIRI.

Pulmonary haemorrhage in NSCLC

Patients with squamous histology are at higher risk of developing serious pulmonary bleeding, however, no excess of Grade 5 pulmonary haemorrhage was observed in Cyramza treated patients with squamous histology in REVEL. NSCLC patients with recent pulmonary bleeding (>2.5 ml or bright red blood) as well as patients with evidence of baseline tumour cavitation, regardless of histology, or those with any evidence of tumour invasion or encasement of major blood vessels have been excluded from clinical trials (see section 4.3). Patients receiving any kind of therapeutic anticoagulation were excluded from the REVEL NSCLC clinical trial and patients receiving chronic therapy with non-steroidal anti-inflammatory drugs or anti-platelet agents were excluded from the REVEL and RELAY NSCLC

clinical trials. Aspirin use at doses up to 325 mg/day was permitted (see section 5.1).

Infusion-related reactions

Infusion-related reactions were reported in clinical studies with Cyramza. The majority of events occurred during or following a first or second Cyramza infusion. Patients should be monitored during the infusion for signs of hypersensitivity. Symptoms included rigors/tremors, back- pain/spasms, chest pain and/or tightness, chills, flushing, dyspnoea, wheezing, hypoxia, and paraesthesia. In severe cases symptoms included bronchospasm, supraventricular tachycardia, and hypotension. Cyramza should be immediately and permanently discontinued in patients who experience a Grade 3 or 4 IRR (see section 4.2).

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. Patients with uncontrolled hypertension were excluded from the trials: Cyramza treatment should not be initiated in such patients until and unless their pre-existing hypertension is controlled. Patients who are treated with Cyramza should have their blood pressure monitored. Cyramza should be temporarily discontinued for severe hypertension until controlled with medical management. Cyramza should be permanently discontinued if medically significant hypertension cannot be controlled with antihypertensive therapy (see section 4.2).

Posterior Reversible Encephalopathy Syndrome

Cases of posterior reversible encephalopathy syndrome (PRES), including fatal cases, have been rarely reported in patients receiving Cyramza. PRES symptoms may 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). Discontinue Cyramza in patients who experience PRES. The safety of reinitiating Cyramza in patients who develop PRES and recover is not known.

Aneurysms and artery dissections

The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating Cyramza, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Impaired wound healing

The impact of Cyramza has not been evaluated in patients with serious or non-healing wounds. In a study conducted in animals, Cyramza did not impair wound healing. However, since Cyramza is an antiangiogenic therapy and may have the potential to adversely affect wound healing, Cyramza treatment should be withheld for at least 4 weeks prior to scheduled surgery.

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, Cyramza should be discontinued until the wound is fully healed (see section 4.2).

Hepatic impairment

Cyramza should be used with caution in patients with severe liver cirrhosis (Child-Pugh B or C), cirrhosis with hepatic encephalopathy, clinically significant ascites due to cirrhosis, or hepatorenal syndrome. There are very limited efficacy and safety data available in these patients. Cyramza should only be used in these patients if the potential benefits of treatment are judged to outweigh the potential risk of progressive hepatic failure.

In HCC patients, hepatic encephalopathy was reported at a higher rate in the Cyramza-treated patients compared to the placebo-treated patients (see section 4.8). Patients should be monitored for clinical signs and symptoms of hepatic encephalopathy. Cyramza should be permanently discontinued in the event of hepatic encephalopathy or hepatorenal syndrome (see section 4.2).

Cardiac Failure

In pooled data from ramucirumab clinical trials, cardiac failure was reported at a numerically higher incidence in patients receiving ramucirumab in combination with a variety of chemotherapy regimens, or erlotinib, compared to chemotherapy or erlotinib alone. This increased incidence was not observed in patients receiving ramucirumab compared to placebo from single agent clinical trials. In the post-marketing setting, cardiac failure was observed for ramucirumab, mostly in combination with paclitaxel. Patients should be monitored for clinical signs and symptoms of cardiac failure during treatment, and suspension of treatment should be considered if clinical signs and symptoms of cardiac failure develop. See section 4.8.

Fistula

Patients may be at increased risk for the development of fistula when treated with Cyramza. Cyramza treatment should be discontinued in patients who develop fistula (see section 4.2).

Proteinuria

An increased incidence of proteinuria was reported in patients receiving Cyramza as compared to placebo. Patients should be monitored for the development, or worsening of proteinuria during Cyramza therapy. If the urine protein is ≥ 2+ on a dipstick, a 24 hour urine collection should be performed. Cyramza therapy should be temporarily discontinued if the urine protein level is ≥ 2 g/24 hours. Once the urine protein level returns to < 2 g/24 hours, treatment should be resumed at a reduced dose level. A second dose reduction is recommended if a urine protein level ≥ 2 g/24 hours reoccurs. Cyramza therapy should be permanently discontinued if the urine protein level is > 3 g/24 hours or in the event of nephrotic syndrome (see section 4.2).

Stomatitis

An increased incidence of stomatitis was reported in patients receiving Cyramza in combination with chemotherapy as compared to patients treated with placebo plus chemotherapy. Symptomatic treatment should be instituted promptly if stomatitis occurs.

Renal impairment

There are limited safety data available for patients with severe renal impairment (calculated creatinine clearance 15 to 29 ml/min) treated with Cyramza (see sections 4.2 and 5.2).

Reversible Posterior Leukoencephalopathy Syndrome (RPLS)

RPLS has been reported with a rate of < 0.1% in clinical studies with Cyramza. Confirm the diagnosis of RPLS with MRI and discontinue Cyramza in patients who develop RPLS. Symptoms may resolve or improve within days, although some patients with RPLS can experience ongoing neurologic sequelae or death.

Thyroid Dysfunction

Monitor thyroid function during treatment with Cyramza. In RAISE, the incidence of hypothyroidism reported as an adverse event was 2.6% in the Cyramza plus FOLFIRI-treated patients and 0.9% in the placebo plus FOLFIRI-treated patients.

Elderly patients with NSCLC

A trend towards less efficacy with increasing age has been observed in patients receiving Cyramza plus docetaxel for the treatment of advanced NSCLC with disease progression after platinum-based chemotherapy (see section 5.1). Comorbidities associated with advanced age, performance status and the likely tolerability to chemotherapy should therefore be thoroughly evaluated prior to the initiation of treatment in the elderly (see sections 4.2 and 5.1).

For Cyramza used in combination with erlotinib for the first line treatment of NSCLC with activating EGFR mutations, patients aged 70 years and older compared to patients under 70 years of age, experienced a higher incidence of grade ≥3 adverse events and all grade serious adverse events.

Sodium restricted diet

Each 10 ml vial contains less than 1 mmol sodium (23mg), that is to say essentially 'sodium-free'. Each 50 ml vial contains approximately 85 mg sodium. This is equivalent to approximately 4% of WHO recommended maximum daily intake of 2g sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No clinically meaningful changes in the exposure of either Cyramza or its concomitant drugs in the approved combinations, including paclitaxel, docetaxel, erlotinib and irinotecan (or its active metabolite, SN-38), were observed in patients with solid tumors.

4.6 Fertility, pregnancy and lactation

Fertility

There are no data on the effect of Cyramza on human fertility. Female fertility is likely to be compromised during treatment with Cyramza based on studies in animals (see section 5.3).

Women of childbearing potential/Contraception in females

Women of childbearing potential should be advised to avoid becoming pregnant while on Cyramza and should be informed of the potential hazard to the pregnancy and foetus. Women of childbearing potential should use effective contraception during and up to 3 months after the last dose of Cyramza treatment.

Pregnancy

There are no data from the use of Cyramza in pregnant women. Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). As angiogenesis is critical to maintenance of

pregnancy and to foetal development, the inhibition of angiogenesis following Cyramza administration may result in adverse effects on pregnancy, including the foetus. Cyramza should only be used if the potential benefit to the mother justifies the potential risk during pregnancy. If the patient becomes pregnant while being treated with Cyramza, she should be informed of the potential risk to the maintenance of pregnancy and the risk to the foetus. Cyramza is not recommended during pregnancy and in women of childbearing potential not using contraception.

Lactation

It is unknown whether Cyramza is excreted in human milk. Excretion in milk and oral absorption is expected to be low. As a risk to breast-fed newborns/infants cannot be excluded, breast-feeding should be discontinued during treatment with Cyramza and for at least 3 months after the last dose.

4.7 Effects on ability to drive and use machines

Cyramza has no or negligible influence on the ability to drive and use machines. If patients experience symptoms affecting their ability to concentrate and react, it is recommended that they do not drive or use machines until the effect subsides.

4.8 Undesirable effects

The most serious adverse reactions associated with Cyramza treatment (as a single agent or in combination with cytotoxic chemotherapy) were:

- Gastrointestinal perforation (see section 4.4)
- Severe gastrointestinal haemorrhage (see section 4.4)
- Arterial thromboembolic events (see section 4.4)
- Posterior reversible encephalopathy syndrome (see section 4.4)

The most common adverse reactions observed in patients treated with Cyramza monotherapy are: peripheral oedema, hypertension, diarrhoea, abdominal pain, headache, proteinuria and thrombocytopenia.

The most common adverse reactions observed in patients treated with Cyramza in combination with chemotherapy are: fatigue/asthenia, neutropenia, diarrhoea, epistaxis and stomatitis.

The most common adverse reactions observed in patients treated with Cyramza in combination with erlotinib are: infections, diarrhoea, hypertension, stomatitis, proteinuria, alopecia and epistaxis.

Tables 6 and 7 below list the adverse drug reactions (ADRs) from placebo controlled phase III clinical trials associated with ramucirumab used either as a monotherapy treatment for gastric cancer and HCC or in combination with different chemotherapy regimens or erlotinib for the treatment of gastric cancer, mCRC and NSCLC. ADRs are listed below by MedDRA body system organ class. The following convention has been used for classification of frequency for ADR tables:

Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to < 1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known (cannot be estimated from the available data)

Within each frequency grouping, ADRs are presented in order of decreasing seriousness.

Table 6: ADRs reported in patients treated with Cyramza as monotherapy in phase 3 clinical trials (REGARD, REACH-2 and REACH patients with alpha fetoprotein ≥ 400 ng/ml)

System Organ Class (MedDRA)	Very Common	Common	Uncommon
Blood and lymphatic system disorders	Thrombocytopenia[a]	Neutropenia[a]	
Metabolism and nutrition disorders		Hypokalaemia[a,b] Hyponatraemia[a] Hypoalbuminaemia[a]	
Nervous system disorders	Headache	Hepatic encephalopathy[c]	
Vascular disorders	Hypertension[a,d]	Arterial thromboembolic events[a]	
Respiratory, thoracic, and mediastinal		Epistaxis	

disorders			
Gastrointestinal disorders	Abdominal pain[a,e] Diarrhoea	Intestinal obstruction[a]	Gastrointestinal perforation[a]
Skin and subcutaneous tissue disorders		Rash[a]	
Renal and urinary disorders	Proteinuria[a,f]		
General disorders and administration site disorders	Peripheral oedema	Infusion-related reactions[a]	

[a] Terms represent a group of events that describe a medical concept rather than a single event or preferred term.

[b] Includes: hypokalaemia and blood potassium decreased.

[c] Based on study REACH-2 and REACH (single-agent ramucirumab in HCC). Includes hepatic encephalopathy and hepatic coma.

[d] Includes: blood pressure increased and hypertension.

[e] Includes: abdominal pain, abdominal pain lower, abdominal pain upper, and hepatic pain.

[f] Includes one case of nephrotic syndrome

Table 7: ADRs reported in patients treated with ramucirumab in combination with chemotherapy or erlotinib in phase 3 clinical trials (RAINBOW, REVEL, RAISE and RELAY)

System Organ Class (MedDRA)	Very Common	Common	Uncommon
Infections and infestations	Infections[j,k]	Sepsis[a,b]	
Blood and lymphatic system disorders	Neutropenia[a] Leukopenia[a,c] Thrombocytopenia[a] Anaemia[j]	Febrile neutropenia[d]	

Metabolism and nutrition disorders		Hypoalbuminaemia[a] Hyponatraemia[a]	
Nervous system disorders	Headache[j]		
Cardiac disorders			Cardiac failure
Vascular disorders	Hypertension[a,e]		
Respiratory, thoracic, and mediastinal disorders	Epistaxis	Pulmonary haemorrhage[j,l]	
Gastrointestinal disorders	Stomatitis Diarrhoea	Gastrointestinal haemorrhage events[a,f] Gastrointestinal perforation[a] Gingival bleeding[j]	
Skin and subcutaneous tissue disorders	Alopecia[j]	Palmar-plantar erythrodysaesthesia syndrome[g]	
Renal and urinary disorders	Proteinuria[a,h]		
General disorders and administration site disorders	Fatigue[a,i] Mucosal inflammation[d] Peripheral oedema		

[a] Terms represent a group of events that describe a medical concept rather than a single event or preferred term.

[b] Based on study RAINBOW (ramucirumab plus paclitaxel).

[c] Based on study RAINBOW (ramucirumab plus paclitaxel). Includes: leukopenia and white blood cell count decreased.

[d] Based on study REVEL (ramucirumab plus docetaxel).

[e] Includes: blood pressure increased, hypertension, and hypertensive cardiomyopathy.

[f] Based on study RAINBOW (ramucirumab plus paclitaxel) and study RAISE (ramucirumab plus FOLFIRI).

Includes: anal haemorrhage, diarrhoea haemorrhage, gastric haemorrhage, gastrointestinal haemorrhage, haematemesis, haematochezia, haemorrhoidal haemorrhage, Mallory-Weiss syndrome, melaena, oesophageal haemorrhage, rectal haemorrhage, and upper gastrointestinal haemorrhage.

[g] Based on study RAISE (ramucirumab plus FOLFIRI).

[h] Includes cases of nephrotic syndrome.

[i] Based on study RAINBOW (ramucirumab plus paclitaxel) and study REVEL (ramucirumab plus docetaxel).

Includes: fatigue and asthenia.

[j] Based on study RELAY (ramucirumab plus erlotinib).

[k] Infections includes all preferred terms that are part of the System Organ Class Infections and infestations. Most common (≥1%) Grade ≥3 infections include pneumonia, cellulitis, paronychia, skin infection, and urinary tract infection.

[l] Includes haemoptysis, laryngeal haemorrhage, haemothorax (a fatal event occurred) and pulmonary haemorrhage

Clinically relevant reactions (including Grade ≥3) associated with antiangiogenic therapy observed in ramucirumab-treated patients across clinical studies were: gastrointestinal perforations, infusion-related reactions and proteinuria (see sections 4.2 and 4.4).

Colorectal Cancer

Cyramza in combination with FOLFIRI

In the RAISE study, in mCRC patients treated with Cyramza plus FOLFIRI, the most frequent (≥1%) ADR that led to the discontinuation of Cyramza was proteinuria (1.5%). The most frequent (≥1%) ADRs leading to discontinuation of one or more components of FOLFIRI were: neutropenia (12.5%), thrombocytopenia (4.2%), diarrhoea (2.3%) and stomatitis (2.3%). The most frequent component of FOLFIRI to be discontinued was the 5-FU bolus.

Adverse reactions from other sources

Table 8: ADRs associated with ramucirumab reported in clinical trials and through post-marketing reporting

System Organ Class (MedDRA)	Common	Uncommon	Rare	Not known
Neoplasms benign, malignant and unspecified (including cysts and polyps)	Haemangioma			
Blood and lymphatic system disorders			Thrombotic microangiopathy	
Endocrine disorders	Hypothyroidism			
Nervous system disorders			Posterior reversible encephalopathy syndrome	
Cardiac disorders				Cardiac failure[a]
Vascular disorders				Aneurysms and artery dissections
Respiratory, thoracic and mediastinal disorders	Dysphonia			

[a] In the post-marketing setting, cardiac failure has been observed for ramucirumab mostly in combination with paclitaxel. See section 4.4.

Paediatric population

No new safety concerns were identified based on the limited number of paediatric patients treated with ramucirumab monotherapy in study I4T MC JVDA (see section 5.1). One patient in this study had progressive widening of distal femoral growth plate. The impact of this finding on growth is not known.

4.9 Overdose

There is no data on overdose in humans. Cyramza has been administered in a Phase 1 study up to 10 mg/kg every two weeks without reaching a maximum tolerated dose. In case of overdose, supportive therapy should be used.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies ATC code: L01XC21

Mechanism of action

Vascular Endothelial Growth Factor (VEGF) Receptor 2 is the key mediator of VEGF induced angiogenesis. Cyramza is a human receptor-targeted antibody that specifically binds VEGF Receptor 2 and blocks binding of VEGF-A, VEGF-C, and VEGF-D. As a result, Cyramza inhibits ligand stimulated activation of VEGF Receptor 2 and its downstream signalling components, including p44/p42 mitogen-activated protein kinases, neutralising ligand-induced proliferation and migration of human endothelial cells.

Clinical efficacy and safety

Gastric cancer

RAINBOW

RAINBOW, a global, randomised, double-blind, study of Cyramza plus paclitaxel versus placebo plus paclitaxel, was conducted in 665 patients with locally recurrent and unresectable or metastatic gastric cancer (including GEJ adenocarcinoma) following platinum- and fluoropyrimidine-containing chemotherapy, with or without anthracycline. The primary endpoint was overall survival (OS) and the secondary endpoints included progression free survival (PFS) and overall response rate (ORR). Patients were required to have experienced disease progression during, or within 4 months after the last dose of first-line therapy and with ECOG PS 0-1. Patients were randomised in a 1:1 ratio to receive Cyramza plus paclitaxel (n=330) or placebo plus paclitaxel (n=335). Randomisation was stratified by geographic region, time to progression from the start of first-line therapy (< 6 months versus ≥ 6 months) and disease measurability. 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.

A majority (75%) of patients randomised in the study received prior platinum and fluoropyrimidine combination therapy without anthracycline. The remainder (25%) received prior platinum and fluoropyrimidine combination therapy with anthracycline. Two-thirds of the patients experienced disease progression while still on first-line therapy (66.8%). Baseline patient demographics and disease characteristics were generally balanced between arms: the median age was 61 years; 71% of patients were male; 61% were Caucasian, 35% Asian; the ECOG PS was 0 for 39% of patients, 1 for 61% of patients; 81% of patients had measurable disease and 79% had gastric cancer; 21% had GEJ adenocarcinoma. The majority of patients (76%) had experienced disease progression within 6 months from the start of first-line therapy. For patients treated with Cyramza plus paclitaxel the median duration of therapy was 19 weeks, and for patients treated with placebo plus paclitaxel the median duration of therapy was 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. A similar percentage of patients discontinued treatment due to adverse events: 12% of patients treated with Cyramza plus paclitaxel compared with 11% of patients treated with placebo plus paclitaxel. Post discontinuation systemic anti-cancer therapy was given to 47.9% of patients receiving Cyramza plus paclitaxel and 46.0% of patients receiving placebo plus paclitaxel.

Overall survival was statistically significantly improved in patients receiving Cyramza plus paclitaxel compared with those receiving placebo plus paclitaxel (HR 0.807; 95% CI: 0.678 to 0.962; p=0.0169). There was an increase in median survival of 2.3 months in favour of the Cyramza plus paclitaxel arm: 9.63 months in the Cyramza plus paclitaxel arm and 7.36 months in the placebo plus paclitaxel arm. Progression-free survival was statistically significantly improved in patients receiving Cyramza plus paclitaxel compared with those receiving placebo plus paclitaxel (HR 0.635; 95% CI: 0.536 to 0.752; p< 0.0001). There was an increase in median PFS of 1.5 months in favour of the Cyramza plus paclitaxel arm: 4.4 months in the Cyramza plus paclitaxel arm and 2.9 months in the placebo plus paclitaxel arm. Objective response rate (complete response [CR] + partial response [PR]) was significantly improved in patients receiving Cyramza plus paclitaxel compared with those receiving placebo plus paclitaxel (Odds ratio 2.140; 95% CI: 1.499 to 3.160; p=0.0001). The ORR in the Cyramza plus paclitaxel arm was 27.9% and in the placebo plus paclitaxel arm was 16.1%. Improvements in OS and PFS were consistently observed in pre-specified subgroups based on age, sex, race and in most other pre-specified subgroups. Efficacy results are shown in Table 9.

Table 9: Summary of efficacy data – Intent to treat ITT population

	Cyramza plus paclitaxel N=330	Placebo plus paclitaxel N=335
Overall survival, months		
Median (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, months		
Median (95% CI)	4.4 (4.2, 5.3)	2.9 (2.8, 3.0)
Hazard ratio (95% CI)	0.635 (0.536, 0.752)	
Stratified log-rank p-value	<0.0001	
Objective response rate (CR +PR)		
Rate- percent (95% CI)	27.9 (23.3, 33.0)	16.1 (12.6, 20.4)
Odd ratio	2.140 (1.449, 3.160)	
Stratified CMH p-value	0.0001	

Abbreviations: CI = confidence interval, CR = complete response, PR = partial response, CMH= Cochran-Mantel-Haenszel

Figure 1: Kaplan-Meier curves of overall survival for Cyramza plus paclitaxel versus placebo plus paclitaxel in RAINBOW

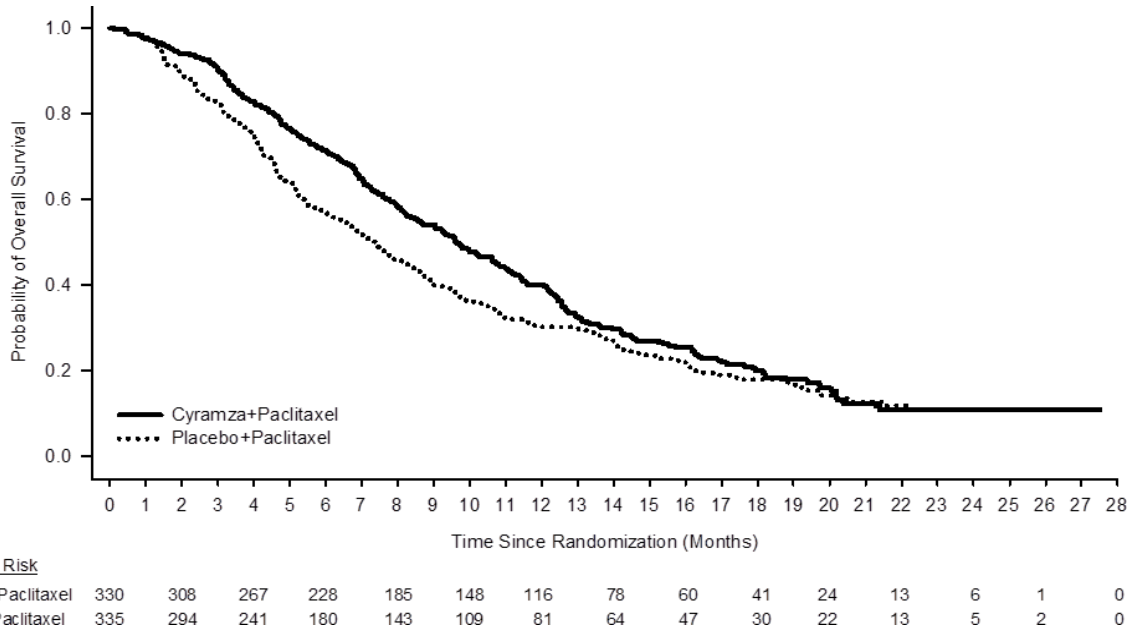
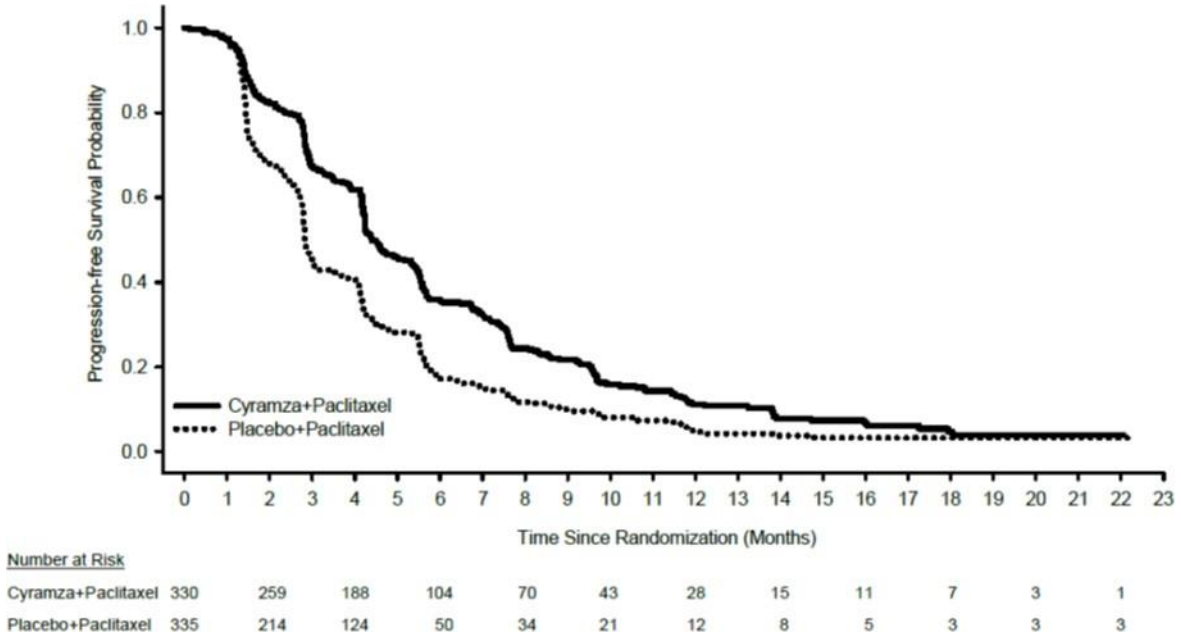


Figure 2: Kaplan-Meier curves of progression-free survival for Cyramza plus paclitaxel versus placebo plus paclitaxel in RAINBOW



REGARD

REGARD, a multinational, randomised, double-blind study of Cyramza plus BSC versus placebo plus BSC, was conducted in 355 patients with locally recurrent and unresectable, or metastatic gastric cancer (including GEJ adenocarcinoma) following platinum- or fluoropyrimidine-containing chemotherapy. The primary endpoint was OS and secondary endpoints included PFS. Patients were required to have experienced disease progression during, or within 4 months after the last dose of first-line therapy for metastatic disease, or during adjuvant treatment or within 6 months after the last dose of adjuvant therapy, and had ECOG PS 0-1. To be included in the study, patients were required to have total bilirubin of ≤ 1.5 mg/dl and AST and ALT ≤ 3 times ULN, or ≤ 5 times ULN if liver metastases were present.

Patients were randomised in a 2:1 ratio to receive an intravenous infusion of Cyramza 8 mg/kg (n=238) or placebo (n=117) every 2 weeks. Randomisation was stratified by weight loss over the prior 3 months (≥ 10% versus < 10%), geographic region, and location of the primary tumour (gastric versus GEJ). Baseline demographics and disease characteristics were balanced. The ECOG PS was 1 for 72% of patients. There were no patients with Child-Pugh B or C liver cirrhosis enrolled in REGARD. 11% of patients treated with Cyramza and 6% of patients on placebo discontinued therapy due to adverse

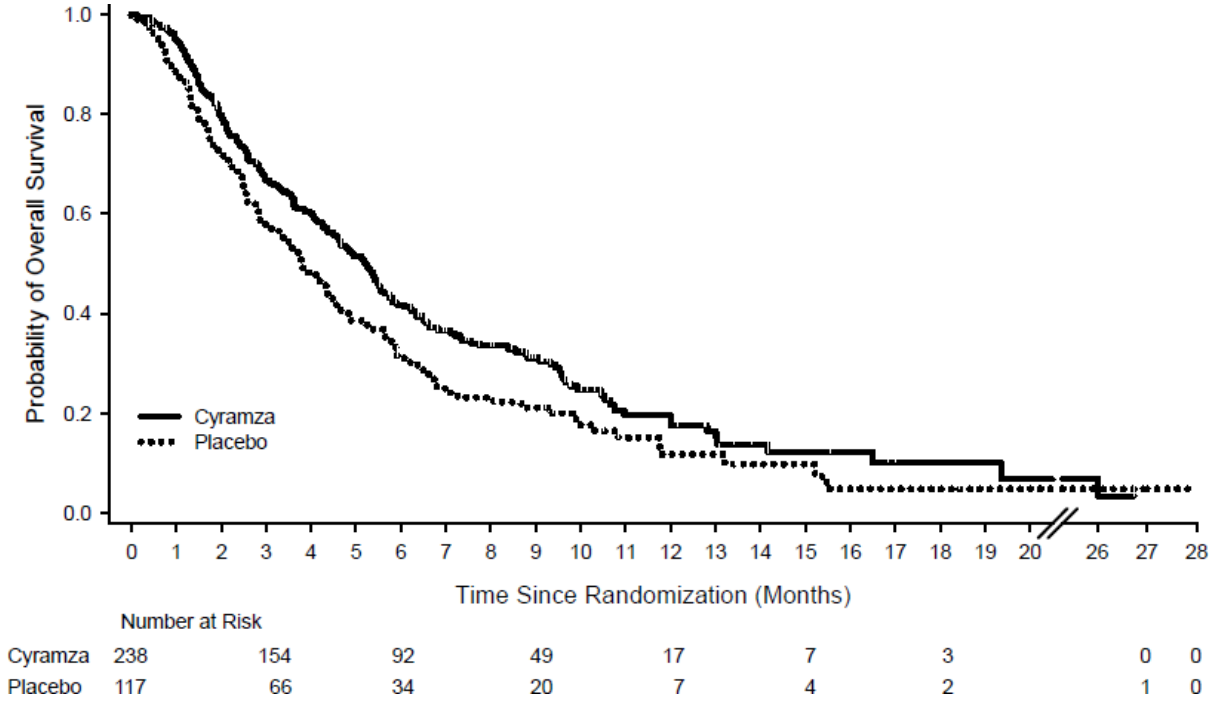
events. Overall survival was statistically significantly improved in patients receiving Cyramza as compared with patients receiving placebo (hazard ratio [HR] 0.776; 95% CI: 0.603 to 0.998; p=0.0473), corresponding to a 22% reduction in the risk of death and an increase in median survival to 5.2 months for Cyramza from 3.8 months for placebo. Progression-free survival was statistically significantly improved in patients receiving Cyramza as 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 10.

Table 10: Summary of efficacy data – ITT population

	Cyramza N=238	Placebo N=117
Overall survival, months		
Median (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, months		
Median (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% (95% CI)	40.1 (33.6, 46.4)	15.8 (9.7, 23.3)

Abbreviations: CI = confidence interval

Figure 3: Kaplan-Meier curves of overall survival for Cyramza versus placebo in REGARD



Based on limited data from REGARD patients with HER2-positive gastric or GEJ adenocarcinoma and patients previously treated with trastuzumab (in RAINBOW), it is considered unlikely that Cyramza has a detrimental effect or that it has no effect in patients with HER2-positive gastric cancer. *Post hoc* unstratified subgroup analyses from RAINBOW patients previously treated with trastuzumab (n= 39) suggested a survival benefit in such patients (HR 0.679, 95% CI 0.327, 1.419) and demonstrated a benefit for progression free survival (PFS) (HR 0.399, 95% CI 0.194, 0.822).

Non-small cell lung cancer (NSCLC)

RELAY

RELAY was a global, randomised, double-blind, phase 3 study of Cyramza plus erlotinib versus placebo plus erlotinib that randomised (1:1) 449 previously untreated patients with metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 19 deletion or exon 21 (L858R) activating mutations at study entry. Eligible patients were ECOG PS 0 or 1. Patients with CNS metastases or known T790M EGFR mutations at baseline were excluded from the study. Patients at a high risk of bleeding, cardiovascular events, including those who had experienced any arterial thrombotic event within 6 months of enrolment, were also excluded from the study.

Demographics and baseline characteristics were balanced between arms. 77% of patients were Asian and 22% were Caucasian. Patients treated with Cyramza plus erlotinib experienced a statistically

significant improvement in progression-free survival (PFS) compared to patients treated with placebo plus erlotinib (Table 10). Consistent results were observed across subgroups including exon 19 deletions and exon 21 (L858R) substitution, age, race (Caucasian HR: 0.618, Asian HR: 0.638), smokers and never smokers. Overall survival data were immature at the time of the final PFS analysis (17.6% maturity). RELAY efficacy results are shown in Table 11 and Figure 4.

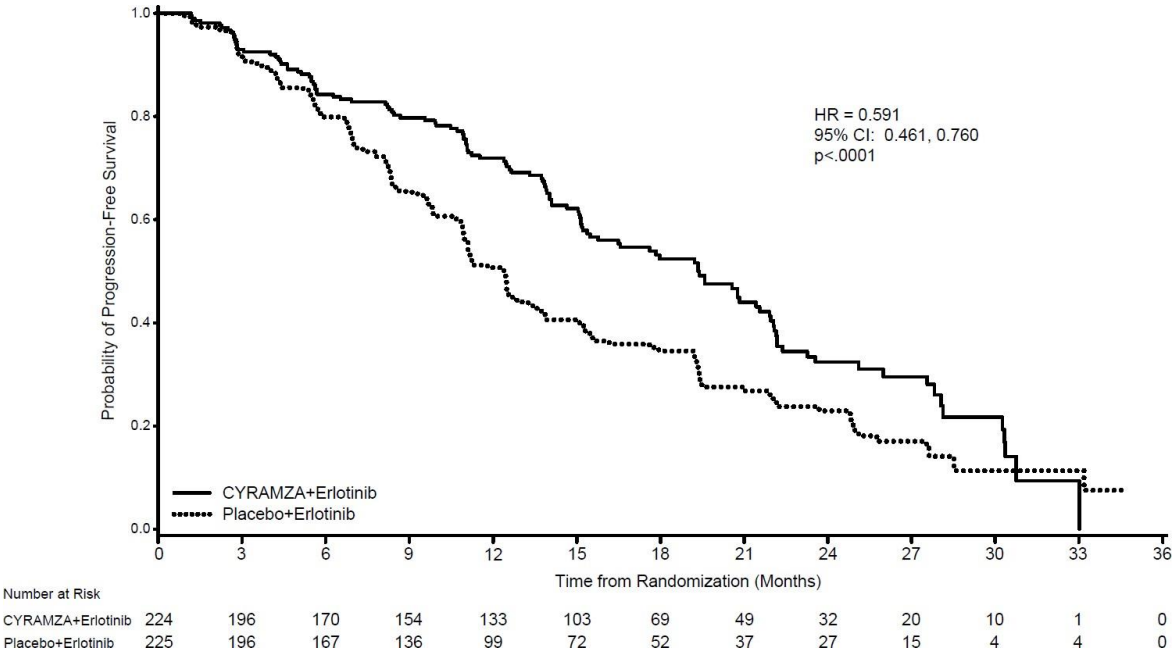
Table 11: Summary of efficacy data in RELAY – Intent to treat (ITT) population

	Cyramza plus erlotinib N=224	**Placebo plus erlotinib N=225**
Progression-free Survival		
Number of events (%)	122 (54.5)	158 (70.2)
Median – months (95% CI)	19.4 (15.38, 21.55)	12.4 (10.97, 13.50)
Hazard Ratio (95% CI)	0.591 (0.461, 0.760)	
Stratified Log-rank p-value	<0.0001	
Interim Overall Survival		
Number of deaths (%)	37 (16.5)	42 (18.7)
Median – months (95% CI)	NR	NR
Hazard Ratio (95% CI)	0.832 (0.532, 1.303)	
Stratified Log-rank p-value	0.4209	
Objective Response Rate (Complete Response + Partial Response)		
Rate – percent (95% CI)	76 (70.8, 81.9)	75 (69.0, 80.3)
CR, n (%)	3 (1.3)	2 (0.9)
PR, n (%)	168 (75.0)	166 (73.8)
Duration of Response	**N = 171**	**N = 168**
Number of events (%)	101 (59.1)	128 (76.2)
Median – months (95% CI)	18.0 (13.86, 19.78)	11.1 (9.69, 12.29)
Hazard Ratio (95% CI)	0.619 (0.477, 0.805)	
Unstratified Log-rank p-value	0.0003	

Abbreviations: CI = confidence interval, NR= not reached, CR = complete response, PR = partial

response. A hierarchal testing procedure was employed to test OS. OS was tested only if PFS was significant. Both endpoints were alpha-protected.

Figure 4: Kaplan-Meier curves of progression free survival for Cyramza plus erlotinib versus placebo plus erlotinib in RELAY



REVEL

REVEL, a randomised, double-blind, study of Cyramza plus docetaxel versus placebo plus docetaxel, was conducted in 1253 patients with locally advanced or metastatic squamous or non-squamous NSCLC with disease progression on or after one platinum-based therapy. The study excluded patients whose only prior treatment for advanced NSCLC was a tyrosine kinase [epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK)] inhibitor. The primary endpoint was OS. Patients were randomised in a 1:1 ratio to receive Cyramza plus docetaxel (n=628) or placebo plus docetaxel (n=625). Randomisation was stratified by geographic region, gender, prior maintenance, and ECOG PS. Cyramza at 10 mg/kg or placebo and docetaxel at 75mg/m^2 were each administered by intravenous infusion on day 1 of a 21-day cycle.

Baseline patient demographics and disease characteristics were generally balanced between arms: the median age was 62 years; 67% of patients were male; 82% were Caucasian, 13% Asian; the

ECOG PS was 0 for 32% of patients, 1 for 67% of patients; 73% of patients had non-squamous histology and 26% had squamous histology. The most common prior therapies included pemetrexed (38%), gemcitabine (25%), taxane (24%), and bevacizumab (14%). 22% of patients received prior maintenance therapy. The median duration of docetaxel therapy was 14.1 weeks for the ramucirumab plus docetaxel arm (with a median of 4.0 infusions received) and 12.0 weeks for the placebo plus docetaxel arm (with a median of 4.0 infusions received).

OS was statistically significantly improved in patients receiving Cyramza plus docetaxel compared with those receiving placebo plus docetaxel (HR 0.857; 95% CI: 0.751 to 0.979; p=0.024). There was an increase in median survival of 1.4 months in favour of the Cyramza plus docetaxel arm: 10.5 months in the Cyramza plus docetaxel arm and 9.1 months in the placebo plus docetaxel arm. PFS was statistically significantly improved in patients receiving Cyramza plus docetaxel compared with those receiving placebo plus docetaxel (HR 0.762; 95% CI: 0.677 to 0.859; p<0.001). There was an increase in median PFS of 1.5 months in favour of the Cyramza plus docetaxel arm: 4.5 months in the Cyramza plus docetaxel arm and 3 months in the placebo plus docetaxel arm. ORR was significantly improved in patients receiving Cyramza plus docetaxel compared with those receiving placebo plus docetaxel (22.9% vs. 13.6%, p<0.001). The primary Quality of Life (QoL) analysis showed similar time to deterioration for all Lung Cancer Symptom Scale (LCSS) scores between treatment arms.

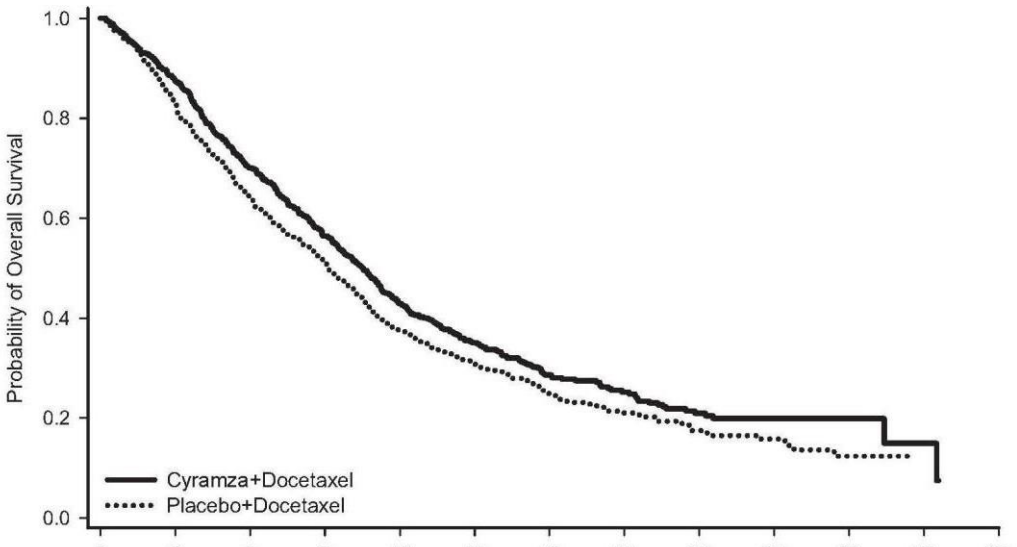
A consistent improvement (Cyramza plus docetaxel vs placebo plus docetaxel) was observed in important subgroups for OS and PFS. OS subgroup results included the following: non-squamous histology [HR 0.83; 95% CI: 0.71 to 0.97; median OS (mOS): 11.1 vs 9.7 months] and squamous histology (HR 0.88; 95% CI: 0.69 to 1.13; median OS [mOS]: 9.5 vs 8.2 months); patients with prior maintenance (HR 0.69; 95% CI: 0.51 to 0.93; mOS: 14.4 vs 10.4 months); time since prior therapy < 9 months (HR 0.75; 95% CI: 0.64 to 0.88; mOS: 9.3 vs 6.97 months); patients < 65 years old (HR 0.74, 95% CI: 0.62 to 0.87; mOS: 11.3 vs 8.9 months). A trend towards less efficacy with increasing age has been observed in patients receiving ramucirumab plus docetaxel for the treatment of advanced NSCLC with disease progression after platinum-based chemotherapy (see section 5.1). No differences in efficacy between treatment arms have been observed in the subgroups of patients ≥65 years old (OS HR 1.10, 95% CI: 0.89, 1.36; median OS [mOS]: 9.2 vs 9.3 months, see section 4.4), patients pre-treated with taxanes (HR 0.81; 95% CI:0.62 to 1.07; mOS 10.8 vs 10.4 months) and those with time since start of prior therapy ≥9 months (HR 0.95; 95% CI: 0.75 to 1.2; mOS: 13.7 vs 13.3 months). Efficacy results are shown in Table 12.

Table 12: Summary of efficacy data –ITT population

	Cyramza plus docetaxel N=628	Placebo plus docetaxel N=625
Overall survival, months		
Median – months (95% CI)	10.5 (9.5, 11.2)	9.1 (8.4, 10.0)
Hazard ratio (95% CI)	0.857 (0.751, 0.979)	
Stratified log-rank p-value	0.024	
Progression free survival, months		
Median (95% CI)	4.5 (4.2, 5.4)	3.0 (2.8, 3.9)
Hazard Ratio (95% CI)	0.762 (0.677, 0.859)	
Stratified log-rank p-value	<0.001	
Objective response rate (CR + PR)		
Rate – percent (95% CI)	22.9 (19.7, 26.4)	13.6 (11.0, 16.5)
Stratified CMH p-value	<0.001	

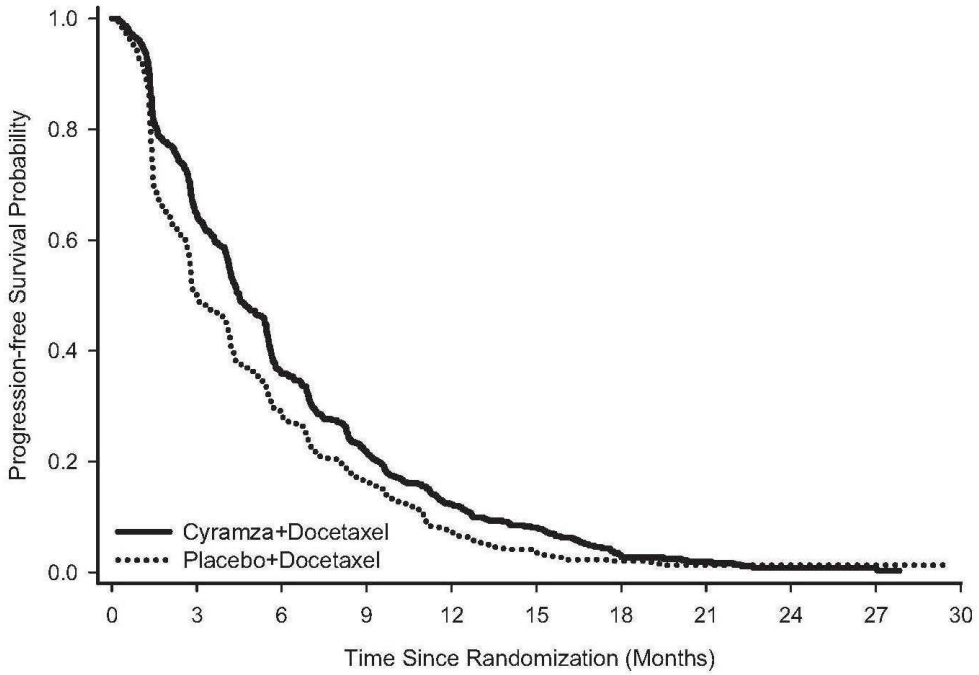
Abbreviations: CI = confidence interval, CR= complete response, PR= partial response, CMH =Cochran-Mantel-Haenszel

Figure 5: Kaplan-Meier curves of overall survival for Cyramza plus docetaxel versus placebo plus docetaxel in REVEL



Number at Risk													
Cyramza+Docetaxel	628	527	415	329	231	156	103	70	45	23	11	2	0
Placebo+Docetaxel	625	501	386	306	197	129	86	56	36	23	9	0	0

Figure 6: Kaplan-Meier curves of progression-free survival for Cyramza plus docetaxel versus placebo plus docetaxel in REVEL



Number at Risk											
Cyramza+Docetaxel	628	383	204	120	59	38	11	7	3	3	0
Placebo+Docetaxel	625	301	172	95	37	17	9	4	3	2	0

Colorectal cancer

RAISE

RAISE was a global, randomised, double-blind, study of Cyramza plus FOLFIRI versus placebo plus FOLFIRI, in patients with mCRC, who had disease progression on or after first-line therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine. Patients were required to have ECOG PS 0 or 1 and to have disease progression within 6 months of the last dose of first-line therapy. Patients were required to have adequate hepatic, renal and coagulation function. Patients with a history of uncontrolled hereditary or acquired bleeding or thrombotic disorders, a recent history of severe (Grade ≥3) bleeding or who had experienced an arterial thrombotic event (ATE) in the 12 months prior to randomisation were excluded. Patients were also excluded if they had experienced any of: an ATE, Grade 4 hypertension, Grade 3 proteinuria, a grade 3-4 bleeding event, or bowel perforation during first-line bevacizumab therapy.

A total of 1072 patients were randomised (1:1) to receive either Cyramza (n=536) at 8 mg/kg or placebo (n=536), in combination with FOLFIRI. All medicinal products were administered intravenously. The FOLFIRI regimen was: irinotecan 180 mg/m2 administered over 90 minutes and folinic acid 400 mg/m2 administered, simultaneously over 120 minutes; followed by bolus 5- fluorouracil(5-FU) 400 mg/m2 over 2 to 4 minutes; followed by 5-FU 2400 mg/m2 administered by continuous infusion over 46 to 48 hours. Treatment cycles on both arms were repeated every 2 weeks. Patients who discontinued one or more components of treatment because of an adverse event were permitted to continue therapy with the other treatment component(s) until disease progression or unacceptable toxicity. The primary endpoint was OS and the secondary endpoints included PFS, objective response rate (ORR) and quality of life (QoL) using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30. Randomisation was stratified by geographic region, tumour KRAS status (mutant or wild-type), and time to disease progression (TTP) after commencing first-line treatment (< 6 months versus ≥ 6 months).

Demographic and baseline characteristics for the ITT population were similar between treatment arms. Median age was 62 years and 40% of patients were ≥ 65 years; 57% of patients were male; 76% were White and 20% Asian; 49% had ECOG PS 0; 49% of patients had KRAS mutant tumours; and 24% of patients had TTP < 6 months after commencing first-line treatment. Post discontinuation systemic anti-cancer therapy was given to 54% of patients receiving Cyramza plus FOLFIRI and 56% of patients receiving placebo plus FOLFIRI.

Overall survival was statistically significantly improved in patients receiving Cyramza plus FOLFIRI compared with those receiving placebo plus FOLFIRI (HR 0.844; 95% CI: 0.730 to 0.976; p=0.0219). There was an increase in median survival of 1.6 months in favour of the Cyramza plus FOLFIRI arm: 13.3 months in the Cyramza plus FOLFIRI arm and 11.7 months in the placebo plus FOLFIRI arm. Progression-free survival was statistically significantly improved in patients receiving Cyramza plus FOLFIRI compared with those receiving placebo plus FOLFIRI (HR 0.793; 95% CI: 0.697 to 0.903; p=0.0005). There was an increase in median PFS of 1.2 months in favour of the Cyramza plus FOLFIRI arm: 5.7 months in the Cyramza plus FOLFIRI arm and 4.5 months in the placebo plus FOLFIRI arm. Efficacy results are shown in Table 13 and Figures 7 and 8.

Pre-specified analyses for OS and PFS by stratification factors were performed. The HR of OS was 0.82 (95% CI: 0.67 to 1.0) in patients with a KRAS wild type tumour, and 0.89 (95% CI: 0.73 to 1.09) in patients with a KRAS mutant tumour. For patients with TTP ≥ 6 months after commencing first-line treatment the HR of OS was 0.86 (95% CI: 0.73 to 1.01), and 0.86 (95% CI: 0.64 to 1.13) in patients with TTP < 6 months after commencing first-line treatment. Pre-specified subgroup analyses for both PFS and OS according to age (< 65 and ≥ 65 years), gender, race, ECOG PS (0 or ≥ 1), number of organs involved, liver metastases only, site of primary tumour (colon or rectum), carcinoembryonic antigen levels (< 200 µg/L, ≥200 µg/L), all showed a treatment effect favouring Cyramza plus FOLFIRI treatment over placebo plus FOLFIRI. In 32 of the 33 pre-specified sub- group analyses for OS, the HR was < 1.0. The one sub-group with HR > 1 was for patients with disease progression from start of first-line bevacizumab treatment of <3 months (HR 1.02 [95% CI: 0.68 to 1.55]). This one sub-group is a group which can be considered to have aggressive disease that is relatively refractory to first-line treatment. In both treatment arms, patients who experienced neutropenia had a longer median OS compared to patients who did not experience neutropenia. The median OS in patients with any grade neutropenia was greater in the ramucirumab arm (16.1 months) than in the placebo arm (12.6 months). Median OS in patients who did not experience neutropenia was 10.7 months in both arms.

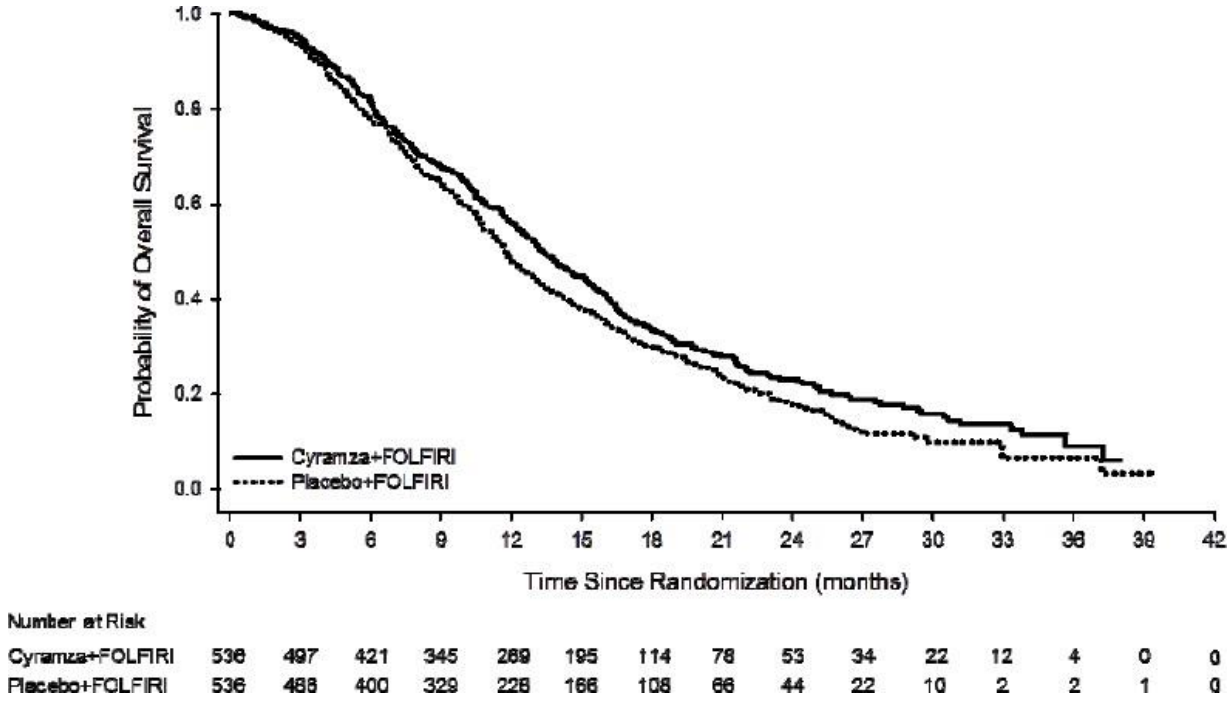
Table 13: Summary of efficacy data –ITT population

	Cyramza plus FOLFIRI N=536	Placebo plus FOLFIRI N=536
Overall survival, months		
Median (95% CI)	13.3 (12.4, 14.5)	11.7 (10.8, 12.7)
Hazard ratio (95% CI)	0.84 (0.73, 0.98)	
Stratified log-rank p-value	0.022	

Progression free survival, months		
Median (95% CI)	5.7 (5.5, 6.2)	4.5 (4.2, 5.4)
Hazard ratio (95% CI)	0.79 (0.70, 0.90)	
Stratified log-rank p-value	<0.001	

Abbreviations: CI = confidence interval

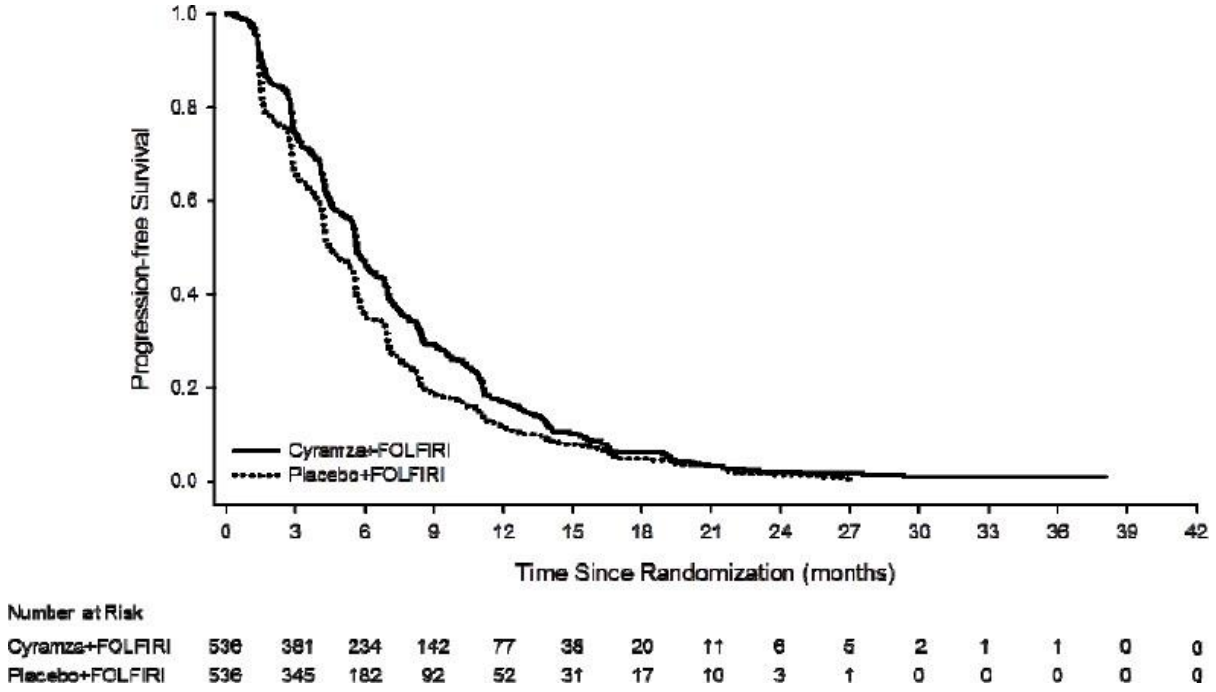
Figure 7: Kaplan-Meier curves of overall survival for Cyramza plus FOLFIRI versus placebo plus FOLFIRI in RAISE



Number at Risk

Cyramza+FOLFIRI	536	497	421	345	289	195	114	78	53	34	22	12	4	0	0
Placebo+FOLFIRI	536	488	400	329	228	166	108	66	44	22	10	2	2	1	0

Figure 8: Kaplan-Meier curves of progression free survival for Cyramza plus FOLFIRI versus placebo plus FOLFIRI in RAISE



The ORR was similar for both treatment arms (13.4% versus 12.5%, ramucirumab plus FOLFIRI versus placebo plus FOLFIRI, respectively). The disease control rate (complete response plus partial response plus stable disease) was numerically higher in patients on the ramucirumab plus FOLFIRI arm as compared to the placebo plus FOLFIRI arm (74.1% versus 68.8%, respectively). For the EORTC QLQ-C30, patients in the ramucirumab plus FOLFIRI treatment arm reported a transient decrease in QoL compared to the patients in the placebo plus FOLFIRI treatment arm in most of the scales. Few between-arm differences were reported after the first month of treatment.

Hepatocellular carcinoma

REACH-2

REACH-2 was a global, randomised, double-blind study of Cyramza plus BSC versus placebo plus BSC that randomised (2:1) 292 patients with HCC who had a serum AFP ≥ 400 ng/ml at study entry. Patients enrolled into the study had disease progression on or after prior sorafenib therapy or were intolerant to sorafenib. Eligible patients were Child Pugh A (score < 7), had creatinine clearance ≥ 60 ml/min, and ECOG PS of 0 or 1. In addition, patients were either Barcelona Clinic Liver Cancer (BCLC) stage B and no longer amenable to locoregional therapy, or were BCLC stage C. Patients with brain metastases, leptomeningeal disease, uncontrolled spinal cord compression, a history of or current hepatic encephalopathy or clinically meaningful ascites, severe variceal bleeding in the 3 months prior

to treatment, or gastric or oesophageal varices at high risk of bleeding were excluded from the study. The primary endpoint was overall survival. The threshold for the elevated AFP study entry requirement for REACH-2 was determined based on the survival results from a pre-specified subgroup, exploratory analysis from REACH, a previously completed, supportive phase 3 clinical study in 565 HCC patients randomised (1:1) to either Cyramza plus BSC or placebo plus BSC that had disease progression on or after prior sorafenib therapy.

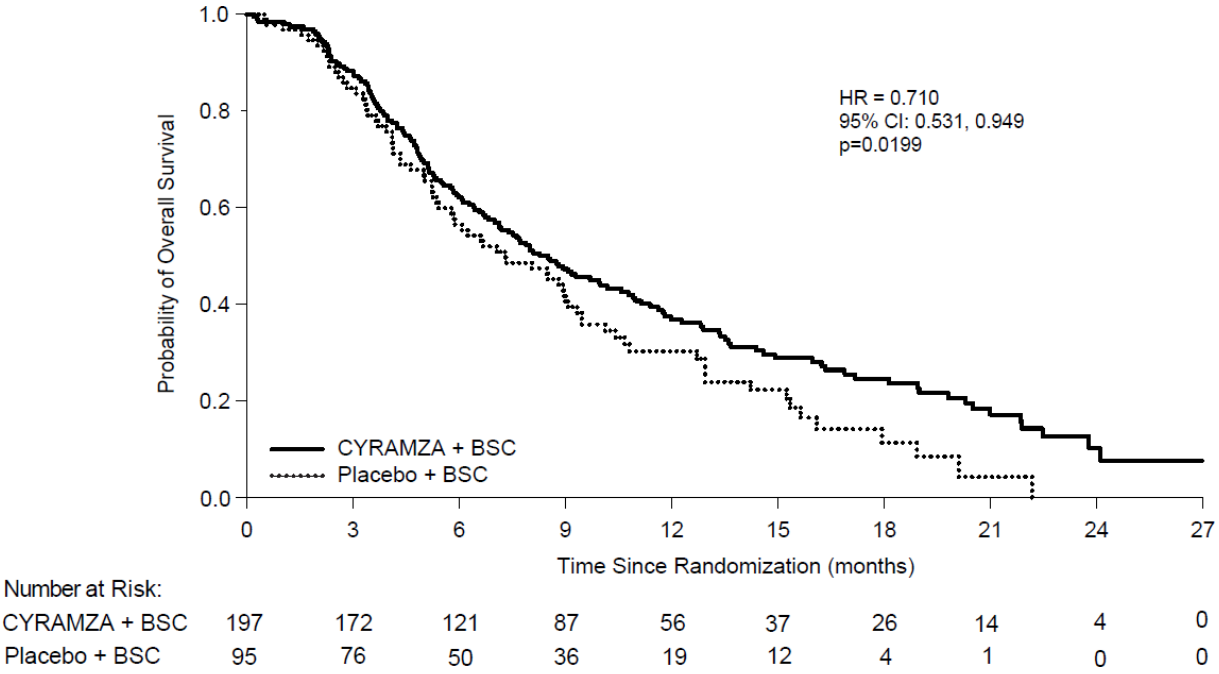
In REACH-2, baseline patient demographics and disease characteristics were generally balanced between arms, except for AFP, which was lower in the placebo arm. Patients treated with Cyramza experienced a statistically significant improvement in OS, compared to placebo (Table 14). The major efficacy outcome in REACH-2 was supported by a statistically significant improvement in progression free survival in Cyramza treated patients compared to placebo treated patients. The relative treatment effect (assessed by HR) of Cyramza compared to placebo was generally consistent across subgroups, including age, race, aetiology of disease and reason for discontinuation of sorafenib (progressive disease vs. intolerance). A relevant exposure-efficacy association was observed for ramucirumab in REACH-2 (see section 5.2). REACH-2 efficacy results are shown in Table 14 and Figure 9.

Table 14: Summary of efficacy data in REACH-2 – Intent to treat (ITT) population

	Cyramza **N=197**	**Placebo** **N=95**
Overall survival, months		
Median (95% CI)	8.51 (7.00, 10.58)	7.29 (5.42, 9.07)
Hazard ratio (95% CI)	0.710 (0.531, 0.949)	
Stratified log-rank p-value	0.0199	
Progression free survival, months		
Median (95% CI)	2.83 (2.76, 4.11)	1.61 (1.45, 2.69)
Hazard ratio (95% CI)	0.452 (0.339, 0.603)	
Stratified log-rank p-value	<0.0001	
Objective Response Rate (CR + PR)		
ORR % (95% CI)	4.6 (1.7, 7.5)	1.1 (0.0, 3.1)
p-value	0.1697	

Abbreviations: CI = confidence interval, CR = complete response, ORR = objective responserate and PR = partial response

Figure 9: Kaplan-Meier curves of Overall Survival for Cyramza versus placebo in REACH-2



Number at Risk:										
CYRAMZA + BSC	197	172	121	87	56	37	26	14	4	0
Placebo + BSC	95	76	50	36	19	12	4	1	0	0

Immunogenicity

Patients in two Phase 3 studies, RAINBOW and REGARD were tested at multiple time-points for anti-drug antibodies (ADAs). Samples were tested from 956 patients: 527 Cyramza treated patients and 429 control treated patients. Eleven (2.2%) of Cyramza treated patients and two (0.5%) of control treated patients developed ADAs. None of the patients with ADAs experienced an IRR. No patients had neutralising antibodies to Cyramza. There is insufficient data to evaluate the effects of ADAs on the efficacy or safety of Cyramza.

Paediatric population

The safety and pharmacokinetics (PK) of ramucirumab, as a single agent, were evaluated in I4T MC JVDA, a multicenter, open label, phase 1 study in paediatric and young adult patients aged 1 to 21 years to determine the recommended phase 2 dose (RP2D). The study consisted of 2 parts. In Part A, ramucirumab was administered at a dose of 8 mg/kg or 12 mg/kg intravenously over 60 minutes every 2 weeks to 23 patients with recurrent or refractory non CNS tumours. A maximum tolerated dose was not reached. The RP2D was determined to be 12 mg/kg when given every 2 weeks. In Part B,

ramucirumab was administered at the RP2D to 6 patients with relapsed or refractory CNS tumours for evaluation of tolerability in this population. No tumour responses were observed in either Part A or B.

5.2 Pharmacokinetic properties

Following the dose regimen of 8 mg/kg every 2 weeks, the geometric means of Cyramza C_{min} prior to administration of the fourth and seventh dose of Cyramza given as a single agent in advanced gastric cancer patients' serum were 49.5 µg/ml (range of 6.3-228 µg/ml) and 74.4 µg/ml (range of 13.8-234 µg/ml), respectively. In HCC patients' serum the geometric means of ramucirumab C_{min} prior to administration of the second, fourth and seventh dose of Cyramza were 23.5 µg/ml (rangeof 2.9-76.5 µg/ml), 44.1 µg/ml (range of 4.2-137 µg/ml) and 60.2 µg/ml (range of 18.3-123 µg/ml), respectively.

Following the dose regimen of 10 mg/kg Cyramza every 3 weeks, the geometric means of Cyramza C_{min} were 28.3 µg/ml (range of 2.5-108 µg/ml) and 38.4 µg/ml (range of 3.1-128 µg/ml) prior to administration of the third and fifth dose, respectively of Cyramza given in combination with docetaxel, in serum from patients with NSCLC.

Following the dose regimen of 10 mg/kg Cyramza every 2 weeks, the geometric means of Cyramza C_{min} were 68.5 µg/ml (range of 20.3-142 µg/ml) and 85.7 µg/ml (range of 36.0-197 µg/ml) prior to administration of the fourth and seventh dose, respectively of Cyramza given in combination with erlotinib, in serum from patients with NSCLC.

Following the dose regimen of 8 mg/kg Cyramza every 2 weeks in combination with FOLFIRI, the geometric means of Cyramza C_{min} were 46.3 µg/ml (range of 7.7-119 µg/ml) and 65.1 µg/ml (range of 14.5-205 µg/ml) prior to administration of the third and fifth dose, respectively, in serum from patients with mCRC.

Absorption

Cyramza is administered as an intravenous infusion. There have been no studies performed with other routes of administration.

Distribution

Based on population pharmacokinetic approach (PopPK), the mean (% coefficient of variation [CV%]) volume of distribution at steady state for Cyramza was 5.4 L (15%).

Biotransformation

The metabolism of Cyramza has not been studied. Antibodies are principally cleared by catabolism.

Elimination

Based on PopPK, the mean (CV%) clearance of Cyramza was 0.015 L/hour (30%) and the mean half-life was 14 days (20%).

Time and dose dependency

There was no clear deviation from dose proportionality in pharmacokinetics of Cyramza from 6 mg/kg to 20 mg/kg. An accumulation ratio of 1.5 was observed for Cyramza when dosed every 2 weeks. Based on simulations using the PopPK model, steady state would be attained by the sixth dose.

Elderly

Based on PopPK, there was no difference in Cyramza exposure in patients ≥ 65 years of age compared to patients < 65 years old.

Renal impairment

No formal studies have been conducted to evaluate the effect of renal impairment on the pharmacokinetics of Cyramza. Based on PopPK, Cyramza exposure was similar in patients with mild renal impairment (calculated creatinine clearance [CrCl] ≥ 60 to < 90 ml/min), moderate renal impairment (CrCl ≥ 30 to < 60 ml/min) or severe renal impairment (CrCl 15 to 29 ml/min) as compared to patients with normal renal function (CrCl ≥ 90 ml/min).

Hepatic impairment

No formal studies have been conducted to evaluate the effect of hepatic impairment on the pharmacokinetics of Cyramza. Based on PopPK, Cyramza exposure in patients with mild hepatic impairment (total bilirubin > 1.0-1.5 upper limit of normal (ULN) and any AST or total bilirubin ≤1.0 ULN and AST > ULN or moderate hepatic impairment (total bilirubin > 1.5-3.0 ULN and any AST) was similar to patients with normal hepatic function (total bilirubin and AST ≤ULN). Cyramza has not been studied in patients with severe hepatic impairment (total bilirubin > 3.0 ULN and any AST).

Paediatric population

Exposure to ramucirumab in paediatric and young adult patients (children >12 months and <21 years) with refractory solid tumours, including CNS tumours following a single dose or multiple doses of 8

mg/kg or 12 mg/kg was similar to the exposure obtained in adult patients. Further, ramucirumab exposure following 12 mg/kg dose was similar across the age range of >12 months to <21 years.

Other special populations

Based on PopPK, the following covariates were found to have no impact on Cyramza disposition: age (range, 19 to 86 years), sex (316 males and 181 females), race (337 White and 139 Asians), and albumin levels (range, 15.5 to 64.8 g/L). These and other factors investigated had < 20 % effect on Cyramza disposition. Body weight is considered a significant co-variate of Cyramza pharmacokinetics supporting the dosing based on body weight.

Exposure response relationships:

Efficacy

Exposure-response analyses indicated that efficacy was correlated with Cyramza exposure across pivotal studies. Efficacy, as measured by improvements in OS, was associated with increasing Cyramza exposure range produced by 8 mg/kg Cyramza given every two weeks and by 10 mg/kg Cyramza given every 3 weeks. An improvement in PFS was also associated with increasing Cyramza exposure for advanced gastric cancer, NSCLC with disease progression after platinum- based chemotherapy, and mCRC.

In the REACH-2 study for HCC, a relevant exposure-efficacy association was observed for Cyramza which showed that only patients with above-median exposure experienced an improvement in OS, compared to placebo, and these exposure-efficacy relationships remained after attempts to adjust for other prognostic factors. A treatment effect on PFS was observed for all exposure levels produced by 8 mg/kg Cyramza given every 2 weeks. No such relation was observed in the RELAY study for NSCLC with 10 mg/kg Cyramza plus erlotinib given every 2 weeks.

Safety

In RAINBOW, the incidences of Grade ≥ 3 hypertension, neutropenia, and leukopenia were also increased with higher Cyramza exposure. In RAISE, the incidences of Grade ≥ 3 neutropenia was increased with higher Cyramza exposure.

In RELAY, no exposure-safety relationship was identified for the selected safety endpoints, including Grade ≥ 3 hypertension, diarrhoea, proteinuria and dermatitis acneiform.

In REVEL, the incidences of Grade ≥ 3 febrile neutropenia and hypertension were also increased with higher Cyramza exposure.

In the pooled data from REACH-2 and REACH (patients with alpha fetoprotein ≥ 400 ng/ml), the incidences of Grade ≥ 3 hypertension was increased with higher Cyramza exposure.

5.3 Preclinical safety data

No animal studies have been performed to test Cyramza for potential of carcinogenicity or genotoxicity.
The target organs identified in repeated dose cynomolgus monkey toxicity studies were kidney (glomerulonephritis), bone (thickening and abnormal endochondral ossification of the epiphyseal growth plate) and female reproductive organs (decreased weight of ovaries and uterus). A minimal grade of inflammation and/or mononuclear cell infiltration was seen in several organs.
Reproductive toxicity studies with Cyramza have not been performed, however, animal models link angiogenesis, VEGF and VEGF Receptor 2 to critical aspects of female reproduction, embryo-foetal development, and postnatal development. Based on Cyramza's mechanism of action, it is likely that in animals, Cyramza will inhibit angiogenesis and result in adverse effects on fertility (ovulation), placental development, developing foetuses and postnatal development.
A single dose of Cyramza did not impair wound healing in monkeys using a full-thickness incisional model.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Histidine
Histidine monohydrochloride
Sodium chloride
Glycine
Polysorbate 80
Water for injection

6.2 Incompatibilities

Cyramza should not be administered or mixed with dextrose solutions.
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 In-use shelf-life

After dilution:

When prepared as directed, infusion solutions of Cyramza contain no antimicrobial preservatives.

Chemical and physical in-use stability of Cyramza in sodium chloride 9 mg/ml (0.9%) solution for injection has been demonstrated for 24 hours at 2°C to 8°C or for 4 hours at below 30°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in- use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10ml or 50ml solution in a vial (Type I glass) with a chlorobutyl rubber stopper, an aluminium seal and a polypropylene cap.

Pack of 1 vial of 10ml or 50ml.

6.6 Special precautions for disposal and other handling

Do not shake the vial.
Prepare the infusion solution using aseptic technique to ensure the sterility of the prepared solution. Each vial is intended for single use only. Inspect the content of the vials for particulate matter and discolouration (the concentrate for solution for infusion should be clear to slightly opalescent and colourless to slightly yellow without visible particles) prior to dilution. If particulate matter or discolouration is identified, discard the vial.

Calculate the dose and volume of Cyramza needed to prepare the infusion solution. Vials contain either 100mg or 500mg as a 10 mg/ml solution of Cyramza. Only use sodium chloride 9 mg/ml (0.9%) solution for injection as a diluent.

<u>In case of prefilled intravenous infusion container usage</u>
Based on the calculated volume of Cyramza, remove the corresponding volume of sodium chloride 9

mg/ml (0.9%) solution for injection from the prefilled 250ml intravenous container. Aseptically transfer the calculated volume of Cyramza to the intravenous container. The final total volume in the container should be 250ml. 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 medicinal products.

In case of empty intravenous infusion container usage

Aseptically transfer the calculated volume of Cyramza into an empty intravenous infusion container. Add a sufficient quantity of sodium chloride 9 mg/ml (0.9%) solution for injection to the container to make the total volume 250ml. 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 medicinal products.

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

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

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 sodium chloride 9 mg/ml (0.9%) solution for injection at the end of the infusion.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. PRODUCT OWNER

Eli Lilly and Company, Indianapolis, Indiana 46285, USA

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