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Human Medicines Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Cyramza

ramucirumab

Procedure no: EMEA/H/C/002829/P46/009

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	11 Sep 2023	11 Sep 2023	☐
☐	CHMP Rapporteur Assessment Report	16 Oct 2023	16 Oct 2023	☐
☐	CHMP members comments	30 Oct 2023	30 Oct 2023	☐
☐	Updated CHMP Rapporteur Assessment Report	6 Nov 2023	6 Nov 2023	☐
☒	CHMP adoption of conclusions:	9 Nov 2023	9 Nov 2023	☐

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1. Introduction

On 29 August 2023, the MAH submitted a completed paediatric study for ramucirumab, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study J1S-MC-JV02 (JV02) is part of a clinical development program. The primary objective of JV02 was to evaluate the efficacy (PFS) of ramucirumab in paediatric patients and young adults with relapsed, recurrent, or refractory synovial sarcoma (SS) in combination with gemcitabine and docetaxel. The study was performed under the construct of the ongoing CAMPFIRE Master Protocol JAAA (JAAA). The investigation consists of JAAA that defines common elements across all study addenda and the individual study addendum that defines the disease-specific investigation requirements. In addition to JV02, Study J1S-MC-JV01 (JV01) is also being performed under the construct of JAAA. JV01 is an ongoing randomized, multicentre, global, Phase 2 study in paediatric patients and young adults with relapsed, recurrent, or progressive desmoplastic small round cell tumour (DSRCT) evaluating the efficacy of ramucirumab in combination with chemotherapy versus chemotherapy alone. Together, JAAA along with JV01 and JV02 describes the investigation in the DSCRT population and SS population, respectively.

Ramucirumab has been approved for use in adults as a single-agent and in combination with various chemotherapeutic agents or erlotinib in the European Union and worldwide for multiple malignancies. The adult registered doses of ramucirumab are 8 mg/kg intravenous (IV) formulation administered every 2 weeks (Q2W) in gastric cancer, colorectal cancer, and hepatocellular carcinoma indications; 10 mg/kg IV formulation administered Q2W in epidermal growth factor receptor-mutated non-small cell lung cancer (NSCLC); and 10 mg/kg IV formulation administered every 3 weeks in NSCLC in patients with disease progression after platinum-based chemotherapy (Cyramza® summary of product characteristics [SmPC]).

Ramucirumab has not been authorised for use in paediatric population; however, it has been studied previously in the completed paediatric I4T-MC-JVDA (JVDA) trial. JVDA was a multicentre, open-label, dose-finding, and dose-escalation study of ramucirumab monotherapy in children aged at least 12 months and patients 21 years of age or below with recurrent solid tumours, including central nervous system tumours. JVDA was submitted to EMA through an Article 46 submission on 03 February 2021 (EMA/H/C/002829/P46). Relevant information is presented in the SmPC.

JV02 was not a part of an agreed paediatric investigation plan. The initially proposed PIP for soft tissue sarcoma was not approved by the EMA paediatric committee (PDCO). The PDCO had raised several concerns on the possible benefit of developing ramucirumab for the treatment of paediatric patients with soft tissue sarcoma as there was not a clear evidence for proof of concept to study a VEGF inhibitor in the paediatric population and no clinical benefit was found in soft tissue sarcoma with another VEGFR inhibitor. Subsequently, the PIP application was withdrawn by the Applicant. The Applicant indicated to reopen the PIP application if compelling clinical proof-of-concept data would become available. Further, product specific waivers were granted for all subsets of the paediatric population for the treatment of gastric cancer and gastro-oesophageal junction adenocarcinoma, intestinal malignant neoplasm, lung malignant neoplasm and liver cancer and urinary tract malignant neoplasm (PIP procedure EMA-002074-PIP01-16).

At the interim futility analysis, JV02 did not meet the 60% confidence in treatment superiority (PFS HR of less than 1 for SS) leading to IDMC's recommendation to suspend enrolment. The study was terminated on 15 March 2023 without formal evaluation of the primary PFS endpoint. The MAH concluded that the overall safety assessment did not reveal any new or unexpected safety findings. The MAH does not propose any changes to the current ramucirumab SmPC with regards to paediatric patients.

2.2. Information on the pharmaceutical formulation used in the study

Ramucirumab was administered as an IV infusion over 60 minutes on Days 1 and 8 Q3W. Intravenous infusion (using the commercial formulation) was considered a suitable formulation for the administration of ramucirumab to both adult and paediatric patients (aged 12 months and above).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- J1S-MC-JV02: A Randomized, Open-Label, Phase 1/2 Study Evaluating Ramucirumab in Paediatric Patients and Young Adults with Relapsed, Recurrent, or Refractory Synovial Sarcoma.

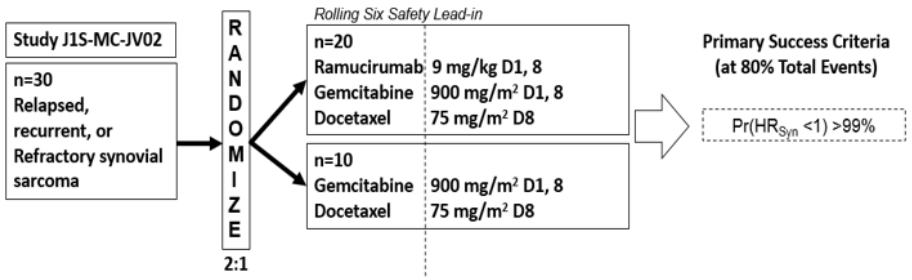
2.3.2. Clinical study

J1S-MC-JV02: A Randomized, Open-Label, Phase 1/2 Study Evaluating Ramucirumab in Paediatric Patients and Young Adults with Relapsed, Recurrent, or Refractory Synovial Sarcoma

Description

JV02 was a randomized (2:1), multicentre, global, Phase 2 study in paediatric patients and young adults aged 36 months to 29 years of age or below with relapsed, recurrent, or progressive SS evaluating the efficacy of ramucirumab (9 mg/kg IV on Days 1 and 8 every 3 weeks) in combination with gemcitabine (900 mg/m2 IV on Days 1 and 8 of a 3-week cycle) and docetaxel (75 mg/m2 IV on Day 8 of a 3-week cycle) (Figure 1). The primary objective (PFS) in JV02 was planned using a Bayesian analysis incorporating information regarding historical control outcomes to augment the control arm of JV02 as well as effect-size observed on JV01 that would provide a posterior probability of treatment superiority.

Figure 1 Illustration of JV02 study design.



Abbreviations: D = day; HR_{Syn} = hazard ratio of synovial sarcoma; JV02 = J1S-MC-JV02; n = number of patients; Pr = probability.

Safety lead in: To assess excessive toxicity associated with the experimental ramucirumab-based combinations, a safety lead-in period would review data on an ongoing basis to inform the rolling 6 decision rules (Skolnik et al. 2008).

Methods

Study participants

Key inclusion criteria:

- between 12 months to 29 years of age or below at the time of study enrolment, while patients from countries in EU should be 36 months to 29 years of age or below and weighing greater than 11 kg at the time of study enrolment
- had either relapsed, recurrent, or rSS
- had measurable or evaluable disease by RECIST 1.1
- had a Lansky (below 16 years of age; Lansky et al. 1987) or Karnofsky (at least 16 years of age; Karnofsky at al. 1948) performance score of at least 50
- received at least 1 prior line of systemic treatment that contains ifosfamide and/or doxorubicin, or any approved therapies for which they are eligible
- not be eligible for surgical resection at the time of enrolment, and
- not have received prior exposure to ramucirumab.

Key exclusion criteria:

- taking any prohibited medications
- bleeding and suffering from thrombosis
- central nervous system, arterial/venous thromboembolic events, transient ischemic attack, cerebrovascular accident, myocardial infarction within 6 months prior to study enrolment
- New York Heart Association Grade 2 or greater congestive heart failure
- serious and inadequately controlled cardiac arrhythmia
- significant vascular disease
- had a history of fistula, GI ulcer or perforation, or intra-abdominal abscess within 3 months of study enrolment
- had a history of hypertensive crisis or hypertensive encephalopathy within 6 months of study enrolment
- had a nonhealing wound, unhealed or incompletely healed fracture, or a compound (open) bone fracture at the time of enrolment, or
- been previously treated and progressed on combination gemcitabine or docetaxel.

Treatments

A ramucirumab dosing regimen of 9 mg/kg IV on Days 1 and 8 Q3W in combination with gemcitabine (900 mg/m^2 IV on Days 1 and 8 of a 3-week cycle) and docetaxel (75 mg/m^2 IV on Day 8 of a 3-week cycle) was planned, assuming no safety findings were reported in the Safety Lead-in Period. Patients received premedication with diphenhydramine or alternative antihistamine within 30 to 60 minutes prior to each infusion with ramucirumab.

Ramucirumab dosing and schedule were based on the RP2D determined in Part A of Study JVDA in conjunction with the schedule of the chemotherapy backbone of gemcitabine or docetaxel. The RP2D in JVDA was defined as the dose achieving the steady-state minimum concentration (Cmin) of 50 µg/mL in a majority of patients, assuming a maximally tolerated dose was not reached. Justification for this target was based on the observed association between ramucirumab exposure and an improvement in OS and PFS in Phase 3 studies in an adult population, in which exposure-response analysis across the studies indicated an EC50 value of approximately 50 µg/mL (Tabernero et al. 2017). A minimum of 50 µg/mL was therefore used as the targeted efficacious concentration level for selection of the RP2D in JVDA.

Patients in the control arm received gemcitabine and docetaxel.

Dose adjustments (suspensions, reductions, or discontinuations) were made based on the clinical assessment of hematologic and nonhematologic toxicities (defined as an AE possibly related to study treatment per investigator judgment) (Table 1).

Table 1 Dose reductions for ramucirumab, gemcitabine, and docetaxel-related toxicities.

	Starting Dose	Dose Reduction	
Study Drug		**First**	**Second**
Ramucirumab	9 mg/kg	7 mg/kg	5 mg/kg
if de-escalated	6 mg/kg	5 mg/kg	4 mg/kg
Gemcitabine[a]	900 mg/m^2	675 mg/m^2	500 mg/m^2
Docetaxel	75 mg/m^2	60 mg/m^2	45 mg/m^2

[a] The infusion time of gemcitabine after its dose reduction may be maintained at 90 minutes or may be shortened to keep a rate of approximately 10 mg/m^2/min according to discretion of the investigator.

Treatment was to continue until evidence of disease progression or other discontinuation criteria were met.

Objectives and endpoints

Objective and endpoints are summarized in Table 2.

Table 2 Objectives and endpoints

Objectives	Endpoints
Primary	
To evaluate the efficacy of ramucirumab in combination with gemcitabine and docetaxel compared with gemcitabine and docetaxel in pediatric and young adult patients with SS	PFS
Secondary	
To evaluate the safety and tolerability of ramucirumab in combination with gemcitabine and docetaxel compared with gemcitabine and docetaxel in pediatric and young adult patients with SS	SAEs, AEs, safety laboratory assessments, and vital signs
To evaluate the efficacy of ramucirumab in combination with gemcitabine and docetaxel compared with gemcitabine and docetaxel in pediatric and young adult patients with SS	• ORR • DoR • CR
To characterize the PK of ramucirumab when coadministered with gemcitabine and docetaxel in pediatric and young adult patients with SS	C_{max} and C_{min}
To assess the immunogenicity of ramucirumab when coadministered with gemcitabine and docetaxel in pediatric and young adult patients with SS	Incidence of immunogenicity
Exploratory	
To explore additional measures of the efficacy of ramucirumab in combination with gemcitabine and docetaxel compared with gemcitabine and docetaxel in pediatric and young adult patients with SS	• OS • PFS2 • Difference in proportion of patients who become eligible for surgical resection of lesions due to documented tumor response while on study therapy
To explore the associations between biomarkers, disease state, and clinical outcomes	Biomarkers may be assessed from blood and tumor tissue samples, unless precluded by local regulations

Abbreviations: AE = adverse event; C_{max} = maximum concentration; C_{min} = minimum concentration; CR = complete response; DoR = duration of response; ORR = overall response rate; OS = overall survival; PFS = progression-free survival; PK = pharmacokinetics; SAE = serious adverse event; SS = synovial sarcoma.

Sample size, randomisation and blinding (masking)

A total of 30 patients were planned to be randomized 2:1 to receive ramucirumab in combination with tumour-specific chemotherapy versus chemotherapy alone, respectively. Randomization was stratified according to staging at relapse (metastatic versus locally advanced).

JV02 was an open-label study; however, the results of the Bayesian futility analysis were blinded to the study team. The study team was to be unblinded only if the prespecified futility criteria were met that would lead to suspension of enrolment and subsequent study termination.

Statistical Methods

Primary endpoint PFS

PFS was defined as the time from randomization until the first investigator-determined objective progression as defined by RECIST 1.1 or death from any cause in the absence of progressive disease. The censoring scheme is shown below (Table 2).

Table 3 Progression-Free Survival/Censoring scheme

Situation[a]	Event/Censor	Date of Event or Censor
Investigator assessed tumor progression or death	Event	Earliest date of PD or death
No tumor progression and no death	Censored	Date of last adequate radiological assessment or date of randomization (whichever is later)[b]
Unless		
No baseline radiological tumor assessment available	Censored	Date of randomization
No adequate postbaseline radiological tumor assessment available and death reported after 2 scan intervals following randomization[b,c]	Censored	Date of randomization
New anticancer treatment started and no tumor progression or death within 14 days	Censored	Date of adequate radiological assessment before (start of new therapy +14 days) or date of randomization (whichever is later)
Tumor progression or death documented immediately after 2 or more scan intervals following last adequate radiological tumor assessment or randomization (whichever is later)[b,c]	Censored	Date of last adequate radiological assessment or date of randomization (whichever is later)[b]

Abbreviations: CR = complete response; PD = progressive disease; PFS = progression-free survival; PR = partial response; SD = stable disease.

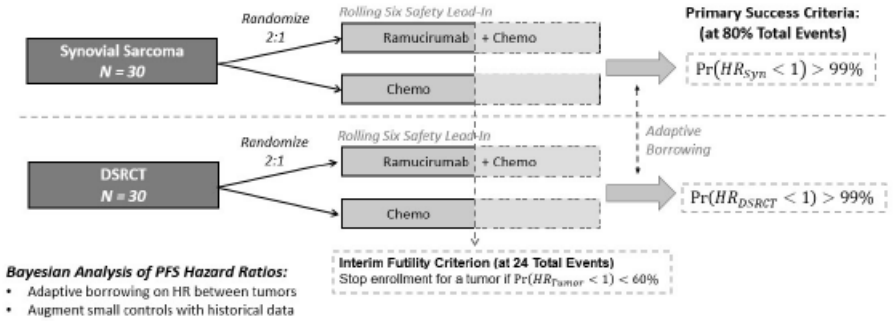
a Symptomatic deterioration (i.e., symptomatic progression that is not radiologically confirmed) will not be considered as tumor progression.

b Adequate radiological tumor assessment refers to an assessment with one of the following responses: CR, PR, SD, or PD.

c Radiologic imaging for tumor assessment will be performed every 6 weeks (±7 days) after randomization (regardless of treatment delays) during the Study Treatment Period, until disease progression OR study completion or 14 months after randomization, whichever occurs first. Refer to footnote b for any patient whose disease has not progressed by 14 months after randomization. Any patient whose disease has not progressed by 14 months after randomization will be evaluated for response every 12 weeks (±7 days) from 14 months after randomization, until disease progression OR study completion OR 3 years after randomization, whichever occurs first; then as per standard clinical practice after that.

The primary endpoint of PFS is analysed via a Bayesian hierarchical Weibull model that allows (1) adaptive borrowing on effect-size (log hazard ratio) between Studies JV01 and JV02 and (2) augmenting with historical control data via the use of informative prior distributions constructed from real-world (RW) control outcomes. A schematic diagram of the studies and their statistical/timing linkages is provided in Figure 2.

Figure 2 JVAA study design.



The stringent primary success criteria for each tumour, Pr(HR < 1) > 99%, was calibrated to ensure that meeting the primary endpoint should imply both statistical significance and large estimated magnitude of patient benefit (additional PFS) for the paediatric/young adult populations of interest.

Based on a large simulation study, when the 99% posterior probability threshold is reached, the associated estimate of the PFS HR is no larger than approximately .51. Under an example assumption of 3 months for control median PFS (and a further assumption of exponentially distributed PFS), the minimal effect size of HR= .51 would correspond to approximately 3 months of additional PFS in this population with high unmet medical need.

Real world data and historical control matching

The prior distributions for PFS on the control arms in Study JV01 and Study JV02 were constructed from PFS outcomes for patients with relapsed DSRCT or SS treated with chemotherapy or pazopanib in the RW setting. These data were obtained from chart reviews conducted at institutions including US sites. Eligible patients were initially diagnosed with DSRCT or SS before age 40 years. This age limit is higher than the eligibility criterion for Studies JV01 and JV02, as pathology and outcomes are not expected to vary based on age in these diseases; therefore, the age range was expanded to facilitate improved matching on other important prognostic factors. Eligible patients must have progressed on at least 1 course of chemotherapy for relapsed, recurrent, or progressive disease in order to estimate PFS for at least 1 line of therapy. Variables to be extracted include patient and baseline/disease characteristics, as well as treatments (surgery, radiotherapy, chemotherapy) and outcomes since initial DSRCT or SS diagnosis. PFS for the historical control data was defined for a given line of therapy as the time from the date of initiating the particular line of therapy to the first date thereafter of documented disease progression or death. Determination of disease progression did not require criteria such as RECIST. The target sample size was 100 charts each for DSRCT and SS at the time of the final analysis.

A propensity-based matching algorithm was utilized to match each of the 20 prospective ramucirumab patients with a historical control patient (conducted separately within each tumour).

Interim Futility Analysis

An interim futility analysis will be triggered when approximately 24 total PFS events have been observed across Studies JV01 and JV02 with a minimum of 8 events in Study JV02. At the interim futility look for Study JV02, the Bayesian analysis must provide a minimum of 60% posterior probability of treatment superiority (PFS HR <1 for SS patients) for enrolment on Study JV02 to continue. Otherwise, enrolment on Study JV02 will be stopped.

Sensitivity analyses

Since the Bayesian model included data exogenous to JV02 (that is, borrowing from historical controls and the JV01 PFS effect-size), the objective of the Bayesian sensitivity analyses was to document the impact of each component of borrowing. Sensitivity analyses investigated the impact of the following aspects of the primary analysis (by analysis that omitted only the mentioned aspect):

1) borrowing from the JV01
2) borrowing from the historical controls
3) borrowing from JV01 and historical controls
4) changing the matching method for the historical controls (Mahalanobis instead of propensity scores).
5) changing the historical controls from data derived to a formal expert elicitation of 6 oncologists specializing in SS and DSRCT. Based on the combined expert prior for JV02, the expected median PFS for the control arm in JV02 was 5.5 months (95% CI: 3.4, 8.0 months).

Additional PFS analyses

Traditional (frequentist) PFS analyses was performed to provide additional context. The nonparametric Kaplan-Meier method was used to estimate the PFS curves and survival rates by treatment arm and the (unstratified) log-rank test was used to compare the treatment arms.

Secondary outcome

Overall response rate (ORR) was defined as the number of patients who achieved a best overall response of CR or PR divided by the total number of patients randomly assigned to the corresponding treatment arm. Confirmation of PR or CR was a prerequisite. The ORR with 80% CI was summarized for each treatment arm.

Duration of response (DoR) was defined as the time from the date that measurement criteria for CR or PR (whichever was first recorded) were first met until the first date that disease was recurrent or documented disease progression was observed, per RECIST 1.1, or the date of death from any cause in the absence of documented disease progression or recurrence.

Pharmacokinetics

In Study JV02, ramucirumab concentrations were collected following administration of ramucirumab 9 mg/kg on Day 1 and Day 8 of 21-day cycles. The aimed PK collection schedule was sparse: at peak (within 0.5 h after end of infusion) following Cycle 1 Day 1 dose and at pre-dose prior to:

- Cycle 1 Day 8
- Cycle 2 Day 1
- Cycle 5 Day 1
- Cycle 9 Day 1, and
- Cycle 13 Day 1 dose administration.

Based on the mean duration of exposure of about 12 weeks (4 cycles) observed in the study, no pre-dose concentrations were collected after Cycle 5 Day 1 (i.e., no concentration data on Cycle 9 Day 1 and Cycle 13 Day 1).

Results

Results for efficacy have been presented by interim futility cut-off date (03 January 2022) and by final data cut-off date (03 February 2023) to ascertain any changes that occurred.

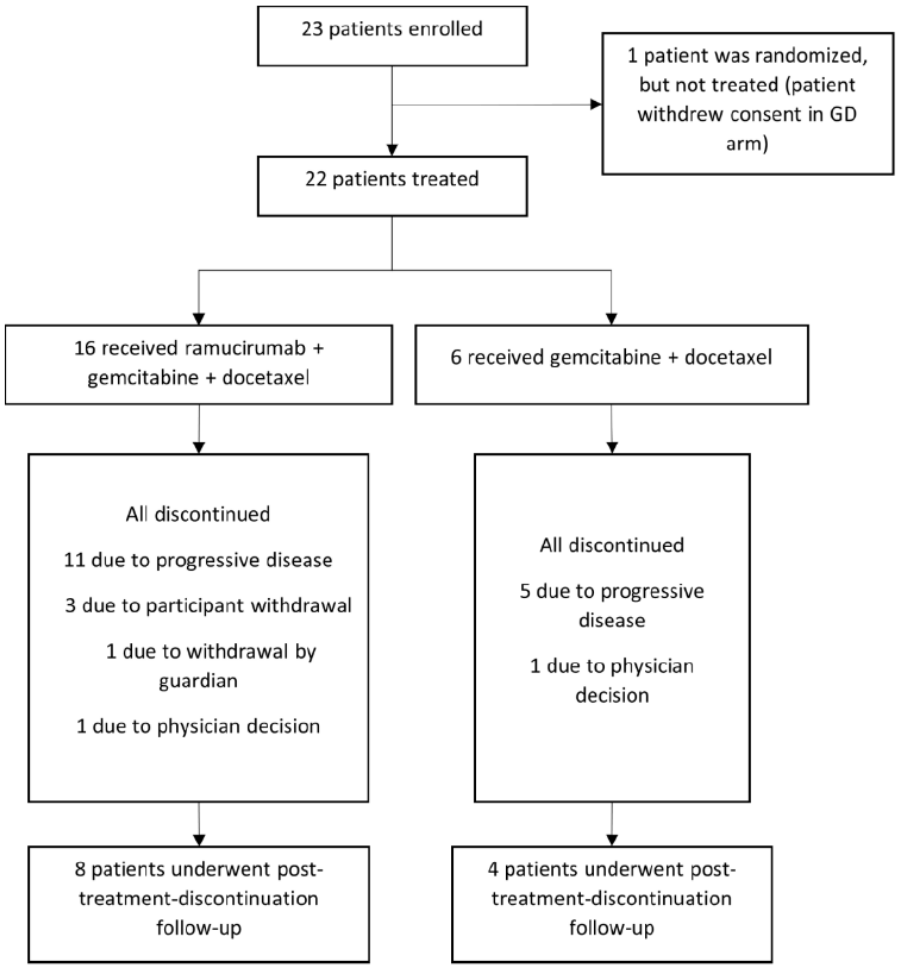
Results for baseline characteristics, concomitant therapy, patient disposition, safety, dose exposure, PK, and immunogenicity have been presented by final data cut-off date (03 February 2023).

Participant flow

At the data cut-off date for the interim futility analysis (03 January 2022), a total of 23 patients were randomly assigned to JV02, of which 22 patients were treated and 5 patients were active in the RAM + GD treatment arm. An IDMC meeting was held on 21 February 2022, resulting in the recommendation to suspend further enrolment in the study pending FDA concurrence of futility. Two out of the 5 patients discontinued the study treatment due to disease progression following the 03 January 2022

data cut-off but prior to the IDMC meeting. The remaining 3 patients discontinued the study treatment without disease progression after the IDMC meeting. With no patients remaining on the study, JV02 was terminated on 15 March 2023, with final data cut-off date of 03 February 2023.

Figure 3 Study participant disposition figure.



Abbreviation: GD = gemcitabine + docetaxel.
Source: lillyce/prd/ly900023/j1s_mc_jv02/csr1/output/shared/smds01_taffy.rtf

Recruitment

The first patient visit was 04 March 2020, the interim futility analysis report date was 03 January 2022 (date of interim data cut-off) and the final analysis date was 03 February 2023 (date of final data cut-off).

Baseline data

Most of the patients were White (78.3%) and male (56.5%). The median age of the patients was 18 years (range 11 to 29 years), with 8 (34.8%) patients being 17 years or younger. The median body weight of the patients was 65.2 kg (40 kg to 110 kg). More males were enrolled in the ramucirumab + gemcitabine + docetaxel (RAM + GD) arm compared with the gemcitabine + docetaxel (GD) arm (10 [62.5%] vs 3 [42.9%]), and there were no patients below the age of 17 years in the GD treatment

arm compared with 8 (50%) patients in the RAM + GD treatment arm. Otherwise, the demographic and baseline clinical characteristics were well balanced across treatment arms (Table 4 and Table 5).

Table 4 Summary of patient demographics and baseline characteristics – ITT population

	RAM + GD (N = 16)	GD (N = 7)	Total (N = 23)
Demographic Parameter	**n (%)**	**n (%)**	**n (%)**
Sex, n (%)			
Male	10 (62.5)	3 (42.9)	13 (56.5)
Female	6 (37.5)	4 (57.1)	10 (43.5)
Race, n (%)			
American Indian or Alaska Native	0	0	0
Asian	2 (12.5)	2 (28.6)	4 (17.4)
Black or African American	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
White	13 (81.3)	5 (71.4)	18 (78.3)
Multiple	1 (6.3)	0	1 (4.3)
Ethnicity, n (%)			
Hispanic or Latino	1 (6.3)	1 (14.3)	2 (8.7)
Not Hispanic or Latino	14 (87.5)	6 (85.7)	20 (87.0)
Not reported	1 (6.3)	0	1 (4.3)
Age group, n (%)			
≤17 years	8 (50.0)	0	8 (34.8)
>17 years	8 (50.0)	7 (100.0)	15 (65.2)
Weight (kg)			
N[a]	16	6	22
Median	61.6	78.1	65.2
Min-max	40-110	67-104	40-110
Missing	0	1	1
Lansky PS			
N	3	0	3
Median	100	NA	100
Min-max	100-100	NA	100-100
Missing[b]	13	7	20
Karnofsky PS			
N	3	0	3
Median	100	NA	100
Min-Max	90-100	NA	90-100
Missing	13	7	20
ECOG PS			
0	7 (43.8)	5 (71.4)	12 (52.2)
1	2 (12.5)	1 (14.3)	3 (13.0)
2	0	0	0
Missing	7 (43.8)	1 (14.3)	8 (34.8)

Abbreviations: ECOG = Eastern Cooperative Oncology Group; ITT = intention to treat; max = maximum; min = minimum; n = number of subjects in the specified category; N = number of subjects in intent-to-treat population within the treatment group; NA = not applicable; PS = performance status.

RAM + GD = ramucirumab + gemcitabine + docetaxel; GD = gemcitabine + docetaxel.

[a] The weight was not captured for the patient who was randomly assigned but not treated.

[b] One patient from each arm did not have baseline PS while the other patients underwent an alternative PS assessment.

Source: /lillyce/prd/ly900023/j1s_mc_jv02/csr1/output/shared/smdm01.rtf

Table 5 Summary of baseline characteristics – ITT population

	RAM + GD (N = 16)	GD (N = 7)	Total (N = 23)
Duration of Disease (months)[a]			
N	15	5	20
Median (Q1, Q3)	19 (16, 59)	14 (9, 17)	19 (14, 38)
Min-max	8-107	9-32	8-107
Missing	1	2	3
Metastatic Disease at Relapse, n (%)			
No	1 (6.3)	1 (14.3)	2 (8.7)
Yes	9 (56.3)	6 (85.7)	15 (65.2)
Missing	[b]6 (37.5)	0	6 (26.1)
Lines of Therapy, n (%)			
1	11 (68.8)	3 (42.9)	14 (60.9)
≥2	5 (31.3)	4 (57.1)	9 (39.1)
Time-to-Relapse Group, n (%)			
<2 years	11 (68.8)	6 (85.7)	17 (73.9)
≥2 years	1 (6.3)	0	1 (4.3)
Missing	4 (25.0)	1 (14.3)	5 (21.7)
Tumor Size Group at Initial Diagnosis, n (%)			
<5 cm	5 (31.3)	1 (14.3)	6 (26.1)
≥5 cm	5 (31.3)	5 (71.4)	10 (43.5)
Missing	6 (37.5)	1 (14.3)	7 (30.4)

Abbreviations: CRF = case report form; ITT = intention to treat; IWRS = integrated web response system; max = maximum; min = minimum; n = number of subjects in the specified category; N = number of subjects in the intent-to-treat population within the treatment group; Q = quartile.
RAM + GD = ramucirumab + gemcitabine + docetaxel; GD = gemcitabine + docetaxel.
[a] Duration of disease is the time from date of initial diagnosis to the date of start of study treatment.
[b] Of 6 patients in the RAM + GD treatment arm with missing CRF data for metastatic disease at study entry, 5 had metastatic disease and 1 had locally advanced disease per IWRS (lstcsf01.rtf).
Source: /lillyce/prd/ly900023/j1s_mc_jv02/csr1/output/shared/smptdc01.rtf

Prior cancer therapy

All patients had prior surgery and systemic therapy. Patients in the RAM + GD treatment arm received a median of 2 prior lines of anticancer therapy (range: 1-4) compared with a median of 1 prior line in the GD treatment arm (range: 1-2). The most frequently reported prior therapy was ifosfamide (60.9% overall).

Number analysed

The numbers analysed are presented in Table 6.

Table 6 Analysis populations

Population/Dataset	Description	Number
Intention-to-treat (ITT) population	All randomized patients, regardless of the assigned dose.	23
Safety analysis set	All randomized patients who received any quantity of the study treatment, regardless of their eligibility for the study.	22
Pharmacokinetic analysis set	All randomly assigned patients who received at least 1 full dose of the study treatment and have baseline and at least 1 postbaseline evaluable PK sample.	14
Historical control set	All lines of therapy from historical control patients that are eligible for matching.	22

Abbreviation: PK = pharmacokinetic.

Pharmacokinetic results

Per Table 4 the majority of patients enrolled in Study JV02 were adolescents and young adults (age above 17 years) with minimum age being 11 years. The body weight ranged from 40 kg to 110 kg. Ramucirumab concentrations were collected following administration of 9 mg/kg ramucirumab on Day 1 and Day 8 of a 21-day cycle.

Based on the mean duration of exposure of about 12 weeks (4 cycles) observed in that study, no predose concentrations were collected after Cycle 5 Day 1 (i.e., no concentration data on Cycle 9 Day 1 and Cycle 13 Day 1).

Error! Reference source not found. presents a summary of ramucirumab concentration peak (C_{max}) and trough (C_{min}) concentrations for the PK analysis population consisting of 14 (pediatric and young adult) patients (see Table 6).

Table 7 Ramucirumab concentrations in patients following ramucirumab 9 mg/kg on day 1 an day 8 of a 21-day cycle

	Ramucirumab Serum Concentrations (µg/mL)			
Study	JV02	JV02	JV02	JV02
Cycle	Cycle 1	Cycle 1	Cycle 2	Cycle 5[a]
Study day	Day 1	Day 8	Day 22	Day 85
Day in cycle	Day 1	Day 8	Day 1	Day 1
	C_{max}	C_{min} Trough/predose	C_{min} Trough/predose	C_{min} Trough/predose
n_{PK}	10	9	10	2
Geo mean	231	73.3	55.4	32.4; 41.3
Geo CV%	43	39	24	

Abbreviations: Cmax = maximum peak concentration (within 0.5-hour postdose); Cmin = minimum predose concentration; CV% = percent coefficient of variation; Geo = geometric; n_{PK} = number of subjects used in pharmacokinetic analysis.

[a] Cycle 5 was delayed for approximately 12 days in 2 patients. Hence, the C_{min} predose in Cycle 5 is lower than in Cycle 2. Data of only 2 patients is given from Cycle 5.

The mean peak concentration of 231 µg/mL following 9 mg/kg (JV02) compares well with the reported mean peak concentrations, 165 µg/mL and 285 µg/mL, following 8 mg/kg and 12 mg/kg, respectively, reported in Study JVDA (after accounting for dose difference, given the dose-proportional PK property of ramucirumab at a dose of 8 mg/kg and above).

Efficacy results

Primary endpoint PFS

At the data cut-off date (03 January 2022) for the interim analysis (which was planned at 24 events across JV02 and JV01 and performed on a joint model for JV02 and JV01 simultaneously), a total of 14 PFS events were observed in JV02, including 9 patients (56.3%) in the RAM + GD treatment arm and 5 patients (71.4%) in the GD treatment arm. The additional 10 PFS events required for a total of 24

events needed for the interim analysis were from JV01. PFS data were censored for 7 patients (43.8%) in the RAM + GD treatment arm and 2 patients (28.6%) in the GD treatment arm. The median PFS (estimated via the method of Kaplan and Meier) was 2.07 in the RAM + GD treatment arm and 2.03 in the GD treatment arm (HR 0.71 [80% CI: 0.34, 1.49; p = .544]).

As per the interim analysis of PFS in JV02, the pre-specified joint Bayesian model for JV02 and JV01 simultaneously yielded an estimated probability PFS HR of less than 1 of 20.1% for JV02. The result met the pre-specified criterion for futility, which required that the probability of PFS HR of less than 1 exceed 60% for JV02 to continue enrolment (otherwise enrolment was to be stopped).

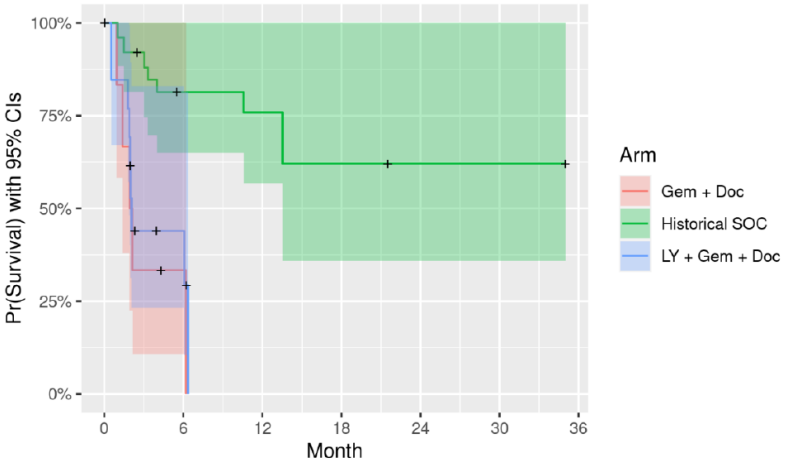
Importantly, pre-specified sensitivity analyses of PFS yielded highly varied estimates of the PFS HR and the probability of PFS HR of less than 1 due to influence from the matched historical controls, which substantially outperformed PFS from the prospectively randomized control patients. However, none of the sensitivity analyses indicated emergence of a clinically meaningful magnitude of effect on PFS (that is, minimally, a desired 3-month increase in median PFS), thus supporting the determination of futility for the study (Table 8 and Figure 4).

Table 8 Summary of PFS results at the time of the futility analysis

Analysis	**Median (months) 98% CrI[a]**	**Median (months) 98% CrI**	**HR (80% CrI)[b] Pr (HR <1) (%)**
	RAM + GD	**GD**	
Primary Bayesian Analysis	3.67 (1.48, 11.53)	6.00 (2.06, 17.98)	1.79 (0.8, 3.07) 20.1
Frequentist Analysis	2.07 (1.90, 6.07)	2.03 (1.38, NR)	0.71 (0.34, 1.49) p-value = .544
Sensitivity 1	3.28 (1.38, 8.98)	6.96 (2.51, 20.83)	2.28 (1.06, 3.83) 8.1
Sensitivity 2	3.45 (1.88, 6.75)	2.49 (1.14, 5.44)	0.72 (0.35, 1.19) 82.7
Sensitivity 3	3.20 (1.74, 6.08)	2.82 (1.28, 6.66)	0.96 (0.45, 1.61) 63.6
Sensitivity 4[c]	3.66 (1.62, 10.00)	5.80 (2.54, 12.79)	1.77 (0.84, 2.94) 17.7
Sensitivity 5	3.66 (1.89, 7.66)	4.44 (2.91, 6.49)	1.37 (0.76, 2.11) 28.2

Abbreviation: CrI = credible interval; HR = hazard ratio; NR = not reached; PFS = progression-free survival; Pr =probability.
RAM + GD = ramucirumab + gemcitabine + docetaxel; GD = gemcitabine + docetaxel.
a Posterior median.
b Posterior mean displayed.
c Mahalanobis distance matching.

Figure 4 Kaplan-Meier survival estimate by arm with historical matched patients (weighted)



Abbreviations: CI = confidence interval; Pr = probability; Arm Gem + Doc and Matched Pts = GD treatment arm and matched patients; LY + Gem + Doc = ramucirumab + gemcitabine + docetaxel treatment arm; SOC = standard of care.

PFS at the time of final analysis (DCO 03 February 2023)

Of the 23 patients in the intent-to-treat population, 6 patients (26%) were censored in this study. These included 4 patients (3 in the RAM + GD treatment arm and 1 in the GD treatment arm) who had no documented progressive disease with regular assessment, 1 patient in the GD treatment arm who had no post-baseline tumour assessment, and 1 patient in the RAM + GD treatment arm who started new anti-cancer treatment.

A total of 17 PFS events were observed: 12 in the RAM + GD treatment arm and 5 in the GD treatment arm. The median PFS was 2.10 months in the RAM + GD treatment arm and 2.03 months in the GD treatment arm (HR 0.75 [80% CI: 0.37, 1.50]).

At the final analysis, the Bayesian model yielded an estimated posterior probability of an HR of less than 1 of 5.1%. This finding is consistent with the result obtained for the interim analysis, which was 20.1%. The corresponding estimated posterior mean PFS HR was 2.62 (80% credible interval 1.19, 4.46). The influence from the matched historical controls substantially still outperformed PFS from the prospectively randomized control patients at the final analysis. Thus, the same conclusion of futility is reached at the final analysis (Table 9).

Table 9 Summary of PFS results at the time of the final analysis

Analysis	Median (months) 98% CrI[a]	Median (months) 98% CrI	HR (80% CrI)[b] Pr (HR <1) (%)
	RAM + GD	GD	
Primary Bayesian Analysis	3.6 (1.58, 9.34)	9.0 (3.17, 26.42)	2.62 (1.19, 4.46) 5.1
Frequentist Analysis	2.1 (2.00, 6.00)	2.0 (1.38, NR)	0.75 (0.37, 1.50) p-value* = .583
Sensitivity 1	3.4 (1.53, 7.91)	10.2 (3.79, 29.27)	3.15 (1.50, 5.23) 1.6
Sensitivity 2	3.6 (2.13, 6.08)	2.6 (1.23, 5.34)	0.69 (0.35, 1.12) 85.4
Sensitivity 3	3.4 (2.00, 5.68)	2.9 (1.37, 6.52)	0.91 (0.44, 1.50) 68.2
Sensitivity 4[c]	3.6 (1.79, 8.01)	6.1 (2.77, 13.06)	1.91 (0.97, 3.09) 11.4
Sensitivity 5	3.7 (2.10, 6.78)	4.5 (2.98, 6.57)	1.37 (0.81, 2.05) 24.3

Abbreviation: CrI = credible interval; HR = hazard ratio; PFS = progression-free survival; Pr = probability, NR = not reached.
RAM + GD = ramucirumab + gemcitabine + docetaxel; GD = gemcitabine + docetaxel.
a Posterior median.
b Posterior mean displayed.
c Mahalanobis distance matching.
* p-value reported for frequentist analysis.

Secondary endpoints

All secondary analyses are presented using the final data cut-off date of 03 February 2023.

- Tumour response was not evaluable for 1 patient (14.3%) in the GD treatment arm.
- Complete response was not recorded in any of the patients in either arm.
- Partial response was recorded in 1 patient (6.3%) in the RAM + GD treatment arm and in 0 patients in the GD treatment arm.
- Stable disease was observed as the best response in both arms, with 7 patients (43.8%) in the RAM + GD treatment arm and 2 patients (28.6%) in the GD treatment arm.
- The disease control rate in the RAM + GD treatment arm versus GD treatment arm was 50.1% versus 28.6%.
- One (6.3%) patient qualified for duration of response in the RAM + GD treatment arm with duration of response of 4.1 months.

Safety results

A total of 16 patients were treated with RAM + GD treatment arm and the remaining 6 patients were randomly assigned to the GD treatment arm. The data cutoff date for safety analysis was 03 February 2023. Median study drug exposure was 11.2 weeks (range: 1-25) and 7.7 weeks (range: 1-25) in the RAM+GD and GD arm, respectively.

Adverse events

An overview of AEs is shown in Table 10.

Table 10 Overview of adverse events – Safety population

Number of Subjects[a]	RAM + GD (N = 16) n (%)	GD (N = 6) n (%)	Total (N = 22) n (%)
Subjects with ≥1 TEAE	15 (93.8)	6 (100.0)	21 (95.5)
Related to study treatment[b]	15 (93.8)	6 (100.0)	21 (95.5)
Subjects with ≥1 CTCAE Grade ≥3 TEAE	14 (87.5)	3 (50.0)	17 (77.3)
Related to study treatment[b]	14 (87.5)	2 (33.3)	16 (72.7)
Subjects with ≥1 SAE	8 (50.0)	2 (33.3)	10 (45.5)
Related to study treatment[b]	6 (37.5)	1 (16.7)	7 (31.8)
Subjects who discontinued study treatment due to an AE	0	0	0
Related to study treatment[b]	0	0	0
Subjects who discontinued study treatment due to an SAE	0	0	0
Related to study treatment[b]	0	0	0
Subjects who died due to an AE within 30 days of discontinuation from the study treatment[c]	0	0	0
Related to study treatment[b]	0	0	0

Abbreviations: AE = adverse event; CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in the specified category; N = number of subjects in the safety population; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
RAM + GD = ramucirumab + gemcitabine + docetaxel; GD = gemcitabine + docetaxel.
[a] Subjects may be counted in more than 1 category.
[b] Includes events that were considered related to the study treatment as judged by the investigator.
[c] Deaths are also included as SAEs and discontinuations due to AEs.
MedDRA Version 25.1
Source: /lillyce/prd/ly900023/j1s_mc_jv02/csr1/output/shared/smaeo01_taffy.rtf

The most commonly reported TEAEs (at least 5 patients in any treatment arm) by decreasing frequency are shown in Table 11. Haematological AEs (neutropenia, anaemia, and thrombocytopenia) were the most commonly reported events in the RAM + GD arm and occurred more frequently compared to GD only. Neutropenia was also the most frequently reported grade ≥3 TEAE. Further, increases in ALAT and ASAT were frequently reported and more commonly compared to the comparator arm.

Table 11 Summary of TEAEs occurring in ≥5 patients – Safety population

	RAM + GD (N = 16)				GD (N = 6)			
	Any Grade		Grade 3/4/5		Any Grade		Grade 3/4/5	
MedDRA Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)
Subjects with ≥1 TEAE	15	(93.8)	14	(87.5)	6	(100.0)	3	(50.0)
Neutropenia[a]	9	(56.3)	8	(50.0)	1	(16.7)	1	(16.7)
Alanine aminotransferase increased	7	(43.8)	3	(18.8)	2	(33.3)	0	(0.0)
Anemia[a]	7	(43.8)	3	(18.8)	2	(33.3)	0	(0.0)
Thrombocytopenia[a]	7	(43.8)	1	(6.3)	1	(16.7)	1	(16.7)
Pyrexia	7	(43.8)	1	(6.3)	1	(16.7)	0	(0.0)
Vomiting	7	(43.8)	1	(6.3)	1	(16.7)	0	(0.0)
Aspartate aminotransferase increased	6	(37.5)	1	(6.3)	1	(16.7)	0	(0.0)
Pain in extremity	6	(37.5)	1	(6.3)	0	(0.0)	0	(0.0)
Constipation	6	(37.5)	0	(0.0)	1	(16.7)	0	(0.0)
Epistaxis	6	(37.5)	0	(0.0)	1	(16.7)	0	(0.0)
Stomatitis	5	(31.3)	0	(0.0)	2	(33.3)	0	(0.0)
Leukopenia[a]	5	(31.3)	4	(25.0)	1	(16.7)	1	(16.7)
Nausea	5	(31.3)	0	(0.0)	1	(16.7)	0	(0.0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in the specified category; N = number of subjects in the safety population; TEAE = treatment-emergent adverse event.
RAM + GD = ramucirumab + gemcitabine + docetaxel; GD = gemcitabine + docetaxel.
[a] Consolidated term.
MedDRA Version 25.1
Source: /lillyce/prd/ly900023/j1s_mc_jv02/csr1/output/shared/smaecon01_taffy.rtf

Most TEAEs were also considered treatment-related TEAEs (Table 12).

Table 12 Summary of related TEAEs consolidated preferred term within system organ class – Safety population

System Organ Class Preferred Term	RAM+GD (N=16) n	(%)	GD (N=6) n	(%)
Subjects >=1 TEAE	15	(93.8)	6	(100.0)
General disorders and administration site conditions	10	(62.5)	5	(83.3)
Fatigue#	5	(31.3)	4	(66.7)
Pyrexia	4	(25.0)	0	
Oedema peripheral	2	(12.5)	0	
Mucosal inflammation	1	(6.3)	0	
Pain	0		1	(16.7)
Investigations	10	(62.5)	3	(50.0)
Alanine aminotransferase increased	5	(31.3)	2	(33.3)
Thrombocytopenia#	6	(37.5)	1	(16.7)
Aspartate aminotransferase increased	5	(31.3)	1	(16.7)
Leukopenia#	4	(25.0)	1	(16.7)
Neutropenia#	4	(25.0)	0	
Lymphocyte count decreased	2	(12.5)	0	
Alanine aminotransferase	1	(6.3)	0	
Blood alkaline phosphatase increased	0		1	(16.7)
Blood and lymphatic system disorders	8	(50.0)	3	(50.0)
Anemia#	5	(31.3)	2	(33.3)
Neutropenia#	5	(31.3)	1	(16.7)
Febrile neutropenia	0		1	(16.7)
Leukopenia#	1	(6.3)	0	
Thrombocytopenia#	1	(6.3)	0	
Gastrointestinal disorders	9	(56.3)	2	(33.3)
Stomatitis	5	(31.3)	2	(33.3)
Nausea	5	(31.3)	1	(16.7)
Vomiting	5	(31.3)	1	(16.7)
Diarrhoea	2	(12.5)	2	(33.3)
Constipation	2	(12.5)	0	
Aphthous ulcer	1	(6.3)	0	
Mallory-Weiss syndrome	1	(6.3)	0	
Odynophagia	1	(6.3)	0	

Abbreviations: N = number of subjects in the analysis population; n = number of subjects with events meeting specified criteria.
- consolidated term
Ram+GD = ramucirumab-9 mg/kg_D1_D8+Gemcitabine-900 mg/m D1_D8+Docetaxel-75 mg/m D8
GD= Gemcitabine-900 mg/m D1_D8+Docetaxel-75 mg/m D8
MedDRA Version 25.1

Deaths and SAEs

Overall, 12 (54.5%) deaths occurred, 8 (50.0%) in the RAM + GD treatment arm, and 4 (66.7%) in the GD treatment arm. All deaths were related to the study disease and occurred during the long-term follow-up period post-study treatment discontinuation.

A total of 8 (50.0%) patients in the RAM + GD treatment arm and 2 (33.3%) patients in the GD treatment arm experienced any-grade SAEs (Table 13). Six patients experienced treatment-related TEAEs in the RAM + GD arm, being pyrexia (n=2), Mallory-Weiss syndrome, platelet count decreased, pneumothorax, sepsis, embolism, and laryngeal haemorrhage (n=1 each). One patient experienced treatment-related SAEs in the GD arm (febrile neutropenia and pneumonia).

Table 13 Summary of serious TEAEs by PT decreasing frequency – Safety population

	RAM + GD (N = 16)				GD (N = 6)			
	Any Grade		Grade 3/4/5		Any Grade		Grade 3/4/5	
MedDRA Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Subjects with ≥1 serious TEAE	8	(50.0)	7	(43.8)	2	(33.3)	1	(16.7)
Pyrexia	2	(12.5)	1	(6.3)	1	(16.7)	0	(0.0)
Pneumothorax	2	(12.5)	2	(12.5)	0	(0.0)	0	(0.0)
Anaphylactic reaction	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)
Febrile neutropenia	0	(0.0)	0	(0.0)	1	(16.7)	1	(16.7)
Mallory-Weiss syndrome	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)
Platelet count decreased	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)
Pneumonia	0	(0.0)	0	(0.0)	1	(16.7)	1	(16.7)
Sepsis	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)
Vomiting	1	(6.3)	1	(6.3)	0	(0.0)	0	(0.0)
Embolism	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)
Laryngeal hemorrhage	1	(6.3)	0	(0.0)	0	(0.0)	0	(0.0)
Pleural effusion	0	(0.0)	0	(0.0)	1	(16.7)	0	(0.0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in the specified category; N = number of subjects in the safety population; PT = preferred term; TEAE = treatment-emergent adverse event.
RAM + GD = ramucirumab + gemcitabine + docetaxel; GD = gemcitabine + docetaxel.
MedDRA Version 25.1; CTCAE Version 4.0.
Source: /lillyce/prd/ly900023/j1s_mc_jv02/csr1/output/shared/smaept02.rtf

Adverse events of special interest (AESI)

A summary of ASEIs is shown in Table 14.

The most frequently reported adverse events of special interests (AESIs) for ramucirumab were

- liver failure/liver injury; most frequently PTs were ALT increased (7 patients, 43.8%) and AST increased (6 patients, 37.5%)
- bleeding/haemorrhage events (8 patients, 50.0%); the most frequent PT was epistaxis (6 patients, 37.5%)
- infusion-related reactions (4 patients, 25.0%), and
- proteinuria (4 patients, 25.0%)

ALT increased was the most frequently reported grade ≥3 AESI (n=3, 18.8%). No dose modifications were required for patients reporting AST increased, whereas 1 patient required a dose omission of docetaxel and dose delays of RAM + gemcitabine for ALT increase. One patient had a RAM dose omission for wound dehiscens and one patient experienced a dose delay of RAM + gemcitabine for proteinuria.

Table 14 Summary of TEAEs of special interest – Safety population

	RAM + GD (N = 16)				GD (N = 6)			
	Any Grade		Grade 3/4/5		Any Grade		Grade 3/4/5	
MedDRA Preferred Term	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Subjects with ≥1 treatment-emergent AESI	11	(68.8)	5	(31.3)	2	(33.3)	0	0
Liver failure and other significant liver injury								
Alanine aminotransferase (ALT) increased	7	(43.8)	3	(18.8)	2	(33.3)	0	0
Aspartate aminotransferase (AST) increased	6	(37.5)	1	(6.3)	1	(16.7)	0	0
Bleeding/hemorrhage events	8	(50)	1	(6.3)	1	(16.7)	0	0
Epistaxis	6	(37.5)	0	0	1	(16.7)	0	0
Mallory-Weiss syndrome	1	(6.3)	1	(6.3)	0	0	0	0
Enterocolitis hemorrhagic	1	(6.3)	0	0	0	0	0	0
Hematuria	1	(6.3)	0	0	0	0	0	0
Laryngeal hemorrhage	1	(6.3)	0	0	0	0	0	0
Retinal hemorrhage	1	(6.3)	0	0	0	0	0	0
Surgery and impaired wound healing								
Wound dehiscence	1	(6.3)	0	0	0	0	0	0
Infusion-related reactions (IRR)	4	(25.0)	1	(6.3)	1	(16.7)	0	0
Rash	1	(6.3)	0	0	1	(16.7)	0	0
Anaphylactic reaction[a]	1	(6.3)	1	(6.3)	0	0	0	0
Dermatitis acneiform	1	(6.3)	0	0	0	0	0	0
Periorbital edema	1	(6.3)	0	0	0	0	0	0
Rash maculopapular	1	(6.3)	0	0	0	0	0	0
Proteinuria	4	(25.0)	0	0	0	0	0	0
Hypertension	1	(6.3)	0	0	0	0	0	0
Thromboembolic events	1	(6.3)	0	0	1	(16.7)	0	0
Embolism	1	(6.3)	0	0	0	0	0	0
Superficial vein thrombosis	0	0	0	0	1	(16.7)	0	0

Abbreviations: AESI = adverse event of special interest; MedDRA = Medical Dictionary for Regulatory Activities; n = number of subjects in the specified category; N = number of subjects in the safety population within the treatment group.

RAM + GD = ramucirumab + gemcitabine + docetaxel; GD = gemcitabine + docetaxel.

[a] One patient experienced Grade 4 anaphylactic reaction, which was not related to the study regimen.

MedDRA Version 25.1 CTCAE Version 4.0.

Source: /lillyce/prd/ly900023/j1s_mc_jv02/csr1/output/shared/smaesi01.rtf

Other significant adverse events – Growth plate abnormalities

Seven out of the 8 patients below 18 years of age in the RAM + GD treatment arm had baseline growth plate assessment via an anterior-posterior radiograph of the proximal tibia. Four (50.0%) patients had an open growth plate at baseline that required monitoring every 4 months while on treatment and at short-term follow-up. Only 1 patient (15-year old male) had ramucirumab exposure long enough to repeat protocol-specified on-treatment assessment of the growth plate during Cycle 7 where there was no recorded growth plate abnormality although the patient did not have any detriment to his height. The remaining 3 patients discontinued study treatment prior to the first on-treatment monitoring of the growth plate. No clinically relevant change was noted in the postbaseline height for all 4 patients with an open growth plate compared to their height at baseline. Given the short exposure to ramucirumab for majority of patients with an open growth plate, it was not possible to conclude its potential negative impact on growth plate that was seen in preclinical studies.

Immunogenicity

Of 22 patients treated in either the RAM + GD or the GD treatment arm of the study, 8 were evaluable for TE ADA, defined as patients with at least 1 non missing test result for ramucirumab ADA for both the baseline period and the postbaseline period. At baseline, among the 8 patients evaluable for TE ADA, 1 (12.5%) was ADA positive. Postbaseline, of the 7 TE ADA-evaluable patients enrolled in the RAM + GD treatment arm, 0 (0.0%) were TE ADA positive.

Dose modifications

A total of 2 (12.5%) patients in the RAM + GD treatment arm discontinued ramucirumab due to AEs. One (6.3%) patient discontinued ramucirumab due to Grade 1 back pain, and 1 patient discontinued due to Grade 4 sepsis. No patients experienced AEs that required a ramucirumab dose reduction. Dosing was delayed in 5 (31.3%) patients and omitted in 3 (18.8%) patients.

2.3.3. Discussion on clinical aspects

JV02 was a global, randomized (2:1), Phase 2 study with the purpose of examining PFS benefit of RAM + GD versus GD in patients with relapsed, recurrent, or rSS. Sixteen patients were treated with RAM + GD at a dose of 9 mg/kg IV on Day 1 and 8 Q3W. The median age of the patients was 18 years (range 11 to 29 years), with 8 (34.8%) patients being 17 years or younger which were all in the RAM + GD arm.

Pharmacokinetics

In a previous Study JVDA in paediatric patients (provided to EMA as part of procedure EMEA/H/C/002829/P46/008), more extensive ramucirumab pediatric PK data were collected following 8 mg/kg and 12-mg/kg dose Q2W. The conclusions of the PK findings in Study JVDA are given below.

- Ramucirumab C_{max} and AUC increased in a dose-proportional manner (1.5-fold) from 8 mg/kg to 12 mg/kg. T_{max}, the time taken to reach C_{max}, occurred as expected, approximately 1 hour after start of infusion.
- Ramucirumab clearance (range 2.5 mL/hr to 28 mL/hr) increased with body weight (range 8.7 kg to 91 kg) and decreased with time following multiple doses, as expected based on adult patient data.
- Ramucirumab volume of distribution was similar to the blood volume and the mean half-life was approximately 10 days, ranging from 5 to 21 days following multiple doses. Ramucirumab exposure in paediatric patients was similar to the ramucirumab exposure reached in adult patients at the corresponding doses of 8 mg/kg and 12 mg/kg.
- Ramucirumab exposure following 12-mg/kg dose was similar across the age range (at least 12 months to 21 years of age or below) of the paediatric patients enrolled at this dose. This supports that the weight-based dosing was appropriate.

Based on this information, the SmPC Section 5.2 was updated afterwards in a type II variation.

The limited ramucirumab PK data collected in the current study JV02 appear as expected based on the prior knowledge of ramucirumab PK in the adolescent population. The data are considered not to add new information as compared to the currently reported information for the adolescent population based on previous Study JVDA in section 5.2 of the SmPC. No further update of section 5.2 is therefore considered necessary.

Conduct of the study

The analysis plan was changed by communications with the FDA (before the interim analysis, but in the context of an open-label study). In particular, analyses without available historical control matches were added and matching also on the value 'missing' for all matching factors allowed. While the latter is questionable, matching without the value of missing was also preplanned.

Methods

PFS was not defined according to the EMA Guideline (EMA/CHMP/27994/2008/Rev.1), e.g. censoring for anti-cancer therapy and missed visits. Credibility and confidence intervals were smaller than usual by using a 80% instead of 95%, which may be acceptable in a phase 2 study. Also, the amount of independent new data (for SS) was more limited than usual by augmenting external information as follows. Firstly, external information from the efficacy (i.e. hazard ratio) of ramucirumab in another patient population (DSRCT) was used under the assumption that the HR in SS and HR in DSRCT were similar. Furthermore, in both patient samples (SS and DSRCT) external information for the control arm was used (by matching historical controls to the randomised ramucirumab patients). The success criterion was to have a model-based Bayesian probability to be sufficiently high (at least 60% for proceeding beyond the futility analysis and at least 99% for the final analysis to claim success). In the context of a phase 2 study this may be acceptable, as the analysis based on only the new independent data was provided as well. Moreover, the impact of each aspect of augmenting the independent new data was investigated.

Efficacy

At the interim futility analysis, JV02 did not meet the proceed-criterion that Bayesian model-based probability that the HR < 1 for SS, was more than 60%. This led to suspension of enrolment per IDMC recommendation. As the study failed (for futility), no formal evaluation of the primary PFS endpoint was performed. In the post-hoc, final analysis, the Bayesian model-probability of PFS HR of less than 1 (PrHR <1) was 5.1%, consistent with the results from the prespecified interim futility analysis of PFS (PrHR <1) that was 20.1%. The prespecified sensitivity analyses also supported the determination of futility for JV02.

Stable disease was the best response observed. There was only one partial response and no complete responses in the experimental arm. These results support the decision to stop the study for futility.

Paediatric patients were only included in the experimental arm and therefore no controlled data are available. In addition, results were not presented separately for the patients below 18 years of age. However, given the obtained results this is not further pursued.

The obtained results support the concerns raised previously by the PDCO on the possible benefit of developing ramucirumab for the treatment of paediatric patients with soft tissue sarcoma as there was not a clear evidence for proof of concept to study a VEGF inhibitor in the paediatric population and no clinical benefit was found in soft tissue sarcoma with another VEGFR inhibitor.

Safety

Acknowledging the limited sample size, the safety profile of RAM + GD was largely consistent with the established safety profiles of the individual treatment components and the disease setting of rSS. Haematological AEs (neutropenia, anaemia, and thrombocytopenia) were the most commonly reported events in the RAM + GD arm and occurred more frequently compared to GD only. Further, increases in ALAT and ASAT were frequently reported and more commonly compared to the comparator arm. Epistaxis, infusion-related reactions and proteinuria were also reported (ASEIs).

No new safety signals or safety-related deaths were reported. The overall safety assessment did not reveal any new or unexpected safety findings. The study did not provide new data on growth plate abnormalities, due to the limited sample size and treatment duration. Safety data were not presented separately for the paediatric population, however given the limited data (8 patients in the experimental arm only), and the lack of efficacy this is not further pursued.

3. CHMP's overall conclusion and recommendation

The MAH submitted a completed paediatric study for ramucirumab in accordance with Article 46 of Regulation (EC) No1901/2006. Study JV02 was a randomized (2:1), multicentre, global, Phase 2 study in paediatric patients and young adults aged 36 months to 29 years of age or below with relapsed, recurrent, or progressive SS evaluating the efficacy of ramucirumab (9 mg/kg IV on Days 1 and 8 every 3 weeks) in combination with gemcitabine (900 mg/m2 IV on Days 1 and 8 of a 3-week cycle) and docetaxel (75 mg/m2 IV on Day 8 of a 3-week cycle). The primary objective (PFS) in JV02 was planned using a Bayesian analysis incorporating information regarding historical control outcomes to augment the control arm of JV02 as well as effect-size observed on JV01 that would provide a posterior probability of treatment superiority. JV01 is an ongoing randomized, multicentre, global, Phase 2 study in paediatric patients and young adults with relapsed, recurrent, or progressive desmoplastic small round cell tumour (DSRCT) evaluating the efficacy of ramucirumab in combination with chemotherapy versus chemotherapy alone. Both JV01 and JV02 were performed under the construct of the ongoing CAMPFIRE Master Protocol JAAA.

It should be noted that JV02 was not a part of an agreed paediatric investigation plan. The initially proposed PIP for soft tissue sarcoma was not approved by the PDCO as they raised several concerns on the possible benefit of ramucirumab in the proposed indication. Subsequently, the PIP application was withdrawn by the Applicant.

At the interim futility analysis, JV02 did not meet the 60% confidence in treatment superiority (PFS HR of less than 1 for SS) leading to IDMC's recommendation to suspend enrolment. The study was terminated on 15 March 2023 without formal evaluation of the primary PFS endpoint. The overall safety assessment in a limited number of patients did not reveal any new or unexpected safety findings.

The Applicant proposes no changes to the ramucirumab SmPC based on the efficacy and safety data, however, potentially relevant paediatric information should be reported in the SmPC and therefore the Applicant should report the available efficacy/safety data in children as indicated below. This is also in line with the previous decision to include data from study JVDA (EMA/H/C/002829/P46).

☒ Fulfilled:

In view of the available data regarding the efficacy and safety of ramucirumab in paediatric patients from study JV02, the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so.

This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.

- The Applicant should briefly describe the efficacy results of study JV02 in section 5.1 under "*Paediatric population".* This should include a short description of the objectives and the design of the study, as well as observed anti-tumour activity.
- In section 4.8 it should be stated that no new safety concerns were reported in the limited number of patients treated in the paediatric study with ramucirumab combination therapy.