15 September 2016
EMA/CHMP/742133/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Lartruvo

International non-proprietary name: olaratumab

Procedure No. EMEA/H/C/004216/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

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List of abbreviations

ADA	Anti-drug Antibody
AE	adverse event
AESI	Adverse event of special interest
ALT	Alanine Aminotransferase
AUC	Area Under The Curve
BCS	Biopharmaceutics Classification System
Cavg	Average concentrations throughout patients treatment
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
Cmax	Peak plasma concentration
Cmin	Minimum concentration
Cmin1	Trough concentrations after the first treatment cycle
CR	Complete response
CRF	Case report form
DLT	Dose limiting toxicity
EC	European commission
EC50	half-maximal effective concentration
ECG	Electrocardiogram
ECL	electrochemiluminescence
ECLU	electrochemiluminescent unit
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EFD	Embryo-Fetal Development
ELISA	Enzyme-Linked Immunosorbent Assay
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	United States Food and Drug Administration
GIST	Gastrointestinal stromal tumour
GLP	Good Laboratory Practices
GLSM	Geometric least-squares mean

HR	Hazard Ratio
i.v.	intra-venous
ICH	International Conference on Harmonization
ICH	Intracranial haemorrhage
Ig	Immunoglobulin
IPF	Idiopathic pulmonary fibrosis
IRR	Infusion related reaction
ITT	intention-to-treat
IV	intravenous
LMS	leiomiosarcoma
LSN338786	IMC-1E10 murine surrogate antibody
LY3012207	IMC-3G3 olaratumab
MA	Marketing Authorization
MAA	marketing authorisation application
MAPK	Mitogen-activated protein kinases
MCC	Matched-Case Control Analyses
MedDRA	Medical Dictionary for Regulatory Activities
MOF	minimum objective function
mRNA	Messenger RNA
MTD	maximum tolerated dose
NAS	new active substance
NCA	Non compartmental analysis
NOAEL	no-observed-adverse-effect level
NOEL	no-observed-effect level
NSCLC	Non-Small Cell Lung Cancer
ORR	objective response rate
OS	overall survival
PAE	Porcine Aortic Endothelial
PD	Progressive disease
PDCO	Paediatric Committee
PDGFR	Platelet derived growth factor receptor

PDGFRα	platelet-derived growth factor receptor alpha
PDX	Patient-Derived Xenografts
PFS	progression free survival
PI	Patient information
PK/PD	Pharmacokinetic/Pharmacodynamic
PopPK	population pharmacokinetics
PR	Partial response
PT	preferred term
RMP	Risk management plan
RT-qPCR	Quantitative real-time PCR
SAE	serious adverse event
SAP	Statistical analysis plan
SCM	step-wise covariate modelling
SD	Stable disease
SDS-PAGE	Sodium Dodecyl Sulphate - PolyAcrylamide Gel Electrophoresis
SmPC	Summary of Product Characteristics
SOC	System Organ Class
SPR	Surface Plasmon Resonance
STS	soft tissue sarcoma
TCGA	The Cancer Genome Atlas
TE-ADA	Treatment-emergent Anti-drug antibodies
TEAE	Treatment emergent adverse event
TE-SAE	Treatment emergent Serious adverse event
TK	Toxicokinetics
Tmax	Time to peak plasma concentration
US	United States
Vdss	Volume Of Distribution At Steady State
VPC	visual predictive check
WTE	body weight at the time of study entry

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Eli Lilly Nederland B.V. submitted on 29 January 2016 an application for marketing authorisation to the European Medicines Agency (EMA) for Lartruvo, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 23 April 2015.

Lartruvo was designated as an orphan medicinal product EU/3/15/1447 on 12 February 2015. Lartruvo was designated as an orphan medicinal product in the following indication: Treatment of soft tissue sarcoma.

The applicant applied for the following indication "Lartruvo is indicated in combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin".

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that Olaratumab was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Lartruvo as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0290/2015 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0290/2015 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No

847/2000, the applicant submitted a critical report addressing the possible similarity with authorised orphan medicinal products.

Applicant's request(s) for consideration

Conditional marketing authorisation

The applicant requested consideration of its application for a Conditional marketing authorisation in accordance with Article 14(7) of the above mentioned Regulation.

Accelerated assessment

The applicant requested accelerated assessment in accordance to Article 14 (9) of Regulation (EC) No 726/2004.

New active Substance status

The applicant requested the active substance Olaratumab contained in the above medicinal product to be considered as a new active substance in comparison to Trabectedin previously authorised in the European Union as Yondelis, as the applicant claimed that Olaratumab differs significantly in properties with regard to safety and/or efficacy from the already authorised active substance.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 26 March 2015. The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Aranzazu Sancho-Lopez Co-Rapporteur: Daniela Melchiorri

- The application was received by the EMA on 29 January 2016.
- Accelerated Assessment procedure was agreed-upon by CHMP on 28 January 2016.
- The procedure started on 25 February 2016.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 24 May 2016. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 May 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 26 May 2016. In accordance with Article 6(3) of Regulation (EC) No 726/2004, the Rapporteur and Co-Rapporteur declared that they had completed their assessment report in less than 80 days.
- During the meeting on 9 June 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP. The PRAC Assessment Overview and Advice was sent to the applicant on 9 June 2016.
- During the meeting on 23 June 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 23 June 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 August 2016.

- The following GCP inspection(s) were requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - GCP inspections at two investigator sites and at the sponsor site in the USA performed on the following dates 18-24 April 2016, 9-13 May 2016 and 17-20 May 2016. The outcome of the inspection carried out was issued on 13 June 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 September 2016.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 9 September 2016.
- During the meeting on 12-15 September, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a conditional marketing authorisation to Lartruvo on 15 September 2016.
- The CHMP adopted a report on similarity of Lartruvo with Yondelis on 23 June 2016.

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Soft tissue sarcoma (STS) is a rare group of heterogeneous mesenchymal tumours. There are more than 50 histological subtypes of STS, associated with distinct clinical profiles, response to individual therapy and prognosis.

2.1.2. Epidemiology

STS accounts for less than 1.0% of all adult malignant cancer. Average incidence in the European Union (EU) is approximately 4.7 per 100,000 (Stiller et al. 2013). Around 23.000 new cases are expected per year in the European Union (Gatta, et al. 2011). STS has a high mortality rate and accounts approximately for 2% of total cancer-related mortality (Burningham et al. 2012, Sharma et al. 2013).

STS affect patients much younger than common carcinomas do, even teenagers and children.

2.1.3. Aetiology and pathogenesis

Although STS clinical variety probably reflects a similar richness in molecular alterations, platelet-derived growth factor alpha (PDGFRα) has been implicated in the pathogenesis of many subtypes. Mesenchymal cells are PDGFR-positive and an autocrine loop is hypothesized to occur between sarcoma cells and themselves or stroma cells (Miettinen, 2006).

2.1.4. Clinical presentation, diagnosis and stage / prognosis

Soft tissue sarcomas (STSs) are ubiquitous in their site of origin and are often managed with multimodality treatment. All patients with an unexplained deep mass of soft tissues, or with a superficial lesion of soft tissues having a diameter of >5 cm should be referred to reference centres for sarcomas and/or within reference networks treating a high number of patients annually (ESMO 2014).

Depending on tumour stage, 5-year overall survival rates range from 15% to 90% (Howlader et al. 2014; Gatta et al. 2011; ESMO 2014; NCI 2014). The median survival time in patients with metastatic STS is 11 to 15 months, and a small subgroup of these patients achieve long term survival. Survival is more dependent upon disease biology rather than solely upon treatment-associated consideration (Van Glabbeke, et al., 1999).

2.1.5. Management

Surgery is the gold-standard, and often only, curative treatment. Surgery is often confronted with difficult clinical dilemmas among optimal resection with adequate disease-free margins and limb-preservation. STS outside extremities, like those arising in the head-and-neck region, viscera or retroperitoneum, are characterized by worse outcomes, reflecting difficulties in obtaining wide en-bloc resections.

Radiotherapy is often used to control local-recurrence in aggressive histological subtypes and/or when appropriate margins cannot be obtained, but it has no effect on cure rates. There has been a long debate around adjuvant chemotherapy. After several controlled clinical trials and meta-analysis, it is now widely accepted that combination chemotherapy with anthracyclines and high-dose ifosfamide has a real but modest impact in survival upon chemo-sensitive STS subtypes (Casali, 2015) when full doses of such a highly toxic treatment can be administered, which is not the case in most patients over 40 years-old.

Some STS histological subtypes, when in advanced stage, are treated with well-defined chemotherapeutic regimes, i.e. rhabdomyosarcoma. In others, like gastrointestinal stromal tumours (GIST) and a few more, targeted therapy has become the gold standard. But most cases are either resistant to systemic therapy (like low-grade liposarcoma) or are to be treated with general-purpose chemotherapy based on uncontrolled, decades-old studies, with doubtful impact on survival. Little advance has been made neither in the chemotherapy nor in the targeted-therapies eras. According to RARECARE (Gatta et al, 2011), an Europe-wide surveillance project for rare cancers, 40 to 60% of all STS cases will be in the advanced stage at some point of their clinical course, most of them presenting with lung metastases. Their 5-year survival rates do not exceed 50%, similar to what was to be expected forty years ago.

A brief account of current first-line therapies for advanced-STS is outlined below. Clinical research has been confronted with a lack of knowledge regarding the molecular drivers of most sarcomas and with the usual difficulties surrounding rare diseases. Not the easiest issue to deal with, STS enormous heterogeneity challenges sarcoma clinical researchers with the dilemma of choosing between small but cohesive trials on the one hand, and large ones but including a heterogeneous mix of different diseases on the other.

Anthracyclines such as doxorubicin have a response rate of 10% to 30% (Bramwell et al, 2003) and are considered standard of care, if only because they are the oldest agents to be introduced in the palliative treatment of disseminated STS. It is to be emphasized that no controlled trial has ever been conducted to prove an overall survival (OS) advantage of anthracyclines over best supportive care. Nevertheless, doxorubicin is widely considered the only legitimate comparator for clinical trials in the first-line setting of advanced STS.

Adding ifosfamide to doxorubicin has been extensively investigated (Judson et al. 2014) but has failed to show a consistent OS benefit while increasing toxicity.

Dacarbazine, a promising compound due to its initial response rate, failed to become a standard of care because of its toxicity and low single-agent activity (Radaelli, 2014) and is now reserved for certain second-line combination schemes.

Pazopanib is a potent and selective multi-targeted receptor tyrosine kinase inhibitor that blocks tumour growth and inhibits angiogenesis. Recently approved for non-lipomatous advanced STS second-line treatment, it has demonstrated improved progression-free survival (PFS) in the second-line setting, but with limited survival benefit, if any (Wilky et al. 2013). There are ongoing trials recruiting treatment-naïve patients.

The combination of gemcitabine with docetaxel is used off-label for the treatment of metastatic STS fairly frequently in the EU and USA. The combination was shown to yield superior PFS and OS compared to gemcitabine alone, but with increased toxicity (Maki et al. 2007). Although most research has been done in pretreated patients, many experts move this combination to the front-line treatment in certain STS, like angiosarcoma, due to a its unusual high response rate.

Trabectedin is indicated for the treatment of adult patients with advanced STS, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents. It is more active in L-sarcomas (leiomyosarcoma and liposarcoma) than in other varieties (Sapponara, 2016). Initially rejected in USA but conditionally approved by the EMA based on PFS data, it has recently been accepted by the FDA after further research revealed an advantage also in OS.

In summary, front-line advanced-disease treatment of the vast majority of STS subtypes patients still rely on doxorubicin, a 40-year old drug, based on historical non-controlled research. Although some progress has been made in the second-line setting, it has not translated into OS benefits in the first-line treatment. New effective wide-spectrum systemic therapeutic options for the first-line treatment of patients with advanced or metastatic STS is an unmet medical need.

About the product

Olaratumab is an antagonist of platelet derived growth factor receptor-α (PDGFR-α), expressed on tumour and stromal cells. Olaratumab is a targeted, recombinant, fully human immunoglobulin G subclass 1 (IgG1) monoclonal antibody that specifically binds PDGFR-α, blocking PDGF AA, -BB, and -CC binding and receptor activation. As a result, in vitro olaratumab inhibits PDGFR-α pathway signalling in tumour and stromal cells. In addition, in vivo olaratumab has been shown to disrupt the PDGF R-α pathway in tumour cells and inhibit tumour growth.

The Applicant claimed the following indication which has been approved by the CHMP:

Lartruvo is indicated in combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin.

Olaratumab therapy must be initiated and supervised by physicians experienced in oncology. Patients should be monitored during the infusion for signs and symptoms of infusion-related reactions (IRRs) in a setting with available resuscitation equipment.

The recommended dose of olaratumab is 15 mg/kg administered by intravenous infusion on days 1 and 8 of each 3 week cycle until disease progression or unacceptable toxicity. Lartruvo is administered in combination with doxorubicin for up to 8 cycles of treatment, followed by Lartruvo monotherapy in patients whose disease has not progressed. Doxorubicin is given on day 1 of each cycle following the Lartruvo infusion.

After dilution in sodium chloride 9 mg/mL (0.9 %) solution for injection, olaratumab is administered as an intravenous infusion over approximately 60 minutes. In order to accommodate larger infusion volumes that may be needed for patients requiring higher doses, the duration of infusion should be increased such that the maximum infusion rate of 25 mg/minute is not exceeded.

Premedication

Premedication with an H1 antagonist (e.g., diphenhydramine) and dexamethasone (or equivalent medicinal products) should be given, intravenously, 30–60 minutes prior to the olaratumab doses on days 1 and 8 of

cycle 1 in all patients. For subsequent cycles, premedication with an H1 antagonist (e.g., diphenhydramine) should be given intravenously 30–60 minutes prior to each dose of olaratumab.

For patients who experience Grade 1 or 2 IRR , the infusion should be interrupted and paracetamol, H1 antagonist and dexamethasone (or equivalent medicinal products) administered as needed. For all subsequent infusions, premedication with the following (or equivalent medicinal products) diphenhydramine hydrochloride (intravenously), paracetamol, and dexamethasone, should be given.

In the event that intravenous administration of an H1 antagonist is not possible, equivalent alternative premedication should be given (e.g. oral diphenhydramine hydrochloride at least 90 minutes prior to the infusion).

Posology adjustments for olaratumab

For dose adjustment recommendations related to doxorubicin, refer to the current doxorubicin prescribing information.

Infusion-related reactions (IRRs)

Recommendations for the management of olaratumab IRRs are provided in table 1.

Table 1 – Management recommendations for infusion-related reactions (IRRs)

Toxicity grade[a]	Management recommendations (any occurrence)
Grade 1-2	• Stop the infusion • Paracetamol, H1 antagonist and dexamethasone should be administered as needed (see premedication section) • Once the reaction has resolved, resume infusion at a 50 % decreased infusion rate.[b] • Monitor patient for worsening of condition. • For subsequent infusions, please see premedication section.
Grade 3-4	• Immediately and permanently discontinue treatment with olaratumab (see section 4.4).

[a] Grade per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03

[b] Once the infusion rate has been reduced for a Grade 1 or 2 infusion-related reaction, it is recommended that the lower infusion rate be utilized for all subsequent infusions. The infusion duration should not exceed 2 hours.

Other non-haematology toxicities

For serious Grade ≥3 non-haematologic toxicity deemed related to olaratumab, the dose of olaratumab should be withheld until toxicity is ≤ Grade 1 or has returned to pretreatment baseline. For subsequent infusions, the dose should be reduced to 12 mg/kg for serious Grade 3 toxicities and to 10 mg/kg for Grade 4 toxicities. If a Grade 3 toxicity recurs despite the dose reduction, reduce dose further to 10 mg/kg. In case of recurrence of a Grade 4 toxicity, treatment with olaratumab should be permanently discontinued.

Neutropenia

If neutropenic fever/infection or Grade 4 neutropenia lasting longer than 1 week occurs, administration of olaratumab should be temporarily discontinued until the absolute neutrophil count is 1,000 / µL or higher and then the dose of olaratumab should be resumed at the reduced dose of 12 mg/kg. If neutropenic fever/infection or Grade 4 neutropenia lasting longer than 1 week recurs despite dose reduction, further reduce dose to 10 mg/kg (see section 4.2 of the SmPC).

Type of Application and aspects on development

The CHMP agreed to the applicant's request for an accelerated assessment as the product was considered to be of major public health interest. This was based on the outstanding longer survival observed for olaratumab in combination with doxorubicin compared to monotherapy with doxorubicin as observed in the pivotal study JGDG.

In addition, the applicant requested a conditional marketing authorisation and put forward the following claims:

- The benefit-risk balance is positive.
- It is likely that the applicant will be able to provide comprehensive data.

The applicant has initiated a confirmatory Phase 3 study, Study I5B-IE-JGDJ (JGDJ), in patients with advanced STS; the first patient visit in Study JGDJ occurred in September 2015. Approximately 460 patients will be included in this study, with enrolment estimated to be complete in the second half of 2017. Enrolment has been planned to take into account the potential for early approvals in one or more regions or countries, and assumes that once a country has approved the drug, no further patients would likely be included in the study from that region. Approximately 40% of the patients are planned to come from North America, 30% from EU, and 30% from other regions. The applicant is confident that the confirmatory Phase 3 Study JGDJ can be completed even if accelerated assessment is granted.

- Unmet medical needs will be addressed, as the improvement seen in OS in Study JGDG represents an unprecedented benefit to patients with STS.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required. The applicant's claim is based on the acceptable and monitorable safety profile and the limited other effective options available to patients with STS

2.2. Quality aspects

2.2.1. Introduction

Olaratumab is a fully human IgG1 monoclonal antibody produced in murine (NS0) cells by recombinant DNA technology. Olaratumab specifically binds platelet-derived growth factor receptor-α (PDGFR-α), expressed on tumour and stromal cells.

Lartruvo is presented as concentrate for solution for infusion. Each 50 mL vial contains 500 mg of olaratumab formulated at pH 5.5 with mannitol, glycine, sodium chloride, a histidine buffer, polysorbate 20 and water for injections. Sodium chloride 9 mg/mL (0.9 %) solution for injection is used as a diluent for administration of the product.

2.2.2. Active Substance

General information

Olaratumab is a glycoprotein (molecular weight: 154.6 kDa; 147.2 kDa excluding the glycan mass) composed of two heavy chains (γ1-chain) molecules consisting of 457 amino acid residues each and two light chains (κ-

chain) molecules consisting of amino acid residues each. There are twelve intra-chain and four inter-chain disulfide bonds. There are two glycosylation sites on Asn30 and Asn307 of the heavy chain in the Fab and Fc regions respectively.

Manufacture, characterisation and process controls

Source, history and generation of the cell substrate

Olaratumab is produced in mouse myeloma NS0 cells.

The general scheme for the transfection, selection, cloning, identification and subsequent banking of the olaratumab production cell line was presented.

Cell banking system

A two-tier cell banking system of Master Cell bank (MCB) and Working Cell Bank (WCB) is used for the manufacture of the active substance. A thorough description of the cell bank system has been provided, demonstrating stability of the construct and suitability of the MCB and WCB to be used for production.

The protocol for the preparation of a replacement WCB is presented. A description of the characterisation of cells at the limit of *in vitro* cell age used for production and the tests characterising these cells including evaluation of viral safety have been provided.

Manufacturing process and controls

The active substance is manufactured at ImCLone Systems LLC, 33 ImClone Drive, Branchburg, New Jersey, NJ 08876, USA.

The process controls applied to critical steps and intermediates during the manufacture of olaratumab active substance include critical process parameters, critical in-process controls (IPCs), in-process specifications and operational process parameters:

- Critical process parameter is a process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality per ICH Q8 [R2].

- Critical IPC is a check (i.e. tests or measurements) performed during production to monitor and, if appropriate, adjust the process to ensure active substance or finished product critical quality attributes will be met.

- In-process specification is a test or analytical procedure with defined acceptance criteria that is performed at the end of a unit operation to verify suitability for further processing per ICH Q8 [R2] and ICH Q9.

- Operational process parameter is a process parameter whose variability under normal operating conditions, when controlled within an established range, has no impact on a critical quality attribute. The operational process parameter limits and ranges are controlled within the batch records to ensure consistency in batch manufacture.

The control strategy for the olaratumab active substance manufacturing process was developed in accordance with the principles of quality risk management. A risk assessment was performed to identify process parameters with the potential for having an effect on active substance critical quality attributes. Additional studies were conducted to confirm the relationships of the identified process parameters and critical quality

attributes. Results of these studies were assessed, in conjunction with historical clinical trial process experience and platform knowledge, to establish the appropriate ranges for each unit operation.

Process validation

Process validation for olaratumab active substance manufacturing process was performed at the Branchburg commercial manufacturing site to demonstrate that the commercial-scale manufacturing process performs consistently and is capable of meeting pre-determined acceptance criteria.

Prospective process validation (also referred to as process consistency) was performed using the intended commercial process. Process was used for the registrational clinical trial JGDG. The process validation of the olaratumab active substance manufacturing process was performed using consecutive runs. The clearance of process-related impurities was evaluated for selected unit operations in the olaratumab active substance manufacturing process. The process does not produce process intermediates requiring long term storage. Unless otherwise noted, active substance manufacturing was performed at. Process intermediates may be held prior to commencing the subsequent unit operation. The hold time limits were set based on the shortest of the three longest hold times at commercial-scale for each process intermediate but not less than hours.

The prospective, commercial-scale process validation successfully confirmed the olaratumab control strategy and demonstrated that the commercial manufacturing process performs consistently. In order to ensure that the manufacturing process remains in a state of control during commercial production, a monitoring plan has been established for routine production. Routine monitoring ensures that the manufacturing process remains capable of consistently delivering quality product and demonstrates robustness of the process control strategy.

Membranes, resins and filters reuse were validated, along with reprocessing at the filtration level.

Manufacturing process development

A comparability exercise was performed to demonstrate comparability of active substance manufacturing processes and batches during development.

The comparability assessment to support changes consisted of the application of a battery of analytical tests to active substance samples. Analytical testing comprised routine active substance release tests and additional biochemical characterisation assays. Test results were compared qualitatively and, where appropriate, quantitatively.

Characterisation

The structure of olaratumab has been elucidated using an extensive battery of physicochemical, biophysical and biological techniques. Structural elucidation and characterisation was performed mainly on lots produced using the proposed commercial manufacturing process. All available data are consistent with the proposed structure of olaratumab.

The product- and process-related impurities in olaratumab were characterised.

Specification

Specification for olaratumab was established based on the quality of the product used in toxicological and clinical testing, the stability of olaratumab, process variability, the variability of the analytical methods used to analyse the active substance, and ICH guidelines.

The potency of olaratumab is determined based on its mechanism of action by an assay.

The analytical procedures used to release active substance batches have been described and validated as also the analytical procedures used for IPCs.

Genealogy of batches produced up to now is documented

Reference standard

A two-tiered reference standard (RS) program for olaratumab has been implemented, which includes a primary reference standard (PRS) and a working (secondary) reference standard (WRS).

The PRS batch will be used to qualify future WRS batches. The WRS batch will be used for release, stability, and characterisation testing of olaratumab active substance and finished product.

Stability

The Applicant claimed a shelf life of 24 months for the commercial active substance olaratumab stored at the recommended storage condition of 2-8°C in the intended container.

2.2.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

The finished product is presented as a solution for intravenous infusion, 10 mg/mL intended for single use. Olaratumab is formulated in an aqueous buffered solution at pH 5.5, containing an histidine buffer (L-histidine and L-histidine monochloride), sodium chloride, mannitol, glycine and polysorbate 20. All excipients comply with the European Pharmacopoeia. Lartruvo is provided as a 500 mg/50 mL presentation (pack of one vial). The finished product is diluted with 0.9% sodium chloride prior to administration.

Manufacture of the product and process controls

Olaratumab finished product is manufactured at Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana (IN) 46285, USA.

Olaratumab finished product is manufactured as a sterile, non-pyrogenic solution at a concentration of 10 mg/mL and aseptically filled into vials.

Olaratumab active substance is received from Branchburg under temperature controlled conditions (2-8°C) and stored at 2-8°C. The finished product manufacturing process consists of dilution of the bulk active substance in buffer that contains L-histidine, L-histidine monohydrochloride, sodium chloride, glycine, mannitol and polysorbate 20. The finished product solution is sterile filtered and aseptically filled into glass vials (500 mg/50 mL), stoppered and crimp sealed. The filled vials are 100% visually inspected. Once vials are labelled and placed in secondary packaging, identity is confirmed. Vials are removed from storage and transferred to the packaging area. Vials are labelled and placed in secondary packaging. Identity of the labeled vials is confirmed via physicochemical analysis. Olaratumab finished product is stored and shipped at 2-8°C. Reprocessing of the batch is not allowed.

Olaratumab finished product is packaged in a depyrogenated Type I tubing glass vial with a chlorobutyl elastomer stopper that has a FluroTec lamination on the plug and a cross-linked silicone coating on the top and sides of the flange. The stopper is secured with a two piece polypropylene flip-top aluminium seal.

Operating ranges for process parameters and acceptance criteria for controls are provided for parameters/controls that have been determined to be critical to ensuring that the critical quality attributes are met. This determination of criticality was based on a risk analysis.

The overall process validation program is prospectively performed to confirm that the manufacturing process for the finished product is robust and capable of consistently yielding final product that conforms to all quality, safety and efficacy attributes and pre-determined specifications.

A comparability exercise was performed to support changes introduced during development to the finished product.

Reference standard

The reference standard information for the finished product is the same as described for the active substance.

Stability of the product

An evaluation of shelf-life of the finished product using both the new available Primary and Supportive lots data, following ICH Q1E guideline and considering the revised specifications has been performed. It is noted that the Applicant commits to notify any out-of-specification occurring during the finalisation of the ongoing stability studies, in accordance with local requirements.

On the basis of the information provided, the claimed shelf life of 24 months for the commercial finished product stored at the recommended storage condition (2-8°C) is acceptable.

This product is preservative free and therefore the prepared dosing solution should be used immediately. If not used immediately, the dosing solution should be stored under refrigeration for up to 24 hours at 2°C to 8°C and up to an additional 8 hours at room temperature (up to 25 °C) assuming dilution has taken place using acceptable aseptic techniques. Storage times include the duration of infusion.

Adventitious agents

Animal-sourced materials such as foetal bovine serum (FBS), bovine insulin, bovine transferrin, bovine serum albumin (BSA), and cholesterol were used in the generation of the cell line utilised for the production of olaratumab. The country of origin, the vendor and the relevant Certificates of Suitability from EDQM in place at the time of cell line generation and cell banking have been provided. For the commercial manufacturing Process, additional viral risk mitigation is introduced. Overall, information regarding the raw materials of biological origin used in the manufacturing process of olaratumab active substance is deemed acceptable. Compliance with the TSE Guideline (EMEA/410/01 – rev. 3) is considered sufficiently demonstrated.

The testing programme of cell banks and all unprocessed bulk harvest batches for virus contamination is considered adequate and in compliance with ICH Q5A. No adventitious agents, mycoplasma, microbial or viral, were detected.

Overall reduction factors are satisfactory and demonstrate the efficacy of the olaratumab manufacturing process to remove/inactivate possible viral contaminants.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality aspects of this dossier are well presented and the information it contains is considered comprehensive.

A Major Objection was raised during the review regarding the validation of the finished product manufacturing process. Satisfactory information has been submitted and therefore this issue was considered solved. A number of Other Concerns were also identified which have been satisfactorily addressed by the Applicant.

Active substance

Manufacture, characterisation and process controls

In relation to the cell banks, the Applicant was asked to provide the protocol to be followed to demonstrate the stability of the MCB (quality profile and acceptance criteria) in case a replacement WCB is not implemented within a five-year timeframe. The Applicant was also requested to submit a full scale qualification protocol for the replacement of the WCB to be assessed prior approval of the present marketing authorisation application. The requested information has been provided and so these issues are considered solved.

The manufacturing process of the active substance is considered appropriately described. A number of minor clarifications were requested and are now considered solved.

The Applicant states that refiltration (final filtration) will only be permitted in the event of a filter integrity test or container closure integrity failure. The Applicant has clarified that, in the event of closure integrity failure, refiltration is only permitted if microbial control of the batch was first demonstrated by meeting the pre-filtration action limits. This clarification is accepted. The Applicant states that product quality testing will be performed pre- and post-reprocessing for the first three olaratumab commercial batches that are re-filtered at the virus reduction nanofiltration unit operation.

Since the criticality of process parameters and IPCs is evaluated on the basis of the impact on critical quality attributes, the Applicant was asked to justify how the acceptance criteria for the critical quality attributes were initially determined. This has been presented and found acceptable.

Characterisation

Overall, the characterisation exercise performed by the Applicant is considered adequate to address the complex pattern of glycosylation of olaratumab. *Control of active substance*

Tightening of some acceptance values was requested based on manufacturing experience. The Applicant revised the specification which is now considered acceptable. *Stability*

The Applicant claimed a shelf life of 24 months for the commercial active substance olaratumab stored at the recommended storage condition of 2-8°C.This was considered acceptable.

Finished medicinal product

Pharmaceutical development

The suitability of the container closure system used for the finished product was supported by studies on stability in several conditions (including agitation and photostability), extractables and leachables. Updated results from this study were requested and submitted. The issue is considered solved.

Manufacture of the product and process controls

In relation to the description of the manufacturing process, the information presented is considered sufficient.

Control of finished product

The finished product release and stability specifications proposed are, in general, acceptable, as it covers most of the relevant characteristics of the product. Acceptance criteria are generally well justified, although some further justifications and/or tightening were required after the initial assessment. *Stability*

A 24 month shelf life is proposed for the finished product and is considered acceptable on the basis of the stability data provided at the time of submission and during the procedure.

Adventitious agents

From a virus and TSE risk perspective, the product is suitable for the marketing authorisation.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Overall, the quality of Lartruvo is considered to be in line with the quality of other approved monoclonal antibodies. The different aspects of the chemical, pharmaceutical and biological documentation comply with existing guidelines. The fermentation and purification of the active substance are adequately described, controlled and validated. The active substance is well characterised with regard to its physicochemical and biological characteristics, using state-of-the-art methods, and appropriate specifications are set. The manufacturing process of the finished product has been satisfactorily described and validated. The quality of the finished product is controlled by adequate test methods and specifications.

Viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The overall Quality of Lartruvo is considered acceptable. Several Recommendations on Quality aspects, agreed by the Applicant, are listed in Section 2.2.6.

2.2.6. Recommendations for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommended several points for investigation.

2.3. Non-clinical aspects

2.3.1. Introduction

A series of in vitro pharmacodynamic (PD) studies were conducted to characterize the nonclinical pharmacology of olaratumab, including its specific binding to PDGFRα, ligand-blocking activity, and functional inhibition of ligand-induced PDGFRα signalling. The antitumor activity of olaratumab alone and in combination with chemotherapy in mice containing human xenograft tumours was also demonstrated. In addition, a

murine surrogate antibody (LSN338786, IMC-1E10) for olaratumab that binds to mouse PDGFRα was tested for its anti-tumour activity and the enhancement of the effect of chemotherapy on a human lung xenograft by targeting mouse stroma.

The nonclinical pharmacokinetic (PK) characterization of olaratumab was conducted in mice. Studies were also conducted to characterize the PK and toxicokinetics (TK) of the murine surrogate antibody, LSN338786 (IMC-1E10). Olaratumab and IMC-1E10 were administered intravenously (i.v.) in these studies, which is the intended clinical route of administration.

The toxicity and TK of olaratumab, as well as evidence of antidrug antibodies (ADA) to olaratumab and their potential impact on olaratumab TK, were characterized in GLP-compliant studies after administration to cynomolgus monkey (established as an appropriate species for toxicity testing based on similar binding affinity of Olaratumab to human and monkey PDGFRα), by i.v. infusion over 5, 13 and 39 weeks, followed by recovery periods of 7 or 8 weeks. Safety pharmacology endpoints (cardiovascular, respiratory, and central nervous system) were evaluated in these repeat-dose studies. Studies to assess genotoxicity, carcinogenicity, and developmental and reproductive toxicity studies were not conducted with olaratumab. However, to assess reproductive and developmental toxicity, a scientific literature review was included in the submission and an embryo-foetal study using mouse surrogate antibody of olaratumab (1E10) is being conducted.

2.3.2. Pharmacology

Primary pharmacodynamic studies

In vivo studies

Binding and Species cross-reactivity of Olaratumab

Olaratumab binding to PDGFRα was evaluated by ELISA and surface plasmon resonance (SPR). The antibody bound human PDGFRα immobilized onto ELISA plates with an affinity higher than a commercial anti-PDGFRα mouse monoclonal antibody. The results are shown below.

Olaratumab Binding to	Kon (1/Ms)	Koff (1/s)	KD (M)	Rmax	Chi^2
Human-PDGFRα-Fc (30nM)	9.02E+05	2.96E-04	3.29E-10	15.89	0.155
Cynomolgus-PDGFRα-Xa-Fc (30nM)	7.48E+05	4.51E-04	6.03E-10	14.86	0.111
Dog-PDGFRα-Xa-Fc (30nM)	1.21E+06	2.64E-03	2.18E-09	6.726	0.024
Rabbit-PDGFRα-Xa-Fc (900nM)	2.04E+05	8.31E-03	4.07E-08	1.337	0.005

Effect of Olaratumab on PDGFRα Phosphorylation and PDGFRα- Mediated Signal Transduction

Inhibition of PDGF AA and PDGF BB Binding to PDGFRα by IMC-3G3 and other anti- PDGFRα antibodies, was evaluated in porcine aortic endothelial (PAE) Rα cells. Inhibition of PDGFRα phosphorylation and MAPK and Akt activation induced by PDGF-BB, was also tested in the same cell line. Imatinib as well as a neutralizing murine monoclonal antibody from R&D Systems were included in this experiment as positive control inhibitors.

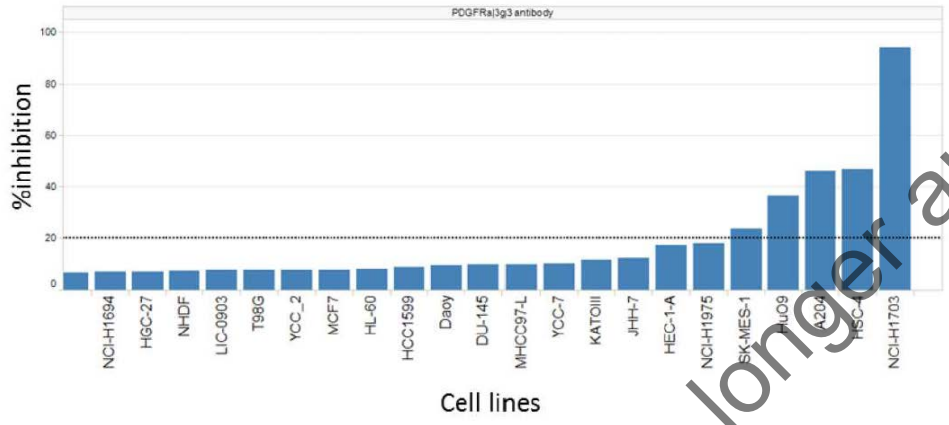
Among the panel of anti- PDGFRα antibodies produced, 3G3 and F12 were more efficient in inhibiting the binding of radiolabelled PDGF AA to immobilized receptor (IC_{50} 0.24 and 0.16 nM, respectively) or to PDGFRα

expressed on the surface of PAE Rα tumour cells (IC_{50} 0.58 and 0.51 nM, respectively). These two antibodies were also the more efficient in inhibiting the binding of PDGF BB to immobilized PDGFRα (IC_{50} 0.43 and 0.55 nM, respectively). Inhibition of PDGF-AA-induced PDGFRα phosphorylation by IMC-3G3 was dose dependent, with 50% inhibition achieved at 0.25 nM.

Effect of Olaratumab on Tumour Cell Proliferation and Characterization of Responsive Cell Lines

The effect of olaratumab on the cell growth *in vitro* was evaluated at 100 µg/mL on a panel of 317 cancer cell lines that were genetically characterized.

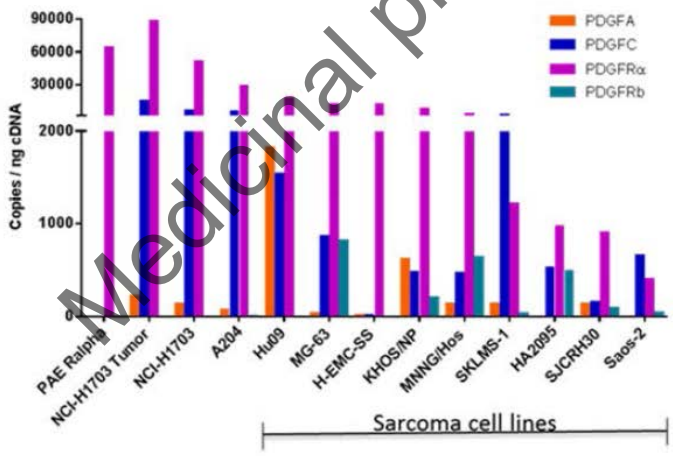
The results are shown below:



Olaratumab-sensitive cancer cell lines as well as additional sarcoma cell lines were characterized for *PDGFA*, *PDGFC*, *PDGFRA*, and *PDGFRB* mRNA expression and for cell-surface levels of PDGFRα. Quantitative real-time PCR (RT-qPCR) was then performed with the cDNA and TaqMan Gene Expression assays from Life Technologies for quantification of total *PDGFRA*, *PDGFA*, *PDGFC*, and *PDGFRB*.

The results are shown below:

A.

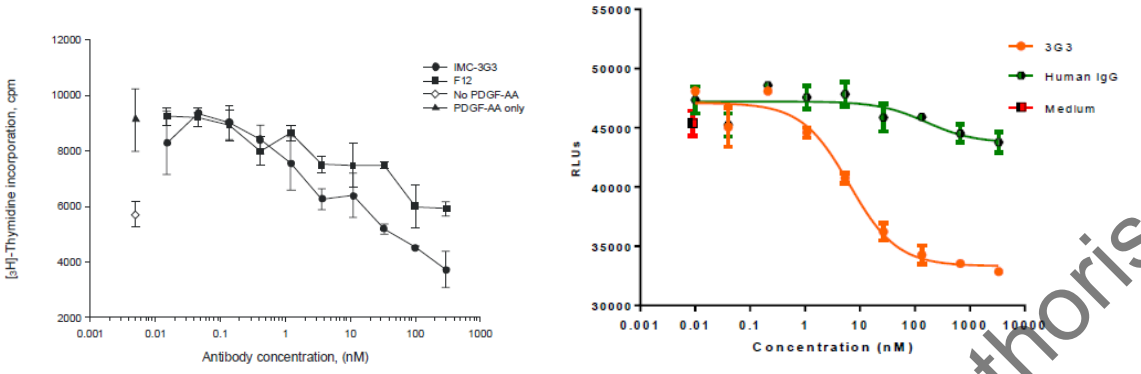


B.

Cell Line	Tumor type	PDGFRα cell-surface level (ABC)
PAE Rα		337,052
NCI-H1703	NSCLC	189,496
A204	Rhabdoid	72,526
Hu09	Osteosarcoma	36,449
MG-63	Osteosarcoma	152,087
H-EMC-SS		73,550
MNNG-HOS	Osteosarcoma	15,122
HA2095	Synovial Sarcoma	14,631
SK-LMS-1	Leiomyosarcoma	12,088
KHOS-NP	Osteosarcoma	10,547
Saos-2	Osteosarcoma	5,798
SJCRH30	Rhabdomyosarcoma	4,935
U118	Glioblastoma	66,046
WS-1	Normal Fibroblast	18,579

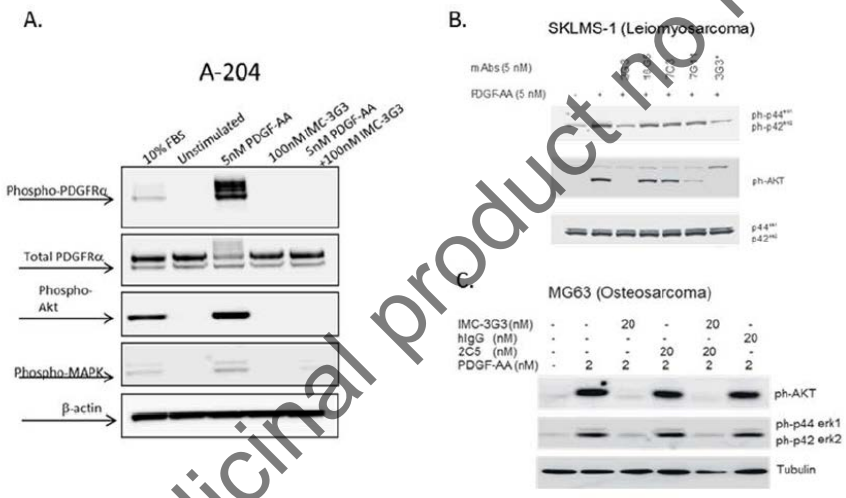
Effect of Olaratumab on PDGFRα-Mediated Proliferation of Sarcoma and Rhabdoid Cancer Cell Lines

The effects of IMC-3G3 on inhibition of PDGF-AA-stimulated cell mitogenesis and viability of SKLMS-1 (Leiomyosarcoma) and HuO9 (Osteosarcoma) cells grown in full serum were evaluated. The results are shown below (left, SKLMS-1 cell line; right: HuO9 cell line):



Effect of Olaratumab on PDGFRα-Mediated Signal Transduction of Sarcoma and Rhabdoid Cancer Cell Lines

A-204 (Rhabdoid) and NCI-H1703 (NSCLC) cells were pretreated with Olaratumab before stimulation with PDGF-AA. Inhibition of pPDGFRα, Akt and MAPK phosphorylation was determined by examining cell lysates through Western blotting with antibodies specific for phospho-PDGFR alpha, phospho-Akt & phospho-MAPK. The results are shown below:



Effect of Olaratumab on PDGF-induced activation of PDGFRα on Prostate Stromal Cells and Lung Cancer-associated Fibroblasts

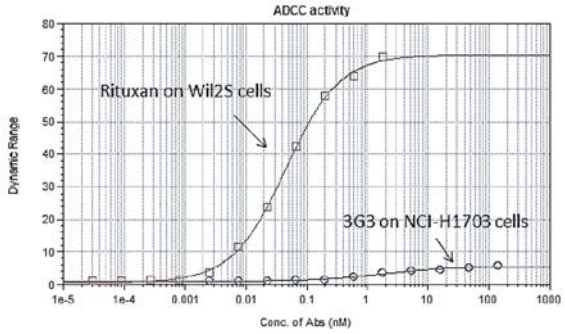
In these studies, human WS-1 skin fibroblasts, prostate stromal cells and lung cancer-associated fibroblasts (CAF) were grown. Cells were treated with antibodies followed by the addition of PDGF-AA or PDGF-AA and PDGF-CC cocktail, or PDGF BB or DD. The results are described as follows:

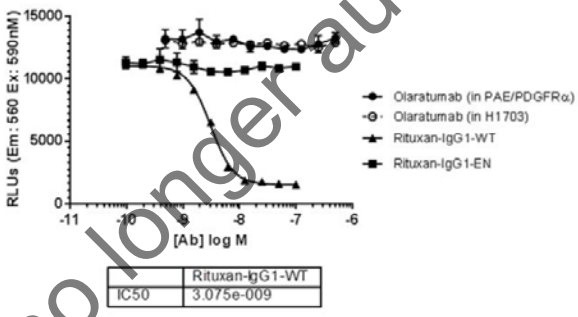
Olaratumab was demonstrated to inhibit the proliferation of commercial prostate stromal cells induced by stimulation with PDGF AA with an IC_{50} of 1.39 nM, this inhibition was associated with the reduction of PDGFRα phosphorylation.

In CAFs, treatment with the PDGF-AA and –CC ligand cocktail resulted in phosphorylation of the receptor and the downstream effector proteins AKT and ERK Doxorubicin co-adminstration had no discernible effect on effector protein phosphorylation. Olaratumab pretreatment resulted in nearly complete reduction in p-ERK and p-AKT (to baseline levels) relative to IgG controls. olaratumab also inhibited the phosphorylation of PDGFRα in human WS-1 skin fibroblasts stimulated with any of the PDGFR ligands including those α-selective, such as AA and CC homodimers, but also the β-specific DD homodimer.

Lack of Antibody-Dependent Cytotoxicity (ADCC) and Complement-Dependent Cytotoxicity (CDC) Induced by Olaratumab

ADCC activity via FcγRIII was evaluated in a reporter assay containing a human target tumour cell line (NCI-H1703 lung cancer; approximately 200,000 PDGFRα/cell) and an effector cell line (Jurkat cells engineered to express cell-surface FcγRIII, and a luciferase gene under the control of an NFAT-regulated promoter). The results are described below (left: ADCC; right: CDC):



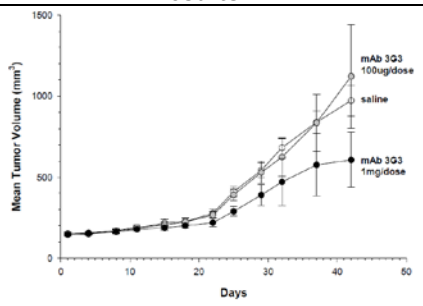


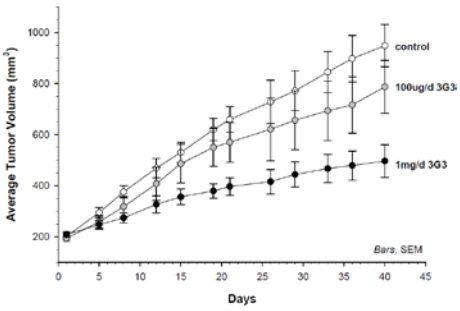
	Rituxan-IgG1-WT
IC50	3.075e-009

In vivo studies

Studies of Olaratumab in Murine Xenograft Models of Human Cancer

IMC-3G3 monotherapy activity (lots were not declared in all studies)

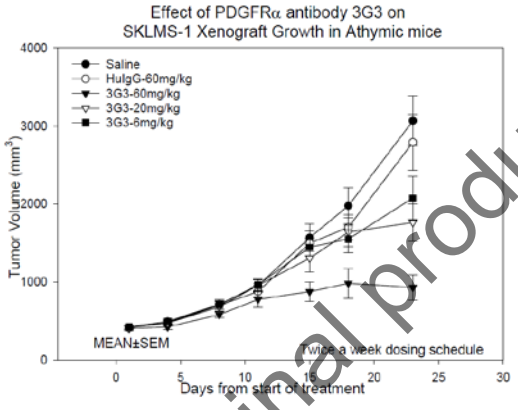
Report number / Type of Study	Xenograft Model	Dosage / Dosing period	Results
2042-03 Monotherapy Activity	SKLMS-1 leiomyo-sarcoma	IMC-3G3, 0.1 mg/dose, M-W-F IMC-3G3, 1.0 mg/dose, M-W-F Saline, 0.5 mL/dose, M-W-F 42 days	

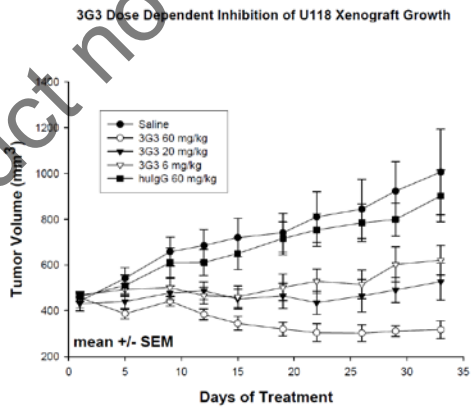
2020-03 Monotherapy Activity	U118 glioblastoma	IMC-3G3, 0.1 mg/dose, M-W-F IMC-3G3, 1.0 mg/dose, M-W-F Saline, 0.5 mL/dose, M-W-F 42 days	
3478-05 Monotherapy Activity	SKLMS-1 leiomyo-sarcoma	IMC-3G3 (lot P5-469-1), 40 mg/kg, M-W-F Human IgG, 40 mg/kg, M-W-F Saline, 10 mL/kg, M-W-F	IMC-3G3 inhibited the growth of SKLMS-1 xenografts
4881-10 **Monotherapy activity**	A204 Rhabdoid	IMC-3G3, 40 mg/kg, M-W-F Human IgG, 40 mg/kg M-W-F	IMC-3G3 inhibited the growth of A204 rhabdoid xenografts

PK/PD studies

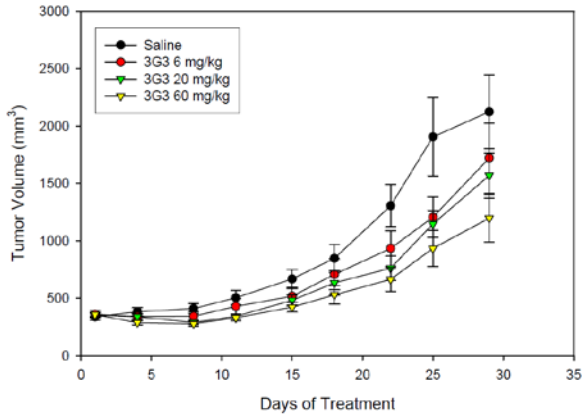
The PK/PD of olaratumab were evaluated in SKLMS-1 and U118 xenograft models of leiomyosarcoma and glioblastoma, respectively. In addition to antitumor activity, plasma concentrations of Olaratumab associated with an efficacious dose were determined.

The results are shown below:





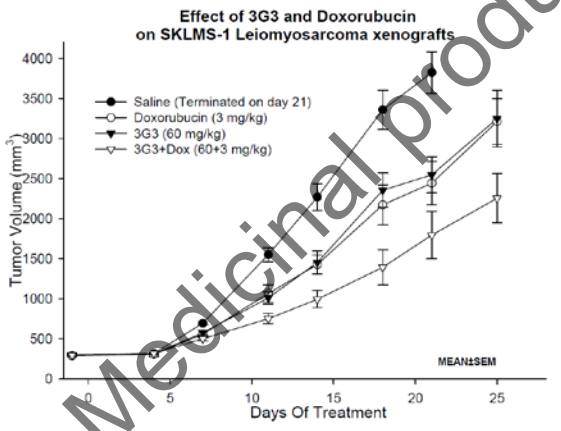
The aim of another study was: 1) To determine the pharmacokinetic (PK) parameters associated with efficacious doses of a fully human antibody against PDGFRα, 3G3, in an SKLMS-1 Leiomyosarcoma cell line xenograft model. 2) To compare the pharmacokinetics of 3G3 after the first or multiple doses. Nu/nu mice (female, 7-8 weeks) were injected subcutaneously with 5 X106 SKLMS-1 cells/mouse. The results are shown below:

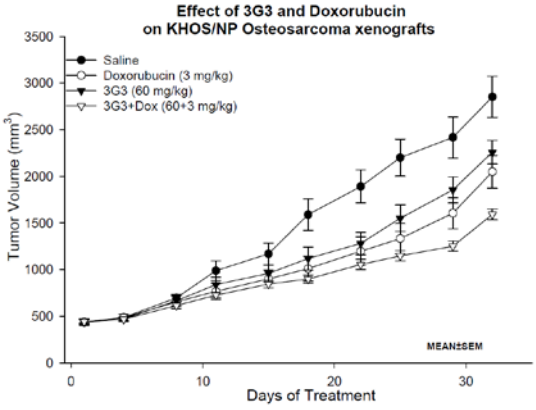


Olaratumab plus Chemotherapy Combination Studies in Sarcoma Cell-line and Patient-derived Xenograft Models

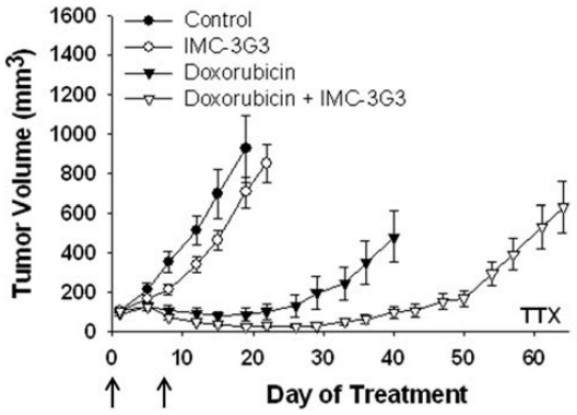
The association of olaratumab with doxorubicin (3 mg/kg) was tested in established SK-LMS-induced tumours in immunodeficient mice. Olaratumab alone induced a reduction of tumour volumes at day 24 of about 30 %, lower than that expected and the reduction did not reach statistical significance. Both doxorubicin alone and the combination significantly reduced tumour growth at the same time point, inducing a reduction of about 70% and 50% with the combination and the chemotherapy alone, respectively, the difference between these two arms was also not statistically significant.

In other studies, subcutaneous tumour xenografts were established by injecting SKLMS-1 (5×10^6 cells/mouse) or KHOS/NP (1×10^6 cells/mouse) into female athymic nude mice. Mice were treated with saline solution, doxorubicin, olaratumab and a combination of the 2 treatments. Results are shown in the figures below:

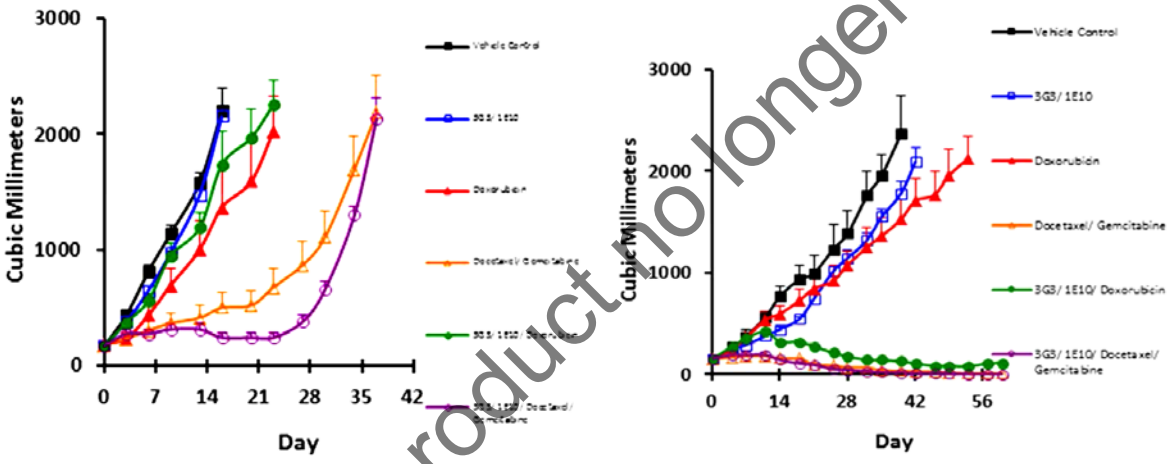




In an additional study, a xenograft model (TTX) derived from an osteosarcoma tumour biopsy, utilized 4 to 6 week old female Balb/c mice. Mice were treated with Olaratumab alone doxorubicin alone, or the combination of these two monotherapies. See figure below:

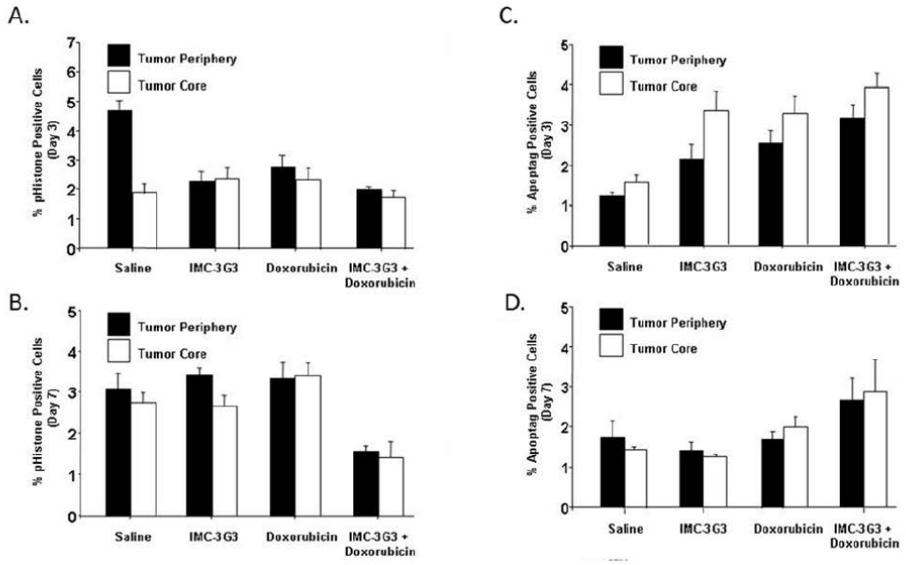


Olaratumab was also tested in PDX leiomyosarcoma (Model ST1547) and liposarcoma (Model ST658). Patient-derived xenograft. The results are shown below (Left figure: Model ST658; right figure: Model ST1547)



Mechanism of action (MoA) Study in a Sarcoma Model

A study examined the mechanism for increased activity of IMC-3G3 in Combination with the cytotoxic agent doxorubicin, compared to monotherapy activity, in the SKLMS-1 leiomyosarcoma tumour xenograft model. Tumours were harvested from mice 3 or 7 days after starting treatment with saline (10 µL/gm), IMC-3G3 (60 mg/kg, twice per week and a loading dose of 214 mg/kg), doxorubicin (3 mg/kg, twice per week), or IMC-3G3 plus doxorubicin. See figures below.



Mechanism of Action Studies in Non-Sarcoma Models

An overview of MOA studies in non-sarcoma models is provided below:

Xenograft Model	Dosage	Dosing Period	Conclusion	Report Number or Publication
U118 glioblastoma	IMC-3G3, 60 mg/kg, 2x/week (loading dose 214 mg/kg) Human IgG, 60 mg/kg, 2x/week (loading dose 214 mg/kg)	7 days	IMC-3G3 reduced PDGFRα and MAPK phosphorylation, and Ki-67 expression	3132-04
PC-3ML prostate	IMC-3G3, 60 mg/kg, 2x/week (loading dose 214 mg/kg)	21 and 28 days	IMC-3G3 reduces the size of established skeletal metastases	Russell et. al. 2010
A549 NSCLC	1E10, 40 mg/kg and Hu IgG, IP; M-W-F	36 days	Treatment with 1E10 significantly inhibited the growth of A549 tumors	4749-10
A549 NSCLC	cisplatin, 1 mg/kg 1X per week; gemcitabine 25 mg/kg, 2X per week; 1E10, 2X per week, or chemotherapy plus 1E10	36 days	1E10 enhanced the effect of cisplatin-gemcitabine chemotherapy in A549 xenografts	Gerber et. al. 2012

Secondary pharmacodynamic studies

No secondary pharmacology studies have been submitted in this application.

Safety pharmacology programme

No dedicated safety pharmacology studies have been submitted in this application.

Pharmacodynamic drug interactions

No dedicated pharmacodynamic drug interactions studies have been submitted in this application.

2.3.3. Pharmacokinetics

The studies conducted to evaluate the pharmacokinetics and toxicokinetics of olaratumab are shown in Table below.

Study Type	Species	Route of Administration	Dose Levels (mg/kg)	Report Number
Single-Dose PK	CD-1 mouse (female only)	I.P.	20	2139-03
Multiple-Dose PK/PD	Nude mouse (female only)	I.P.	6, 20, 60	3015-04
Single-Dose PK	Nude mouse (male only)	I.P.	20, 60	8315118
5-Week Repeat-Dose TK	Cynomolgus monkey	I.V.	5, 16, 50	7573-104
13-Week Repeat-Dose TK	Cynomolgus monkey	I.V.	7.5, 24, 75	7573-105
39-Week Repeat-Dose TK	Cynomolgus monkey	I.V.	7.5, 24, 75	8201-235

Abbreviations: I.P. = intraperitoneal, I.V. = intravenous, PK = pharmacokinetics, PD = pharmacodynamics, TK = toxicokinetics.

The studies conducted to evaluate the pharmacokinetics and toxicokinetics of IMC-1E10 are shown below:

Study Type	Species	Route of Administration	Dose Levels (mg/kg)	Report Number
Single-Dose PK	CD-1 mouse (female only)	I.V.	5, 150	8315117
Embryo-Fetal Repeat-Dose TK	CD-1 mouse (female only)	I.V.	0.3, 3, 30, 138	8323353

Abbreviations: I.V. = intravenous, PK = pharmacokinetics, TK = toxicokinetics.

An overview of methods of analysis is shown in the table below:

Study Number	Analyte	Species/Matrix	Method	Range (µg/mL)	Inter-Assay Precision (%CV)	Inter-Assay Accuracy (Mean %Recovery)	Stability Data
182531	IMC-3G3	Mouse serum	ELISA	1 to 100[a]	3.04 to 6.99	-4.65 to 1.80	Study 8315118: 3 F/T cycles at -70°C. 13 days at -70°C[b]
a Assay Dynamic Range is 2 to 200 ng/mL at a minimum required dilution 1:500. b Storage stability will be further evaluated at -20 °C and at -70 °C at approximately 1 and 3 months. Abbreviations: F/T = freeze/thaw.							
VR1386a	IMC-3G3	Monkey serum	ELISA	1 to 20 [b]	3.64 to 10.54 [c]	-1.90 to 7.92 [c]	Study 7573-104 7 days at 2°C to 8°C. 3 F/T cycles at -70°C. Study 7573-105 3 months at -20°C and 7 months at -70°C.

AR3173	IMC-3G3	Monkey serum	ECL	0.040 to 7.5 [d]	9.2 to 22.3	-8.7 to 3.5	Study 8201-235 24 hours at RT. 5 F/T cycles at -70ºC. 5 months at -70ºC.
a Qualified non-GLP method. b Assay Dynamic Range is 5 to 100 ng/mL at a minimum required dilution 1:200. c Values include both manual and automated (Biomek-based) methods evaluated during validation. d Assay Dynamic Range is 0.40 to 75 ng/mL at a minimum required dilution 1:100. Abbreviations: F/T = freeze/thaw, RT = room temperature.							
Quantitation of IMC-1E10							
8322-970	IMC-1E10	Mouse serum	ELISA	0.025 to 2.5 [b]	4.0 to 20.3	-6.7 to 18.3	Study 8315117 Not determined
8322-971	IMC-1E10	Mouse Serum	ELISA (Total IgG Capture)	0.075 to 2 [c]	9.0 to 17.7	-5.8 to 6.8	Study 8323353 26 hours at RT. 5 F/T cycles. Freezer stability is ongoing and will be established for approximately 1 year.
Abbreviations: F/T = freeze/thaw, RT = room temperature. a Qualified non-GLP method. b Assay Dynamic Range is 2.5 to 250 ng/mL at a minimum required dilution 1:10. c Assay Dynamic Range is 7.5 to 200 ng/mL at a minimum required dilution 1:10.							

Two methods were developed to detect the presence of anti-drug antibodies (ADA) against olaratumab in the serum of monkeys treated with olaratumab. The assay supporting 5-week and 13-week toxicity study sample analysis did not demonstrate a high degree of drug tolerance. The revised assay format used to support the 39-week study utilized an acid dissociation step. This validated assay demonstrates both adequate sensitivity and drug tolerance needed to support accurate interpretation of immunogenicity and TK results.

Absorption

The single-dose PK of olaratumab after i.p. administration was investigated in female CD-1 mice to determine a dosing regimen suitable for efficacy studies in tumour-bearing mice (Report 2139-03). The estimated T½ determined after administration of a single 20 mg/kg i.p. dose was 7.4 days.

The single-dose PK of olaratumab following i.p. administration as a solution in PBS was further characterized in male nude athymic mice (Report 8315118). Systemic exposure to olaratumab increased with dose in mice, but increases were less than dose proportional with an approximate doubling between 20 and 60 mg/kg. The mean T½ determined after administration of a single i.p. dose was approximately 5.7 days. AUC_{0-t} values (where t is 0 to 480 hours postdose) following administration of olaratumab 20 and 60 mg/kg (30000 and 60200 µg.hr/mL), were similar to AUC_{0-inf} ones (34300 and 66200 µg.hr/mL).

A pilot mouse PK study was conducted with the mouse surrogate mAb IMC-1E10 (Report 8315117). The PK parameters of IMC-1E10 were determined following a single 5 mg/kg or 150 mg/kg I.V. bolus dose to non-fasted female CD-1 mice. The estimated T½ range in this study was 65 to 71 hours (2.7 to 3.0 days), which supported a proposed dosing frequency (every 3 days) in a subsequent embryo-fetal development study.

AUC 0-t values following olaratumab administration at 5 and 150 mg are 1480 (AUC interval is 0 to 288 hours postdose) and 116000 µg.hr/mL (AUC interval is 0 to 360 hours postdose). Clearance of IMC-1E10 appeared to be dose-dependent, whereby clearance at 5 mg/kg was approximately 2.7 times higher than at 150 mg/kg.

Distribution/metabolism/excretion

No specific distribution/metabolism/excretion studies have been submitted in this application.

2.3.4. Toxicology

Single dose toxicity

No single dose toxicity studies were conducted with olaratumab. However, in the 5-week repeat dose study in monkeys (study 7573-104) there was a 2 week delay after the first dose (5, 16, 50 mg/kg), showing no test article-related effects on clinical observations or body weights. In addition, no signs of acute toxicity were observed after administration of the highest single dose of olaratumab (75 mg/kg) in the 13 and 39-week toxicity studies in monkeys (7573-105, 8201-235).

Repeat dose toxicity

The toxicity, TK, and immunogenicity of olaratumab were investigated after administration by i.v. infusion over 5, 13, or 39 weeks to male and female cynomolgus monkeys.

Table 2: Repeat-dose toxicity studies with olaratumab in cynomolgus monkeys.

Study ID	Number/ Group	Dose/Route	Duration	NOEL/ NOAEL (mg/kg/week)	Major findings
7573-104 GLP A Five-Week (4-dose) Toxicity, Toxicokinetic, and Immunogenicity Study of IMC-3G3 Administered Intravenously to Cynomolgus Monkeys with a Recovery Period	3/sex/ group	5M/5F 0 3M/3F 5 mg/kg/week 3M/3F 16 mg/kg/week 5M/5F 50 mg/kg/week IV	5 weeks, 7 weeks recovery	≥50	None
7573-105 GLP A 13-Week Toxicity, Toxicokinetic and Immunogenicity Study of IMC-3G3 Administered Intravenously Weekly to Cynomolgus Monkeys with an 8-Week Recovery Period	3/sex/ group	5M/5F 0 3M/3F 7.5 mg/kg/week 3M/3F 24 mg/kg/week 5M/5F 75 mg/kg/week IV	13 weeks, 8 weeks recovery	≥75	None
8201-235 GLP	3/sex/ group	6M/6F for all dose levels:	39 weeks, 8 weeks recovery	≥75	↑ alanine aminotransferase,

39-Week Intravenous Injection Chronic Toxicity and Toxicokinetic Study with IMC-3G3 in Cynomolgus Monkeys with a 8-Week Recovery Period		7.5, 24, 75 mg/kg/week IV			individual cell necrosis, infiltrates in the liver in one female

Genotoxicity

No genotoxicity studies have been submitted in this application.

Carcinogenicity

No carcinogenicity studies have been submitted in this application.

Reproduction Toxicity

Based on knockout models and a review of the literature, it appears likely that disruption of PDGF/PDGFR signalling would impair the proper functioning and/or development of tissues critical for embryo-foetal development (EFD) leading to embryo-foetal lethality and teratogenicity. Studies in knock out mice have shown developmental abnormalities, including defects in neural tube derivatives, testes, kidneys, heart and vascular system, diaphragm, skeletal system, skin, hair, teeth, eyes, and palate, are likely to result from disruption of PDGFR-α signalling (Morrison-Graham et al. 1992, Soriano 1997, Tallquist and Soriano 2003).

A pilot EFD study (Report 8323353) was conducted using the mouse surrogate antibody of olaratumab (1E10) with the goal of demonstrating the severe developmental abnormalities suggested by the available knock-out mouse data. Only minor developmental variations were observed, however, developmental results from the pilot study were inconclusive based on several confounding factors; including endotoxin contamination in the dose solutions, poor pregnancy rate, and an unusually high number of dosing procedure deaths. Because the pilot study was not interpretable from a developmental perspective, a definitive GLP mouse embryofoetal toxicity and toxicokinetics study (Study 8332306) was subsequently conducted with the olaratumab surrogate mouse antibody (IMC-1E10) administered once every 3 days during organogenesis to pregnant mice. In foetuses collected from the 50 mg/kg (mid dose) and 150 mg/kg (high dose) maternal groups, there were increased incidences of malformations consisting of open eye and partially open eye as well as increased incidences of skeletal variation frontal/parietal additional ossification site confirming a developmental hazard consistent with that previously demonstrated by the knockout mouse model.

No animal studies have been performed to test olaratumab for fertility impairment.

Toxicokinetic data

<u>Study 7573-104</u>

The toxicokinetic behaviour of IMC-3G3 was nonlinear following Doses 1 and 4.

Statistical significance between males and females was observed in mean Cmax and mean AUC_{inf} values in the high dose group only.

After the first I.V. dose, $AUC_{0\text{-}inf}$ increased more than proportionally with dose whereas C_{max} appeared to increase in a dose proportional manner. The elimination T½ for olaratumab increased with dose from approximately 1.6 days to >5 days while clearance decreased in high dose males. Trough serum olaratumab concentrations (C_{min}) measured prior to the second dose (2 weeks following the first dose), were detectable for both males and females. Following the third and fourth doses, most pre-dose serum levels increased relative to their respective values at the second dose, suggesting olaratumab accumulation in serum over time.

Following Dose 4, rapid IMC-3G3 clearance was observed in some animals in all dose groups. In animals with normal IMC-3G3 clearance following Dose 4, exposure generally increased in a greater than dose-proportional manner in all dose groups.

Immunogenicity analysis indicated that all pre-dose samples were negative for antibodies capable of binding IMC-3G3. In the 5-mg/kg group, one of six Dosing Phase Day 35 samples was negative and five samples were reported as positive for an immune response. In the 16-mg/kg group, all Dosing Phase Day 35 samples were reported as negative. In the 50-mg/kg group, nine samples were reported as indeterminate due to the concentration of IMC-3G3 (≥ 10 µg/mL) in the samples and one sample was reported as negative. All Recovery Phase Day 48 samples from the 50-mg/kg group were reported as negative.

In addition, while many indeterminate ADA assignments were made in the 50-mg/kg dose group due to interference from circulating olaratumab, the one animal in the 50-mg/kg group that did exhibit rapid drug clearance on Day 29 after the fourth I.V. dose was negative for ADA on Day 35 in association with Day 36 olaratumab serum concentrations that were below the lower limit of quantification (LLOQ).

Study 7573-105

After a single I.V. dose, the T½ values increased with dose from 2.7 to 5.7 days and clearance decreased with increasing dose level. The estimated volume of distribution at steady state (Vdss) after 13 weekly doses spanned the range of 32 to 39 mL/kg. Examination of Cmax and pre-dose (trough) concentrations at steady state indicated that drug accumulation occurred in all dose groups over the 13-week study. Mean AUC0-inf and Cmax at Week 13 increased up to 2.2-fold and 1.5-fold respectively, across all dose groups relative to the first dose. Clearance decreased up to 57% by Dose 13. Rapid clearance of olaratumab was observed in 5 of 6 animals (3 males and 2 females) in the low-dose group and in 1 male of 6 animals in the mid-dose group, although rapid clearance was not observed in any high dose group animals after repeated doses in the 13-week study. In the low-dose group, the 5 animals that exhibited rapid clearance were all positive for ADA response on Day 91.

Study 8201-325

After IV infusion, IMC-3G3 concentrations slowly declined, generally in a bi-exponential manner. The mean t1/2 values determined only from the recovery animals on Day 267 ranged from 28.2 to 76.1 hours. Mean CL values on Days 120 and 267 ranged from 0.252 to 0.451 mL/hr/kg and generally appear to be dose and time independent.

Mean Vz values determined only from recovery animals on Day 267 ranged from 8.23 to 24.6 mL/kg, did not distribute beyond vasculature, and appeared to be dose independent. No apparent gender differences (> 2-fold) were observed in IMC-3G3 mean Cmax and AUC0-168 values. Values for mean Cmax and AUC0-168

were approximately 40 to 140% higher on Day 120 and 40 to 180% higher on Day 267 than on Day 1, indicating potential accumulation of IMC-3G3 after multiple dosing in cynomolgus monkeys.

The increases in mean Cmax and AUC0-168 for males and females were generally dose proportional.

Several animals (n=8; 5 in Group 2, 2 in Group 3, and 1 in Group 4) had measurable anti-drug-antibody (ADA) on Days 120 and 267, resulting in significantly lower IMC-3G3 concentrations in those animals.

Pre/postnatal development studies have not been submitted in this application.

Local Tolerance

Local tolerance was investigated in the 5-week and 26-week repeat-dose toxicity evaluations in cynomolgus monkeys by clinical observations, and as part of the histopathological evaluations (Reports 7573-104, 7573-105, and 8201-235). Intravenous administration of olaratumab was well tolerated and no treatment-related adverse reactions at the injection site were observed.

Other toxicity studies

Species Strain	Route	Duration of Dosing	Doses	Number of Tissues	Noteworthy Findings	Report
Human	In vitro /immunohistochemical staining	NA	1, 5, and 10 µg/mL	5 tissues for human	Staining of PDGFRα expressing elements using immunohistochemistry could not be achieved with olaratumab (IMC-3G3).	IM1236P
Human, Cynomolgus monkey	In vitro /immunohistochemical staining	NA	3 and 20 µg/mL	3 sources/tissue for human and 2 sources/tissue for monkey	Anti-PDGFRα staining patterns were consistent between the human and cynomolgus monkey tissues.	IM1236

A tissue cross reactivity study using a commercially available rabbit anti-human PDGFRα antibody revealed similar staining patterns in human and cynomolgus macaque tissues, further supporting the use of cynomolgus monkeys for toxicology testing. Many, but not all, of the cell types demonstrating staining with the Anti-PDGFRα antibody in this study have been reported to express PDGFRα.

2.3.5. Ecotoxicity / environmental risk assessment

Olaratumab is a protein, which is expected to biodegrade in the environment and not be a significant risk to the environment. Thus, according to the "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (EMEA/CHMP/SWP/4447/00), olaratumab is exempt from preparation of an Environmental Risk Assessment as the product and excipients do not pose a significant risk to the environment.

2.3.6. Discussion on non-clinical aspects

Olaratumab is a PDGFRα antagonist. The preclinical in vitro PD data show that olaratumab binds to human PDGFRα with high affinity. In addition to blocking ligand-induced receptor phosphorylation and cell mitogenesis in cancer cells and normal stromal fibroblasts, olaratumab inhibits ligand-induced phosphorylation of the downstream signalling molecules Akt and MAPK in multiple tumour cell lines. As a

result, in cultured cancer cells, olaratumab treatment inhibited ligand-dependent growth of human tumour cell lines.

The in vivo studies showed that olaratumab was able to inhibit tumour growth as a single agent in human PDGFRα-expressing tumour xenograft models (glioblastoma, leiomyosarcoma, rhabdoid cancer, NSCLC). In addition, olaratumab is able to downmodulate PDGFRα after one or two doses in a glioblastoma animal model, and reduces the establishment and progression of skeletal metastasis in an animal model of prostate cancer. Combination of olaratumab with doxorubicin in leiomyosarcoma and osteosarcoma models increased tumour growth inhibition compared to either treatment alone.

Overall, Olaratumab has been shown to bind human PDGFRα and to inhibit the activation of the receptor induced by its ligands. The relevance of the signalling pathways involving PDGFRα has been identified in different cancer cell types and in particular in soft tissue sarcomas. The in vitro and in vivo results are deemed relevant for the proposed indication, although the identification of the mechanism of action could not be fully elucidated, in light of the discrepancies noted throughout all studies. The Applicant discussed the necessity of identifying additional biomarkers predictive of olaratumab response. In the context of the ongoing Phase 3 confirmatory trial (JGDJ), the applicant will further explore the expression of PDGFRα, PDGFRβ, PDGF-A, PDGF-B, PDGF-C, PDGF-D, EGF, TGFα, EGFR, VEGFa, CXCR4, TGFb, TOPO2A, and GLI1; and key downstream pathways such as the Akt pathway with the aim of a better understanding of olaratumab's mechanism of action.

Efficacy in reducing tumour growth in experimental animal is associated with plasmatic concentrations above 200 µg/mL, achieved in immunodeficient mice with doses of 60 mg/kg. The evidences obtained in primary pharmacodynamic studies are adequate to support clinical evaluation in humans.

The PK profile of olaratumab was consistent with that expected for a monoclonal antibody, with a T½ of 6-7 days in mice and 2-3 days in monkeys. Systemic exposure increased with dose in mice and monkeys. In repeated dose toxicity studies in monkeys, olaratumab accumulated by a factor of 1.4- to 2.4 between first and last dose. No sex-related differences were observed. Olaratumab ADAs were detected in several serum samples in monkey studies. In mice, the embryo-foetal study suggests that the murine surrogate 1E10 can be transferred from maternal to foetal blood.

Toxicity studies in monkeys showed no olaratumab-related adverse effects, with only a no-adverse mild to moderate increase in alanine aminotransferase levels, minimal individual cell necrosis and moderate infiltrates in the liver observed in one female treated at the highest dose in the 39-week study. In this study, monkey serum C_{min} was 1164 µg/mL at the no observed adverse effect level (NOAEL) of 75 mg/kg, which was approximately 4.5- to 7.5-fold greater than the threshold C_{min} believed to be needed for antitumor activity based on tumour xenograft models (155 to 258 µg/mL). The $AUC_{0-168hr}$ following the last infusion of 75 mg/kg was 284976 µg•hr/mL, which was approximately 16.5-fold greater than olaratumab exposure anticipated for antitumor activity in humans based on animal tumour models (AUC0-96hr = 17184 µg•hr/mL).

Studies to assess the genetic toxicity of olaratumab have not been conducted, which is in line with ICH Guidances S6 and S9. There is no cause for concern based on the mechanism of action and physicochemical makeup of olaratumab as is not expected to react with DNA or other chromatid material.

Carcinogenicity studies are not warranted to support marketing for therapeutics intended to treat patients with advanced cancer (ICHS9). In addition, there were no findings observed in the 39-week repeat-dose study in monkeys that would indicate a carcinogenicity risk; thus, carcinogenicity studies have not been conducted.

Regarding reproductive toxicity, the Applicant has submitted a comprehensive summary of the scientific literature regarding the relevance of PDGF/PDGFRα in embryo-foetal development. PDGFRα activity has been demonstrated in human, mouse and other nonmammalian tissue; however, as olaratumab is the first monoclonal antibody directed specifically to PDGFRα, no information about the toxicity of other compounds of the same class is available. It is acknowledged that due to the wide range of effects of PDGFRα in embryo/neonate viability, brain, lung, eye, skin, CNS and heart development it is highly probable that perturbation of the PDGFR pathway will lead to toxic effects on human embryo-foetal development. However, results of the pilot embryo-foetal development study in mice with the olaratumab surrogate IMC-1E10 show only some non-adverse effects in ossification at high doses, although interpretation of these data was confounded by the presence of endotoxin in dose formulations, poor pregnancy rate and an unusually high number of dosing procedure deaths. The Applicant also submitted the results of a GLP-compliant study (Embryo-foetal developmental and toxicokinetic study in mice given LSN3338786). This study confirmed the increased incidences of malformations (abnormal eyelid development) and skeletal alterations (frontal/parietal additional ossification site) at exposures less than the AUC exposure at the maximum recommended human dose of 15 mg/kg olaratumab. Thus, the potential risk to foetal development was included in section 5.3 of SmPC.

The Applicant also claims regulatory and ethical reasons not to conduct a reprotoxicity study in non human primates. Considering the involvement of PDGFRα in embryo-foetal development, it seems reasonable to believe that even if no adverse effects were observed in primates, patients and prescribers would still be informed with appropriate labelling of the potential risks of olaratumab to reproduction. Also taking into account the severity of the disease and the target population of olaratumab, a reproductive toxicity study in monkeys is not considered indispensable for marketing authorization.

There are no or limited amount of data from the use of olaratumab in pregnant women. As a consequence, olaratumab is not recommended during pregnancy and in women of childbearing potential not using contraception, unless the potential benefit justifies the potential risk to the foetus. Women of childbearing potential should be advised to avoid becoming pregnant while on olaratumab and should be informed of the potential hazard to the pregnancy and foetus. Women of childbearing potential should be advised to use effective contraception during treatment and for at least 3 months following the last dose of olaratumab.

It is not known whether olaratumab is excreted in human milk. Human IgG is excreted in human milk, therefore breast-feeding is not recommended during treatment with olaratumab and for at least 3 months following the last dose.

Olaratumab is composed of natural amino acids, the use of which will not alter the concentration or distribution of amino acids in the environment. Therefore, olaratumab is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The pharmacologic, pharmacokinetic, and toxicological characteristics of olaratumab are well characterized. Non-clinical data reveal no special hazard for humans based on repeat dose toxicity studies in monkeys.

The mechanism of action of olaratumab is not fully understood and the applicant will provide further biomarker evaluation predictive of response within the context of the confirmatory phase 3 study JGDJ.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study Code (location in CTD)	Population	Study Characteristics [Primary Objective]	Dose Regimen of Olaratumab, Route of Administration and Formulation
I5B-IE-JGDG[d] IMCL CP15-0806	Advanced Soft Tissue Sarcoma	Phase 1b non-randomized, Phase 2, randomized, open-label multicenter [Safety, Efficacy]	Phase1b – Olara: 15 mg/kg, Days 1 and 8, Q3W Phase2, Arm A - Olara: 15 mg/kg, Days 1 and 8 + Dox: 75 mg/m^2, Day 1, Q3W Phase 2, Arm B - Dox: 75 mg/m^2, Day 1, Q3W
I5B-IE-JGDB[d] IMCL CP15-0804	Non-Small Cell Lung Cancer, previously untreated locally advanced or metastatic	Phase 2, open-label, non-blinded, randomized, multicenter [Efficacy]	Arm A - Olara: 15 mg/kg, Days 1 and 8, Q3W + P: 200 mg/m^2 + C[b]; Q3W Arm B – P: 200 mg/m^2 + C; Q3W
I5B-IE-JGDD IMCL CP15-0805	Prostate cancer, metastatic, castration refractory following progressive disease or intolerant to docetaxel chemotherapy	Phase 2, open-label, randomized, multicenter [Efficacy]	Arm A - Olara: 15 mg/kg, Days 1, 8 Q3W + M: 12 mg/m^2, Day 1 + Pr: 5 mg, BID daily, Q3W Arm B - M: 12 mg/m^2, Day 1 + Pr: 5 mg, BID daily, Q3W
I5B-IE-JGDE[d] IMCL CP19-0801	Recurrent glioblastoma multiforme	Phase 2, open-label, multicenter [Safety, Efficacy]	Olara: 20 mg/kg, Q2W or Ramucirumab: 8 mg/kg, Q2W
I5B-IE-JGDH[d] IMCL CP15-1008	Previously treated with unresectable and/or metastatic GIST; Cohort 1: with PDGFRα mutations, Cohort 2: without PDGFRα mutations	Phase 2, open-label, two-stage, multicenter, multinational [Safety, Efficacy in 2 molecularly distinct GIST subsets]	20 mg/kg, Q2W
I5B-IE-JGDI	Advanced Soft Tissue Sarcoma	Phase 1, open-label, multicenter [PK, DDI, Safety]	Olara: 15 mg/kg, + Dox: 75 mg/m^2, 21-day Cycle[a]
I5B-IE-JGDC IMCL CP15-0601	Advanced solid tumours and lymphomas	Phase 1, open-label, multicenter, dose-escalation [Safety, MTD]	4, 8, 16 mg/kg, QW, 4 Weeks on, 2 weeks off 15, 20 mg/kg, Q2W, 2 Weeks on, 2 weeks off
I5B-IE-JGDF IMCL CP15-0907	Japanese patients with advanced solid tumours	Phase 1, open-label, single-center, single-arm, dose-escalation [Safety, PK profile]	10 mg/kg, Days 1 and 8 Q3W 20 mg/kg, Q2W, IV 15 mg/kg, Days 1 and 8 Q3W
I5B-IE-JGDA IMCL CP15-0802	Ovarian cancer, platinum-refractory or platinum-resistant advanced	Phase 2, open-label, non-blinded, randomized, multicenter [Efficacy]	Arm A - Olara: 20 mg/kg, Q2W LDox: 40 mg/m^2, Q4W Arm B - LDox 40 mg/m^2, Q4W

Abbreviations: AUC = area under the curve; BID = twice daily; C = carboplatin; CrCl = creatinine clearance; CSR = clinical study report; CTD = Common Technical Document; DDI = drug-drug interaction; Dox = doxorubicin; GIST = gastrointestinal stromal tumours; IV = intravenous; LDox = liposomal doxorubicin; M = mitoxantrone; MTD = maximum tolerated dose; NPK = number of patients with pharmacokinetic assessment; Olara = olaratumab; P = paclitaxel; PDGFRα = platelet-derived growth factor receptor alpha; PK = pharmacokinetics; Pr = prednisone; QW = once every week; Q2W = once every 2 weeks; Q3W = once every 3 weeks; Q4W = once every 4 weeks.

a Detailed description of the study design can be found in the CSR.

b The dose of carboplatin administered was calculated based on the patient's actual body weight at each treatment visit and the target AUC dosing. The dose of carboplatin was calculated in mg as follows, using the modified Calvert formula based on CrCl: Carboplatin dose (in mg) = Target AUC x (CrCl + 25).

c Due to deficiencies associated with the original bioanalytical method, olaratumab concentrations determined using the original bioanalytical method are presented as supportive evidence only in the current application and can be found in the individual study CSRs.

d Studies in the Population PK analysis.

The PK of olaratumab was primarily characterized in a PopPK analysis including data from the following 4 studies.

Table 3: Studies used for the PopPK analysis of olaratumab

Study Code	$N_{Patients}$	Cancer Indication	Dose (mg/kg)
I5B-IE-JGDB (CP12-0715)	50	NSCLC	15
I5B-IE-JGDE (CP12-1026)	7	GBM	20
I5B-IE-JGDG (CP12-0922)	95	STS	15
I5B-IE-JGDH (CP12-0708)	19	GIST	20

2.4.2. Pharmacokinetics

Absorption

Olaratumab is administered as an intravenous infusion only and is therefore completely bioavailable.

Distribution

Traditional protein-binding studies using human serum ALB as conducted for small molecules are not applicable to therapeutic biologics Further, non-specific interactions with plasma proteins were not expected to occur with olaratumab. Therefore, plasma protein binding studies were not conducted with olaratumab.

The population pharmacokinetic (PopPK) model-based mean (CV %) volume of distribution of olaratumab at steady state (Vss) was 7.7 L (16 %).

Elimination

No studies on the metabolism of olaratumab have been performed in humans.

The PopPK model-based mean (CV %) clearance for olaratumab was 0.56 L/day (33 %). This corresponds to a mean terminal half-life of approximately 11 days.

Dose proportionality and time dependencies

Phase 1 Study JGDC was conducted to establish the safety profile and maximum tolerated dose of olaratumab. Patients with advanced solid tumours and lymphomas who no longer responded to standard therapy or for whom no standard therapy was available were enrolled in 5 cohorts. Patients in Cohorts 1 through 3 received doses 4, 8, and 16 mg/kg, respectively. A treatment cycle consisted of olaratumab administered IV, once every week for 4 weeks followed by a 2- week observation period for each 6-week cycle (for a total of 4 doses per cycle). Patients in Cohorts 4 and 5 received doses of 15 mg/kg and 20 mg/kg, respectively. A treatment cycle consisted of olaratumab, administered IV, every 2 weeks for each 4-week cycle, for a total of 2 doses per cycle.

A total of 19 patients were treated with olaratumab as monotherapy in Study JGDC.

An NCA was conducted on 4 patients from Cohort 1, 3 patients from Cohort 2, 5 patients from Cohort 3, 3 patients from Cohort 4, and 3 patients from Cohort 5.

Olaratumab C_{max} and AUC(0-168) increased with dose across the dose range tested. Olaratumab geometric mean $t_{1/2}$ ranged from 3.08 to 8.96 days following both single and multiple infusions.

Table 4: Summary of olaratumab PK parameters following the first dose (Day 1) of olaratumab administered as 1.5-hour IV infusion to cancer patients (Study JGDC)

	Geometric Mean (CV%)				
Dosing Regimen	**4 mg/kg (N=5)[a] qw**	**8mg/kg (N=3) qw**	**16mg/kg (N=5)[a] qw**	**15 mg/kg (N=3) q2w**	**20 mg/kg (N=3) q2w**
C_{max} (µg/mL)	74.4 (31)	196 (39)	538 (4)	477 (38)	760 (116)
t_{max} (h)[b]	2.33 (2.00-5.00)	1.53 (1.50-2.08)	2.32 (2.23-2.58)	2.53 (2.00-2.75)	2.53 (1.73-5.50)
C_{last} (µg/mL)	20.922; 21.861[c]	28.502; 42.378[c]	149 (38)	95.6 (8)	103.601; 103.400[c]
$AUC_{(0-168)}$ (µg•h/mL)	7220; 6910[c]	7860; 14500[c]	40300 (27)	42400 (23)	44500 (66)
$AUC_{(0-\infty)}$ (µg•h/mL)	9600; 9560[c]	10100; 19500[c]	43100[f]	103000; 91900[c]	NC
$t_{1/2}$ (days)[g]	3.44; 3.72[c]	3.08; 3.63[c]	4.46 (3.81-5.08)	7.21 (6.83-7.79)	7.67[f]
CL (L/h)	0.0334; 0.0339[c]	0.0447; 0.0247[c]	0.0293[f]	0.0156; 0.0113[c]	NC
V_z (L)	3.99; 4.36[c]	4.77; 3.11[c]	3.87	3.67; 2.74[c]	NC

[a] n =3 for all parameters. (In the 4 mg/kg dose cohort, Patient #1004 samples were collected only up to 4.2 hr and were excluded from PK analysis; and Patient #1001 samples were collected in Week 2. In the 16 mg/kg dose cohort. Patient #3001 and Patient #3002 sample record showed samples were thawed and removed from PK analysis).
[b] Median (range)
[c] The values separated by semicolon are given when n=2.
[d] The last scheduled sampling time point is 168 hr post the end of infusion.
[e] The last scheduled sampling time point is 336 hr post the end of infusion.
[f] The value is given when n=1.
[g] Geometric Mean (range)
Note: N = number of patients dosed and n= number of observations, NC = Not calculated

There is no indication of a dose-dependent change in the clearance however data available are limited (see figure below).

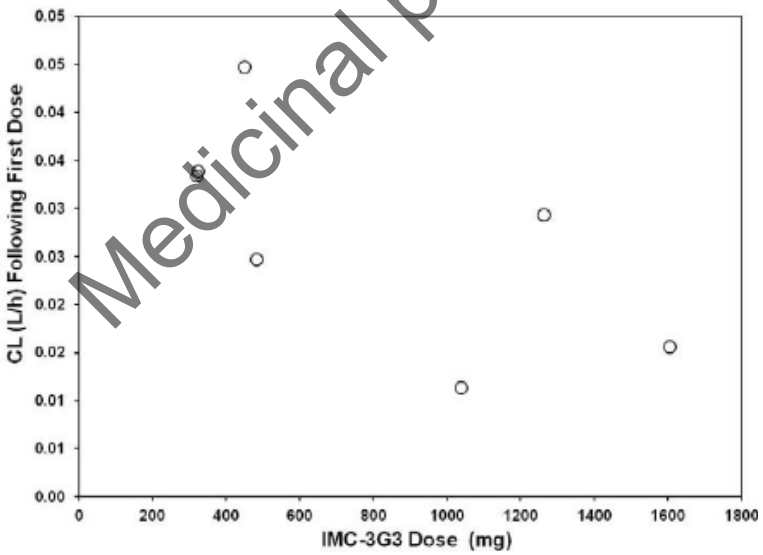


Figure 3: Olaratumab clearance (CL) following the first infusion (first dose) versus dose (Study JGDC)

Study JGDF, a Phase 1, dose-escalation study enrolled Japanese patients with advanced solid tumours who had not responded to standard therapy or for whom no standard therapy was available. Patients were enrolled sequentially into 1 of 3 cohorts, each comprising a minimum of 3 patients. Patients in Cohort 1 received olaratumab at a dose of 10 mg/kg on Days 1 and 8 every 3 weeks, patients in Cohort 2 received a dose of 20 mg/kg every 2 weeks, and patients in Cohort 3 received a dose of 15 mg/kg on Days 1 and 8 every 3 weeks.

A total of 16 Japanese cancer patients were treated with olaratumab.

An NCA was conducted for 3 patients from Cohort 1, 6 patients from Cohort 2, and 6 patients from Cohort 3. Olaratumab $t_{1/2}$ ranged from 4.06 to 9.38 days following single- and multiple dose administration in both dosing schedules.

Table 5: Summary of olaratumab PK parameters following the first dose of olaratumab administered as 1-hour IV infusion to Japanese cancer patients (Study JGDF)

	Geometric Mean (CV%)[a]		
	10 mg/kg (N=3)[b,c]	15 mg/kg (N=6)[c]	20mg/kg (N=6)
Regimen	**q3w**	**q3w**	**q2w**
C_{max} (µg/mL)	362.322; 436.172	587 (40)	735 (29)[h]
t_{max} (h)[d]	1.20; 1.73	1.45 (1.18-9.14)	2.22 (1.27-3.28)[h]
C_{last} (µg/mL)	203.320; 176.762	173 (46)	110 (19)
t_{last}(h)[d]	167.50; 167.37	167.63 (166.95-168.87)	336.21 (335.68-336.34)
$AUC_{(0\text{-}168)}$ (µg•h/mL)	NC	48000 (47)[f]	63400 (21)
$AUC_{(0\text{-}tlast)}$ (µg•h/mL)	35500; 35600	43600 (45)	92500 (20)[e]
$AUC_{(0\text{-}\infty)}$ (µg•h/mL)	NC	NC	126000 (12)[h]
$t_{1/2}$ (Days)[e]	5.33; 6.38	7.29 (6.04-9.38)[g]	6.42 (4.42-8.00)[h]
CL (mL/h/kg)	NC	NC	0.159 (12)[h]

[a] The values separated by semicolon are reported when n = 2
[b] n = 2 for all parameters. For 1 patient samples were not collected for initial 168 hr so excluded from PK analysis.
[c] C_{max}, C_{last}, $AUC_{0\text{-}168}$ and $AUC_{0\text{-}tlast}$ are calculated following the first infusion (Day 1) and $t_{1/2}$ is calculated following second infusion (Day 8) in Day-1 and Day-8 dosing in 21-day cycle (q3w)
[d] Median (range)
[e] Geometric Mean (range)
[f] n = 4
[g] n = 3
[h] n = 5
NC Not calculated
Note: N = number of patients dosed and n= number of observations

The terminal elimination half-life ($t_{1/2}$) ranged from 4.42 to 9.38 days across all dose ranges and dosing schedule. Due to the relative short PK sampling time (336 hours) post end of infusion, the true terminal elimination phase may not have been completely captured and accurately estimated. Therefore, $t_{1/2}$ and its associated parameters including AUC(0-∞) and CL should be interpreted with caution. PK parameters, including AUC(0-∞), CL, and Vz, were not calculated for the 10-mg/kg and 15-mg/kg (q3w) dose groups because of unique dosing schedule (patients received first infusion on Day 1 and second infusion on Day 8 in a 21-day-cycle [q3w]). Olaratumab Cmax following the first infusion appeared to increase with dose.

There was no apparent difference in the time course of olaratumab serum levels between Japanese patients and United States patients (Study JGDC).

- **Time dependency**

In study **I5B-IE-JGDC** Olaratumab showed accumulation after multiple infusions for both dosing schedules, with accumulation ratios (RA,AUC) ranging from 1.50 to 4.26.

Table 6: Summary of olaratumab PK parameters following multiple doses (fourth dose for 4, 8 and 16 mg/kg every week and third dose for 15 and 20 mg/kg every 2 weeks of olaratumab administered as 1-hour IV infusion to cancer patients (Study JGDC)

	Geometric Mean (CV%)				
	4 mg/kg (N=5)[a]	8mg/kg (N=3)	16mg/kg (N=5)	15 mg/kg (N=3)	20 mg/kg (N=3)
$C_{max,mul}$ (µg/mL)	107.348; 164.183	270 (59)	1460 (101)[b]	772.264; 763.292[c]	1610 (39)
t_{max} (h)[d]	2.08 ; 1.58	3.00 (2.00-3.00)	3.17 (1.50-3.42)[b]	1.08; 2.08[c]	3.02(1.18-9.17)
C_{last} (µg/mL)	8.167; 26.929	36.908[i]	188 (46)[e]	152.435; 287.289[c]	208 (27)
$AUC_{(0-168)}$ (µg•h/mL)	9290; 14200	48700; 22800[c]	73600 (53)[e]	70900; 56300	93600 (15)
$AUC_{(\tau)}$ (µg•h/mL)	9290; 14200[f]	48700; 22800[c,f]	73600 (53)[e,f]	114000[g,i]	139000 (13)[g]
$t_{1/2}$ (days)[h]	3.69; 6.33	5.25 (4.25-6.08)	6.46 (4.79-8.71)[e]	8.96[i]	7.71 (5.92-11.3)
CL_{ss} (L/h)	0.0362; 0.0228	0.0223; 0.0213[c]	0.0198 (53)[e]	0.00993[i]	0.0112 (17)
V_{ss} (L)	4.45; 4.92	4.68; 3.99[c]	4.57 (50)[e]	3.01[i]	2.85 (19)
$R_{A,AUC}$[j]	2.08[i]	1.58[i]	2.03 (29)[b]	2.37[i]	4.26; 1.84[c]

[a] n = 2 for all parameters. For Patient #1002 and Patient #1003 data are not available for Week 4 and for Patient # 1004 Week data excluded from analysis since time gap between 1st dose and 4th dose was six weeks and first two infusions were partial infusions.
[b] n= 3
[c] The values separated by semicolon are given when n=2
[d] Median (range)
[e] n = 4
[f] The dosing interval (τ) is 168 hr
[g] The dosing interval (τ) is 336hr
[h] Geometric Mean (range)
[i] The value is given when n=1
[j] Intercycle accumulation of IMC-3G3 calculated as AUC_{τ} (fourth dose for 4, 8, and 16 mg/kg [qw] and third dose for 15 and 20 mg/kg [q2w])/AUC_{0-168} (first dose) for 4, 8, and 16 mg/kg [qw] and AUC_{0-336} for 15 and 20 mg/kg [q2w].
Note: N = number of patients dosed and n= number of observations

In Study **I5B-IE-JGDF**, in all the 3 doses tested, some accumulation of olaratumab was observed following multiple infusions, with intercycle accumulation ratios (RA, AUC) ranged from 1.30 to 1.72.

Table 7: Summary of olaratumab PK parameters following multiple doses (cycle 2) of olaratumab administered as 1-hour IV infusion every 2 weeks (20 mg/kg) and every 3 week dosing (Day 1 and Day 8 dosing in 21 days cycle for 10 and 15 mg/kg) to Japanese cancer patients (Study JGDF)

	Geometric Mean (CV%)[a]		
	10 mg/kg (N=3)[b]	15 mg/kg (N=6)[b,c]	20mg/kg (N=6)[d]
Regimen	**q3w**	**q3w**	**q2w**
C_{max} (µg/mL)	658.391; 546.854[e]	920.832[e]	1160 (91)
t_{max} (hr)[f]	1.74; 2.21[e]	2.18[e]	2.21 (1.70-3.30)
C_{last} (µg/mL)	151.101; 121.188	360.948	181 (37)
t_{last} (hr)[f]	481.75; 500.45	506.60	338.36 (330.09-360.59)
$C_{av,ss}$ (µg/mL)	320; 270	633	365 (29)
$AUC_{(0-168)}$ (µg•h/mL)	53500; 44200	82800	77400 (30)
AUC_{τ} (µg•h/mL)	NC	NC	123000 (29)[g]
$t_{1/2}$ (Days)[h]	4.06; 7.33[i]	8.25[i]	7.33 (5.42-8.83)
CL_{ss} (mL/h/kg)	NC	NC	0.163 (29)
R_A (AUC)[j]	1.55	1.38	1.46 (15)

[a] The value is reported when n = 1 and values separated by semicolon are reported when n = 2
[b] Patient received first infusion on Day 1 and second infusion on Day 8 in 21-day cycle [q3w]
[c] n = 1 for all parameters
[d] n = 3 for all parameters
[e] C_{max}, t_{max} and $AUC_{(0-168)}$ are calculated following the first infusion (Day 1) in Day-1 and Day-8 dosing in 21-day cycle [q3w]
[f] Geometric Mean (range)
[g] Dosing interval (τ) is 336 hour
[h] Geometric Mean (range)
[i] $t_{1/2}$ is calculated following second infusion (Day-8) in Day-1 and Day-8 dosing in 21-day cycle [q3w]
[j] Intercycle accumulation of olaratumab calculated as $AUC_{(0-504)}$ (Cycle 2)/$AUC_{(0-504)}$ (Cycle 1) for 10 and 15 mg/kg (q3w) and $AUC_{(0-336)}$ (Cycle 2)/$AUC_{(0-336)}$ (Cycle 1) for 20 mg/kg (q2w)
NC Not calculated
Note: N = number of patients dosed and n= number of observations

Intra- and inter-individual variability

The population PK model showed a low to moderate inter-individual variability (%CV) for CL (33.3%) and for V1 (15.6%).

Pharmacokinetics in target population

Population pharmacokinetic analysis

A Population PK analysis was performed pooling data from 4 studies (JGDB, JGDE, JGDG, JGDH) where olaratumab was administered at 2 dose levels (15 mg/kg and 20 mg/kg) and with different dose intervals (Days 1 and 8 of a 21-day cycle, and Day 1 of a 14-day cycle). In these studies, olaratumab was administered both as a single agent and in combination with several chemotherapeutic drugs (doxorubicin, paclitaxel/carboplatin) and to patients with several tumour types.

The PK of olaratumab was characterized by means of nonlinear mixed-effect modeling using the program NONMEM Version 7.3. The population PK dataset included data from 171 patients whose ages ranged from 22 to 82 years at study entry and who weighed between 37.3 and 151 kg. The number of PK samples per patient ranged from 1 to 54 with a median of 5 samples.

The PK of olaratumab was well characterized by a 2-compartment PK model, and olaratumab elimination was best characterized by a linear clearance term. The model appeared to perform adequately. The population

estimates of Vss (7.74 L) and CL parameters (0.0233 L/h) were essentially those expected for an IgG antibody.

Nonlinear saturable clearance did not significantly contributed to overall clearance, indicating that at therapeutic doses there is saturation of target-mediated drug disposition. WTE was found to be a significant covariate for both CL and V1. Tumour size was also found to have a significant effect on CL, with a larger tumour burden associated with higher CL. However, taking into account that saturable, target-mediated clearance did not contribute significantly to the overall clearance, this finding is difficult to interpret. Inter-patient variability on the PK parameters of the final PopPK model was 33.3% for CL and 15.6% for V1.

The parameter estimates of the final PopPK model are shown in the table below.

Table 8: Pharmacokinetic and covariate parameter estimates in the final population model

Parameter Description	Population Estimate (%SEE)	Inter-Patient Variability (%SEE)
Structural Model		
Clearance, CL (L/h)	0.0233 (3.67)	33.3% (12.9)
Central Volume of Distribution, V_1 (L)	4.16 (1.79)	15.6% (30.1)
Peripheral Volume of Distribution, V_2 (L)	3.58 (13.2)	
Inter-compartmental clearance rate, Q (hr^{-1})	0.0315 (25.8)	
Covariate Effects		
WTE_{CL}[a]	0.431 (10.2)	
WTE_{V1}[b]	0.610 (12.9)	
$TUMR_{CL}$[a]	0.00158 (25.8)	
Residual Error		
Additive (µg/mL)	10.1 (15.5)	
Proportional	22.5% (18.1)	

Abbreviations: CL = clearance; V_1 = central volume of distribution; SEE = standard error of estimate; $TUMR_{CL}$ = tumor size effect on clearance; WTE_{CL} = body weight effect on clearance; WTE_{V1} = body weight effect on central volume of distribution.

[a] $CL_{ind} = CL * (WTE/median(WTE))^{\wedge}WTE_{CL} * (1 + TUMR_{CL} * (TUMR - median(TUMR))$

[b] $V_{1ind} = V_1 * (WTE/median(WTE))^{\wedge}WTE_{V1}$

Special populations

- **Impaired renal function**

No formal studies have been conducted to evaluate the effect of renal impairment on the PK of olaratumab. Renal function (as calculated by Cockcroft-Gault creatinine clearance [CLcr; range investigated 40.2-250 mL/min]) in the PopPK analysis was found to be non-significant when tested continuously. The effect of renal function on the pharmacokinetics of olaratumab was evaluated based on data from 143 patients: 85 patients had normal renal function, 43 patients had mild renal impairment (CLcr = 60-89 mL/min), and 15 patients had moderate renal impairment (CLcr = 30-59 mL/min). No patients had severe renal impairment.

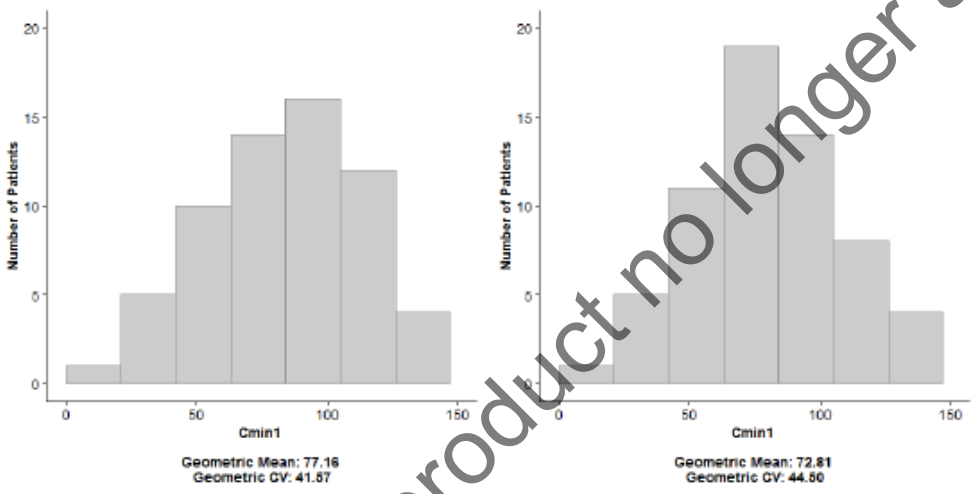
- **Impaired hepatic function**

No formal studies have been conducted to evaluate the effect of hepatic impairment on the PK of olaratumab. Hepatic function in the PopPK analysis (as assessed by alanine aminotransferase [4-88 U/L], aspartate transaminase [5-96 U/L], and total bilirubin [1.71-25.6 µmol/L]) was found to have no significant effect on

the pharmacokinetics of olaratumab. Hepatic function was evaluated based on the Liver Function Classification from the National Cancer Institute Organ Dysfunction Working Group (Ramanathan et al. 2008). The effect of hepatic function on the pharmacokinetics of olaratumab was evaluated based on data from 143 patients: 126 patients had normal hepatic function, 16 patients had mild hepatic impairment , and 1 patient had moderate hepatic impairment. No patients had severe hepatic impairment.

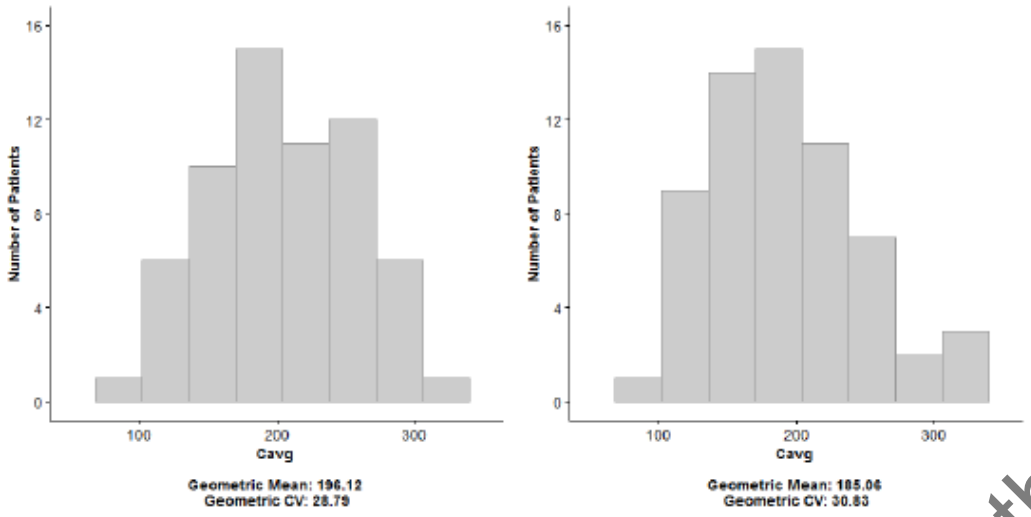
- **Weight**

In the PopPK analysis, body weight was found to have a significant effect on both the CL and V1. The effect of WTE was, however, less than directly proportional on both parameters, with exponent values of approximately 0.5. Compared with flat dosing, the body weight-based dosing paradigm currently adopted for olaratumab is therefore not expected to inflate PK variability on either CL or V1 (Zhang et al. 2012). This was verified by comparing the simulated time course of olaratumab when used at the dose of 15 mg/kg on Days 1 and 8 of a 21-day cycle with that when olaratumab is dosed at the dose of 1200 mg (following the same dosing regimen), which corresponds to the flat dose administered to a patient with the median WTE of 80 kg (see figures below).



Abbreviations: C_{min1} = trough serum concentration at the end of Cycle 1; CV = coefficient of variation.
Simulated distribution of C_{min1} values based on full compliance to dosing schedule. Left graph: distribution of C_{min1} with 15-mg/kg dose. Right graph: distribution of C_{min1} with 1200-mg dose for all patients.

Figure 4: Simulated distribution of Cmin1 in study JGDG following 15 mg/kg or 1200 mg dosing



Abbreviations: C_{avg} = average concentration over patient's entire treatment; CV = coefficient of variation.
Simulated distribution of C_{avg} values based on full compliance to dosing schedule. Left graph: distribution of C_{avg} with 15-mg/kg dose. Right graph: distribution of C_{avg} with 1200-mg dose for all patients.

Figure 5: Simulated distribution of Cavg in study JGDG following 15 mg/kg or 1200 mg dosing

- **Tumour size**

Tumour size at the time of study entry (evaluated as a continuous variable) was found to have an effect on CL, where a higher CL was associated with larger tumour size.

- **Gender, Race, Age**

Sex (84 males, 87 females), age (range, 22 to 82 years), or race (86% Caucasians, 8.8% African Descent, 1.8% Asians, 0.6% Hawaiians or Pacific Islanders, 2.9% others) did not have any effect on the pharmacokinetics of olaratumab.

- **Elderly**

Age, investigated in the range of 22 to 82 years was not a statistically significant covariate on the pharmacokinetics of olaratumab.

Table 9: Number of elderly patients in the PK trials

	Age 65-74 (Older subjects number / total number)	**Age 75-84 (Older subjects number / total number)**	**Age 85+ (Older subjects number / total number)**
PK Trials	7	1	0

- **Children**

No data in children are available The safety and efficacy of olaratumab in children aged 0 to 18 years of age have not yet been established.

Pharmacokinetic interaction studies

No in vitro data is available regarding interaction potential.

As the PopPK analysis was performed using a PopPK database containing olaratumab serum data collected from patients who received olaratumab as a single agent (n = 73) as well as in combination with paclitaxel/carboplatin (n = 45) or doxorubicin (n = 53), the assessment of the effect of doxorubicin and paclitaxel/carboplatin on the PK of olaratumab was performed by means of PopPK modeling. No difference in olaratumab clearance was observed between individuals who received olaratumab or in combination with chemotherapy, regardless of the combination examined. Likewise, there was no difference in V1 between patients who received olaratumab as a single agent and those who received olaratumab in combination with either paclitaxel/carboplatin or doxorubicin. Concomitant chemotherapy (doxorubicin or paclitaxel/carboplatin) had no clinically relevant effect on the pharmacokinetics of olaratumab.

In a dedicated study (JGDI) it was found that olaratumab had no effect on the PK of co-administered doxorubicin.

2.4.3. Pharmacodynamics

Mechanism of action

No mechanism of action studies has been conducted.

Primary and Secondary pharmacology

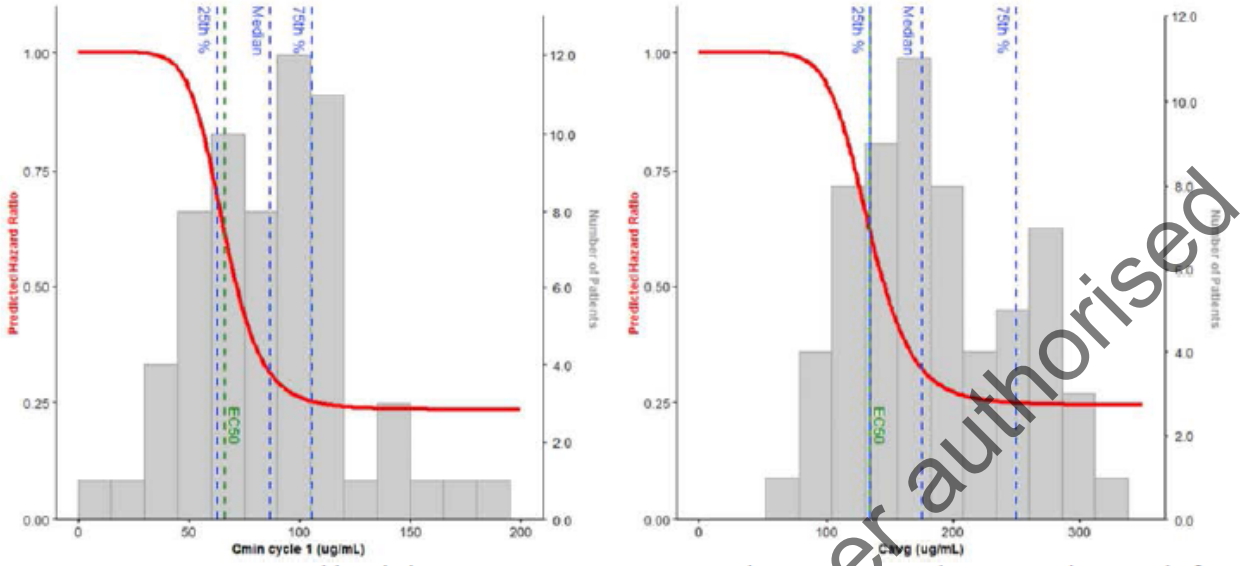
No pharmacodynamic (PD) study has been performed.

A **PK/PD analysis** to characterize the exposure-response relationship for efficacy (PFS and OS) and safety in patients with advanced STS. The source response data were from the final database used in the efficacy analyses for Study JGDG. OS and PFS were described using a time-to-event modelling approach implemented using NONMEM Version 7.3.

The PK exposure parameters were estimated using the final population PK model. Two exposure parameters were selected: 1) individual trough concentrations after the first treatment cycle (C_{min1}); 2) individual average concentrations throughout patients treatment (C_{avg}), defined as the overall AUC throughout the treatment duration divided by the duration of the treatment. For both PK endpoints, the effect of olaratumab on OS was best accounted for by an inhibitory E_{MAX} drug effect model with Hill coefficient on the hazard function.

Estimates for the baseline hazard and E_{MAX} parameters were similar regardless of the PK endpoint considered. For OS, E_{MAX}, with a value of approximately 0.75 in both models, corresponds to a maximum predicted 75% reduction in the hazard ratio, down to value of 0.25. In addition, with values of 66.1 and 134 µg/mL, respectively, the final $EC_{min1}50$ and $EC_{avg}50$ estimates correspond to the 25th percentile of the distribution of C_{min1} and C_{avg} in Study JGDG. ECOG and the number of prior lines of treatment were found to

be the only significant covariates affecting the baseline hazard for both the C_{min1}- and C_{avg}-based models. No covariates were found to impact the parameters describing olaratumab activity itself.



Abbreviations: C_{avg} = average concentration; C_{min1} = trough concentration at end of first cycle; $EC_{avg}50$ = average half-maximal effective concentration; $EC_{min1}50$ = trough half-maximal effective concentration at the end of the first cycle; HR = hazard ratio. Overall survival as predicted by C_{min1}-based model (left panel) and the C_{avg}-based model (right panel). The solid red lines describe the change in HR as a function of C_{min1} and C_{avg}; the grey histograms describe the distribution of olaratumab C_{min1} and Cavg in the JGDG experimental arm together with their quartiles (dashed blue lines); the green dashed lines indicate $EC_{min1}50$ and $EC_{avg}50$.

Figure 6: Predicted effect of olaratumab on the HR for overall survival

The impact of exposure (in terms of C_{min1} and C_{avg}) on efficacy was also evaluated by performing a matched case-control (MCC) analysis comparing OS and PFS in each subgroup of the Investigational Arm, defined by quartiles of C_{min1} and C_{avg}, to that in a matching subgroup of the Control Arm. Each matched subgroup of the Control Arm was selected by matching patients' propensity scores over 7 potential prognostic covariates.

Table 10: Matched-Case Control Analysis of Overall Survival in Phase 2 Study JGDG; Cmin1 and Cavg Quartiles

Olaratumab Exposure Quartiles (µg/mL)	Number of patients/Number of events		Hazard Ratio (95% C.I.)	p-value (Wald's)
	Olara + Doxo	Doxo		
Quartiles based on C_{min1}				
Q1 (12.3 - < 62.8)	15/13	15/12	1.355 (0.617, 2.976)	0.4495
Q2 (≥ 62.8 - < 86.9)	16/10	16/13	0.528 (0.231, 1.206)	0.1299
Q3 (≥ 86.9 - < 105.6)	15/5	15/8	0.386 (0.126, 1.182)	0.0955
Q4 (≥ 105.6 – 188.1)	16/9	16/10	0.812 (0.330, 2.001)	0.6510
Quartiles based on C_{avg}				
Q1 (56 < 134.4)	15/13	15/13	1.024 (0.474, 2.215)	0.9509
Q2 (≥ 134.4 - < 175.2)	16/9	16/14	0.367 (0.158, 0.851)	0.0195
Q3 (≥ 175.2 - < 249.9)	15/7	15/7	0.717 (0.251, 2.046)	0.5345
Q4 (≥ 249.9 – 347.3)	16/8	16/11	0.561 (0.226, 1.397)	0.2145

Abbreviations: C_{avg} = average concentration over patient's entire treatment; C.I. = confidence interval; C_{min1} = trough serum level at the end of the first cycle of treatment; Doxo = doxorubicin; Olara = olaratumab; Q = quartile.

The MCC analysis shows that patients in the lowest exposure quartile tended to experience disease progression within the first 2 to 3 cycles of treatment and, unlike the other quartiles, did not have OS improvement. This was true for both PK parameters, C_{min1} and C_{avg}.

The Applicant hypothesized that patients in the lowest exposure quartile might progress because concentrations do not reach potentially therapeutic levels (C_{min1} ≥ 65.9 µg/mL) early enough during the course of treatment (steady state being not reached before Cycle 3); and, consequently, that clinical outcome for the lowest exposure quartile could be further improved if patients were able to achieve higher serum concentrations earlier in treatment. Based on this hypothesis the Applicant used the developed PopPK model to devise an improved dosing strategy for the Phase 3 Study in STS. This dosing strategy consists of 'loading' doses of 20 mg/kg administered on Days 1 and 8 of Cycle 1 followed by 15 mg/kg administered on Days 1 and 8 of every subsequent cycle. According to the PK model, this dosing strategy would allow steady-state olaratumab serum levels to be achieved as soon as the first cycle, and would significantly reduce the percentage of patient whose C_{min1} falls below 66 µg/mL at the start of treatment. Importantly, with the loading 20 mg/kg dose during the first cycle C_{max} is predicted to remain within the overall range observed in Study JGDG, which had an acceptable and monitorable safety profile. In addition, the exposure-safety analysis showed that the rate of treatment-emergent adverse events (TEAEs) in Study JGDG did not increase with increasing olaratumab serum exposure.

Immunogenicity

The overall incidence of TE-ADA was 3.5% (13 of 370) in all evaluable olaratumab-treated patients from 9 studies. Incidence in STS patients from Study JGDG was 5.9% (5/85). Neutralizing antibodies were detected in all patients who tested positive for treatment-emergent anti-olaratumab antibodies.

Qtc interval

QTc data were collected when olaratumab was administered at the dose of 15 mg/kg. Visual inspection revealed no relationship between ΔQTcF values and olaratumab concentrations. In addition, the 90% confidence interval (CI) for the slope of the regression line contained zero, and the upper limit of the 90% CI at Cmax excluded 10 ms, indicating lack of a concentration-QT effect.

2.4.4. Discussion on clinical pharmacology

The clinical pharmacology of olaratumab is mainly supported by data from studies JGDG, JGDB, JGDD, JGDE, JGDH, JGDI together with the population pharmacokinetic analysis (including data from Studies JGDG, JGDB, JGDIE, JGDH). Pharmacokinetics has mainly been documented in patients with different type of tumours and not in healthy volunteers.PK of olaratumab was sufficiently characterized, mainly by PopPK analysis.

The dose proposed for olaratumab in combination with doxorubicin is 15 mg/kg administered intravenously over 60 minutes on days 1 and 8 of each 3 week cycle. The population pharmacokinetic analysis and exposure response analyses have been essential to support relevant issues about the clinical pharmacology of olaratumab, importantly the dose regimen.

Overall, the bionalytical methods applied for the determination of olaratumab, doxorubicin in human serum as well as for the determination of ADAs are acceptable.

The pharmacokinetics of olaratumab administered as an intravenous (IV) infusion of 15 mg/kg on Days 1 and 8 of a 21-day cycle or 20 mg/kg on Day 1 of a 14-day cycle was well characterized by a 2-compartment model with linear elimination. Nonlinear saturable clearance did not significantly contributed to overall clearance, indicating that at therapeutic doses there is saturation of target-mediated drug disposition. Systemic clearance (CL) and volume of distribution (Vss) at steady state were 0.0233 L/h and 7.74 L, respectively which is in line with data from other IgG mAb. This corresponds to a half-life of approximately 11 days, and a time to steady state of approximately 50 days. Interindividual variability in PK parameters was low to moderate (15.6% to 33.3%). NCA showed that after administration of 15 mg/kg olaratumab on Days 1 and 8 of each 21-day treatment cycle, mean Cmax,ss ranged from 400 to 600 µg/mL, approximately, and mean Cmin,ss ranged from 140 to 190 µg/mL, approximately.

No studies in any special populations (renal impairment, hepatic impairment, age, race, gender) have been performed, which is acceptable for an IgG antibody. Several variables were tested as covariates in the popPK analysis, and only body weight and tumour size were found to have an effect on clearance and volume of distribution and clearance respectively (see sections 5.2 of the SmPC). Dosing per body weight is acceptable.

No pharmacokinetic interactions through metabolic enzymes or transporters are expected for a PDFR - antibody. No interaction was observed in the PK of doxorubicin when administered in combination with olaratumab (JGDI study). The final results of study JGDI will be submitted by the applicant by December 2017 (see RMP). No other formal DDI studies with olaratumab and medicinal products commonly used in cancer patients, including those with STS (e.g. antiemetics, analgesics, anti-diarrheal drugs, oral contraceptives, etc.), have been performed.

As monoclonal antibodies are not metabolised by cytochrome P450 (CYP) enzymes or other drug metabolising enzymes, inhibition or induction of these enzymes by co-administered medicinal products is not anticipated to affect the pharmacokinetics of olaratumab. Conversely, olaratumab is not anticipated to affect the pharmacokinetics of co-administered medicinal products (see section 4.5 of the SmPC).

There was no evidence of prolongation of QTcF following administration of olaratumab.

A Population Pharmacokinetic/Pharmacodynamic analysis of olaratumab was presented. PDGFR-α expression (positive or negative) was not investigated as a covariate but theoretically should influence the effect of olaratumab. On the other hand, an exploratory subgroup analysis of efficacy indicated that the benefit in terms of OS was essentially confined to the PDGFR-α negative subgroup, which appears to be a paradox. Post-hoc analyses performed by the Applicant indicate that PDGFRα status should not have any relevant

effect on the drug disposition. PDGFRα status tested as a covariate in the OS survival model did not provide a statistically significant improvement to the model fit.

A highly significant finding of the exposure-response analysis was that only patients whose Cmin1 was above the lower quartile showed an improvement in OS. This was true for both PK parameters, Cmin1 and Cavg. The Applicant concludes that patients with low serum concentration of olaratumab may benefit from a higher dose and this led to the proposal of a modified posology for the planned phase 3 study, which includes loading doses to be administered in cycle 1. This kind of exposure-response pattern has been proposed for several antibodies but is likely to be confounded by disease factors. The suggested relationship between low exposure and inadequate response may be considered unlikely given that target saturation is anticipated for most patients at the studied dose level. Disease dependent pharmacokinetics is suggested by the inclusion of tumour size in the PopPK model as a covariate on clearance. The attempt to avoid confounding by performing a matched case-control analysis is acknowledged, but can be questioned given the low patient number in each group. The conclusion from the exposure-response model, that low exposure is the primary reason for inadequate response, cannot be considered definitive for the time being. Taking into account that a new dosing strategy is currently under assessment in the ongoing phase III trial further discussion on this issue is expected at the time of data submission.

Regarding immunogenicity, the overall incidence of TE-ADA was 3.5% (13 of 370) in all evaluable olaratumab-treated patients and 5.9% (5/85) in STS patients from Study JGDG. Neutralizing antibodies were detected in all patients who tested positive for treatment-emergent anti-olaratumab antibodies. TE-ADA do not appear to influence olaratumab clearance and exposure. Data are limited, however there is no indication that TE-ADA may negatively affect efficacy. Due to the limited number of patients with ADA (or TE-ADA) who developed IRRs definitive conclusions regarding the relationship between ADA (or TE-ADA) and safety cannot be established from the 370 evaluable patients 3.5% positive for ADA, all of them positive for neutralizing antibodies.

Data on very elderly patients (> 75 years) are very limited. However on the basis of data available, no dose reductions other than those recommended for the general patient population are necessary. (see sections 4.2, 4.8 and 5.1 of the SmPC)

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology of olaratumab is mainly supported by data from studies JGDG, JGDB, JGDD, JGDE, JGDH, JGDI together with the population pharmacokinetic analysis (including data from Studies JGDG, JGDB, JGDE, JGDH) and exposure-response (efficacy, safety) analyses. Pharmacokinetics has mainly been documented in patients with different type of tumours and not in healthy volunteers. There are a number of limitations in the PK data which should also be addressed in the ongoing confirmatory trial (JGDJ).

2.5. Clinical efficacy

2.5.1. Dose response study(ies)

JGDC (IMCL CP15-0601) is a phase 1 multicentre open-label dose escalation study of olaratumab single agent in advanced solid tumours and lymphomas, conducted in 2 US centres between December 2006 and March 2009. The primary objective was to establish the safety profile and maximum tolerated dose (MTD) of

olaratumab in adult (≥ 18 years) patients with advanced solid tumours no longer responding to standard therapy or for which no standard therapy was available. The secondary objectives were the evaluation of pharmacokinetic (PK), immunogenicity, pharmacodynamic and antitumor activity of olaratumab.

Patients in Cohorts 1, 2, and 3 received olaratumab IV weekly at doses of 4 mg/kg, 8 mg/kg, 16 mg/kg, respectively, for a total of 4 doses per cycle, followed by a 2-weeks observation period. Patients in Cohorts 4 and 5 received olaratumab IV every two weeks at doses of 15 mg/kg and 20 mg/kg, respectively for 4 weeks, for a total of 2 doses per cycle. A minimum of 3 patients were planned to be enrolled in each cohort. Toxicity data for each cohort was reviewed prior to dose escalation. No intrapatient dose escalation was allowed.

Twenty (20) patients were enrolled, safety population included 19 subjects and MTD population included 17 patients.

There were no DLTs and the MTD was not determined.

Accrual was closed after 20 patients due to the achievement of serum trough concentrations of Olaratumab (155 µg/mL) in the weekly 16 mg/kg cohort and q2w 15- and 20 mg/kg cohorts that was associated with antitumor activity in preclinical models.

No objective responses were observed in the study. Twelve patients across all 5 cohorts had stable disease (SD) (disease control rate of 63.2%, exact 95% CI: 38.4%, 83.7%), with SD median duration of 3.9 months. The median PFS was 3.4 months (95% CI 1.5, 5.1).

Simulations were run at doses ranging from 15 to 60 mg/kg at various dosing regimens including Day 1 and 8 of a 21-day cycle. The results of the simulations suggest that with a dosing regimen of 15 mg/kg on Days 1 and 8 of a 21-day cycle, a C_{min} of 240 µg/ml could be attained at steady state, which exceeds the target minimum trough levels of IMC-3G3 associated with antitumor activity seen in preclinical tumour xenograft models. Therefore this dosing regimen was selected for the JGDG study.

The phase 1b portion of JGDG study was non-randomized, with all patients assigned to receive olaratumab and doxorubicin according to the same dose and schedule used in the Investigational Arm in the phase 2 portion of the same study. 15 patients were treated. First patient was enrolled in the Phase 1b in October 2010. After 10 patients received 2 cycles of treatment, Phase 1b was closed to enrolment and the Safety Review Committee (SRC) reviewed the safety data, then enrolment for Phase 2 started.

The primary objective of phase 1b was to evaluate the safety profile of olaratumab when administered in combination with doxorubicin to patients with advanced STS. Secondary objectives were to evaluate the PK and immunogenicity of olaratumab in combination with doxorubicin.

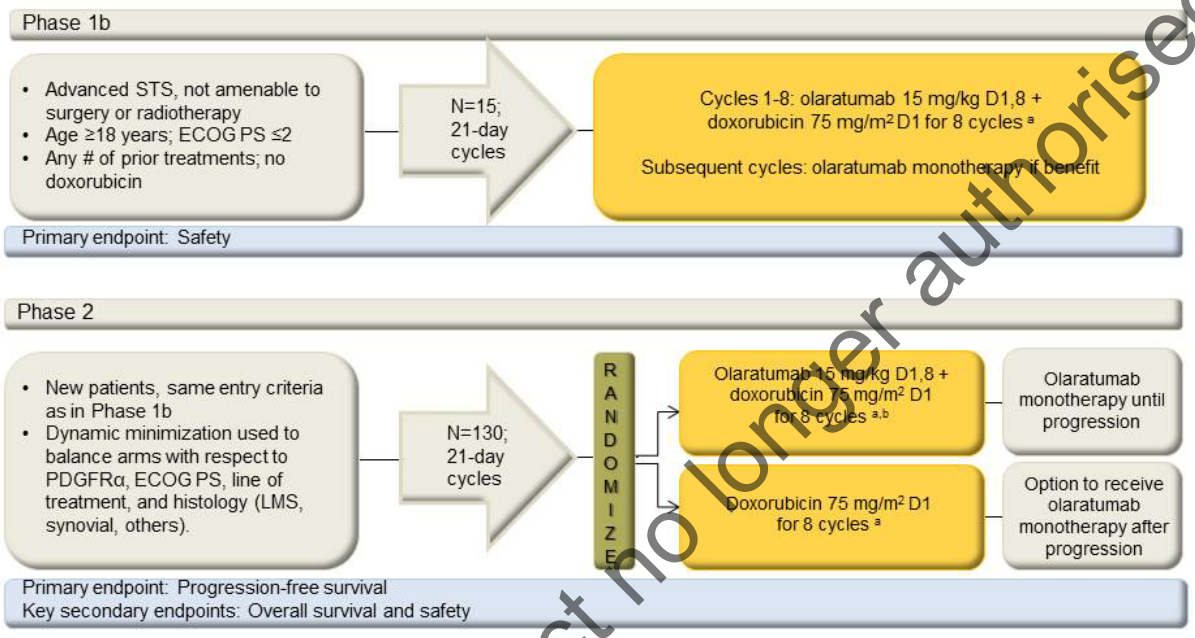
2.5.2. Main study(ies)

I5B-IE-JGDG (JGDG) Study "A Phase 1b/2 Randomized Phase 2 Study Evaluating the Efficacy of Doxorubicin With or Without a Human Anti-PDGFRα Monoclonal Antibody (IMC-3G3) in the Treatment of Advanced Soft Tissue Sarcoma".

Study JGDG was an open-label, multicenter, Phase 1b/2 trial conducted in the United States, which enrolled patients (age ≥18 years) with histologically or cytologically confirmed, advanced STS not amenable to treatment with surgery or radiotherapy.

The Phase 1b portion of the study was nonrandomized, with all patients assigned to receive olaratumab plus doxorubicin. The primary objective of the Phase 1b portion was to evaluate the safety profile of olaratumab in combination with doxorubicin.

In the Phase 2 portion, patients were randomized to receive doxorubicin plus olaratumab or doxorubicin alone. The primary objective of the Phase 2 portion was to compare the PFS of patients treated with olaratumab in combination with doxorubicin versus patients treated with doxorubicin alone.



a. During Cycles 5-8, patients may receive dexrazoxane 750 mg/m² prior to doxorubicin on Day 1, at the investigator's discretion.
b. After 8 cycles of doxorubicin, patients this arm stop doxorubicin and continue with olaratumab monotherapy in the absence of PD or other criteria requiring treatment discontinuation.

Methods

Study Participants

Key inclusion criteria were the following:

- Histologically- or cytologically-confirmed advanced malignant STS, including uterine leiomyosarcoma, not amenable to treatment with surgery or radiotherapy. Kaposi's sarcoma was excluded.
- Measurable disease
- Prior treatment with systemic therapy was not required, nor there was limit on the number of prior treatment regimen (all lines of treatment were allowed)
- ECOG performance status 0-2
- Adequate hepatic, hematologic and renal function. Left ventricular ejection fraction (LVEF) ≥50%
- Age at study entry ≥ 18 years

- Available tumour tissue from either the primary or metastatic tumour for determination of PDGFRα expression.

Key exclusion criteria were the following:

- Kaposi's sarcoma
- Previous treatment with doxorubicin, daunorubicin, idarubicin, and/or other anthracyclines and anthracenediones (ie, mitoxantrone)
- previous therapy with any agent that targets the PDGF or PDGFR
- untreated central nervous system metastases (eligible if clinically stable after treatment and off steroids)

Treatments

In the Phase 2 portion of the study, patients were randomized in a 1:1 ratio to one of the following 2 treatment arms:

- Investigational Arm (Arm A): Olaratumab (15 mg/kg) on Day 1 and Day 8 IV over approximately 60 minutes, plus doxorubicin (75 mg/m²) IV on Day 1 over 15-60 min of each 21-day cycle for up to 8 cycles (Doxorubicin was to be administered 1 hour after the completion of the olaratumab infusion; if premedication was required prior to the first doxorubicin infusion, this was to be given after the completion of olaratumab infusion). In the absence of disease progression or other withdrawal criteria, patients continued to receive subsequent single-agent olaratumab (15 mg/kg) IV on Day 1 and Day 8 of each 21-day cycle, until disease progression, unacceptable toxicity or any other reason for discontinuation.
- Control Arm (Arm B): Doxorubicin (75 mg/m2) IV on Day 1 of each 21-day cycle for up to 8 cycles. Upon documented disease progression on or after completion of single-agent doxorubicin treatment, patients were allowed to receive olaratumab monotherapy until further disease progression or other discontinuation criteria were met.

In order to reduce potential doxorubicin-related cardiotoxicity, patients receiving more than 4 cycles of doxorubicin were allowed to receive dexrazoxane at investigator's discretion on Day 1 of Cycles 5-8 on both Investigational and Control arms, at a ratio of 10:1 to the administered dose of doxorubicin.

Patients were treated until disease progression, development of unacceptable toxicity, noncompliance or withdrawal of consent by the patient, or the investigator made the decision to stop treatment.

Objectives

The primary objective of the phase 2 portion of the study was to compare the PFS in patients with advanced STS not amenable to treatment with surgery or radiotherapy when treated with olaratumab in combination with doxorubicin versus doxorubicin alone.

Secondary objectives were to evaluate and compare the 3-month PFS (PFS-3m), objective response rate (ORR), change in tumour size from baseline to best overall response, and OS of olaratumab in combination with doxorubicin versus doxorubicin alone; and to evaluate the pharmacokinetics and immunogenicity of olaratumab in combination with doxorubicin

Outcomes / endpoints

Primary Endpoint:

To compare PFS in patients with advanced STS not amenable to treatment with surgery or radiotherapy when treated olaratumab in combination with doxorubicin versus doxorubicin alone.

PFS is defined as the time from the date of randomization to the earliest date of documented tumour progression or death from any cause, whichever was first. Tumour assessment is based on RECIST 1.1 criteria as per Investigator assessment.

Secondary Endpoints:

- To evaluate and compare overall survival (OS), 3-month PFS (PFS-3m), objective response rate (ORR), change in tumour size from baseline to best overall response of olaratumab in combination with doxorubicin versus doxorubicin alone;
- To evaluate the PK and immunogenicity of olaratumab in combination with doxorubicin

OS is defined as the time from the date of randomization to the date of death from any cause.

ORR is defined as the proportion of patient achieving a best overall response of complete or partial response (CR + PR), as per Investigator assessment based on RECIST1.1.

A blinded independent review of radiographic scans has been conducted following the final PFS database lock, therefore both PFS and ORR according to Independent Review have been presented as secondary analyses.

Exploratory Endpoints:

- To evaluate the association between tumour PDGFRα expression and clinical outcomes, including PFS, ORR, etc.
- Exploratory objectives in whole blood included, but not were limited to potentially relevant biomarkers of IMC-3G3 pharmacodynamic activity, including PDGF and vascular endothelial growth factor (VEGF) and other factors related to PDGFRα. Biomarkers also included, but were not limited to, analysis of tumour specimens for pericyte coverage, microvessel density, and factors related to PDGFRα. (both phase 1b and 2)

Sample size

The Phase 2 portion of the study was designed with a planned enrolment of 130 patients, assuming a 50% improvement in PFS, or equivalently a PFS hazard ratio (HR) of 0.667 (α = 0.2, with statistical power of 80%). An interim analysis looking at the efficacy data was pre-planned to occur after at least 80 PFS events had been observed. A very minimal nominal α level of 0.0001 was pre-allocated to the interim analysis. The final nominal significance level will be adjusted to 0.1999 (two-sided). A protocol amendment (V3) increased the sample size from 120 to 130 patients, so as to better account for censoring in the analyses of PFS and OS.

Randomisation

Patients enrolled were randomly assigned on a 1:1 basis to the Investigational or the Control Arm, via an interactive system (IVRS, accessed by voice or world-wide web) and employed a dynamic-minimization algorithm according to the following stratification factors:

1) PDGFRα expression (positive vs. negative, IHC assessed)

2) Number of previous lines of systemic treatment (0 vs. ≥1)

3) Histological tumour type (LMS vs. synovial sarcoma vs. other tumour type)

4) Eastern Cooperative Oncology Group (ECOG) performance status (0-1 vs. 2).

Table 11: IVRS randomisation factors (ITT) – Study JGDG

	Number of Patients (%)	
	Investigational Arm N = 66	Control Arm N = 67
PDGFRα (Assay used for stratification)		
Positive	58 (87.9)	59 (88.1)
Negative	8 (12.1)	8 (11.9)
Number of Lines of Previous Systemic Treatment[a]		
0	27 (40.9)	31 (46.3)
≥1	39 (59.1)	36 (53.7)
Histological Tumor Type		
Leiomyosarcoma	25 (37.9)	26 (38.8)
Synovial Sarcoma	1 (1.5)	2 (3.0)
Other	40 (60.6)	39 (58.2)
ECOG PS		
0-1	62 (93.9)	63 (94.0)
2	4 (6.1)	4 (6.0)

Abbreviation: ECOG PS = Eastern Cooperative Oncology Group Performance Status; ITT = intent-to-treat; IVRS = interactive voice response system; N = number of randomized patients; PDGFRα = platelet-derived growth factor receptor alpha.
Data cut-off date: 16 May 2015.
Source: Table JGDG.14.6.
[a] Line of treatment reported in the adjuvant or metastatic setting.

Blinding (masking)

Study JGDG was open-label.

Statistical methods

Primary and secondary endpoints were analysed in the ITT population.

The Kaplan-Meier method was used to estimate the median PFS, together with a two-sided 90% confidence interval (CI). Comparison of PFS between arms was performed using the log-rank test, and hazard ratios were estimated by a Cox proportional hazards regression model. Only when there were a sufficient number of patients in each stratum, the stratified analysis was performed. Otherwise, the stratification factors were treated as covariates in the Cox proportional hazards to estimate the HR and 90% confidence limit.

A re-randomization test was conducted on the ITT population to further evaluate the robustness of the log-rank test results, given the dynamic randomization used.

To show the robustness of primary analysis of PFS, sensitivity analyses were performed using different censoring/event definition scenarios.

Supportive analysis were also performed: hazard ratios for treatment effect were estimated using a multivariate Cox model adjusting for baseline factors of interest (randomization stratification factors, ECOG, CFR, gender, age, duration of disease, platelet, WBC, primary tumour present). A stepwise selection method was also used, with p-value<0.1 as the criteria for adding a variable and p-value ≥0.15 for dropping a variable. The treatment group was not included during stepwise selection, but was included in the final model. HR for the treatment effect along with 95% CI was estimated from the final model.

Overall survival was analysed with the same method used for analyses of the primary endpoint.

The rate of overall response between the treatment groups was compared using the Fisher's Exact Test. The objective response rate comparison was also adjusted by the stratification factor by means of a Cochran-Mantel-Haenszel test if there was sufficient number of patients in each stratum. Two-sided 90% exact CI was determined.

Duration of response was estimated with the Kaplan-Meier method; a 90% CI was provided for the median duration of response.

The maximum change in tumour size was presented using a waterfall plot. The log transformed maximum change was compared using Analysis of Covariance model, with log transformed baseline tumour size and randomization stratification factors as covariates.

Statistical analysis plan (SAP) was amended twice and Addenda were added (see table below):

Table 12: Substantive SAP Amendments and Addenda to Study JGDG

SAP Version *Approval Date*	**Lilly Summary of Important Changes**	**Submission Date to IND (Sequence Number)**
Version 2.0 *01 August 2013*	The main objective of this SAP amendment was to incorporate changes consistent with Protocol Version 4.0, including increase in sample size and institution of interim analysis for efficacy. Additional changes included: • Added sensitivity analysis for PFS and analysis for change in tumor size. • Specified that detailed biomarker analyses would be described in a separate biomarker analysis plan.	NA
Version 3.0 *08 September 2014*	The main objective of this SAP amendment was to incorporate changes consistent with Protocol Version 5.0, including the change in the biomarker objective from a secondary to an exploratory endpoint, change in frequency of radiographic assessment, clarification of timing for final PFS and final OS analyses, and clarification of significance level for efficacy analyses. Additional changes included: • Added a re-randomization test to further evaluate the impact of using minimization randomization. • Sensitivity analysis for PFS using stepwise selection multivariate Cox model was added to further evaluate the impact of baseline factors on the primary analysis of PFS. • Additional supportive analysis was added, excluding Control Arm patients who received olaratumab monotherapy after discontinuation of doxorubicin.	IND121500 28 May 2015 Sequence #0030
SAP Addendum Version 1.0 19 November 2014	This addendum was created to describe the analysis of PFS as determined by Blinded Independent Review Committee.	NA
SAP Addendum Version 2.0 19 May 2015	Editorial change (correction of error in Table of Contents) only.	IND121500 28 May 2015 Sequence #0030

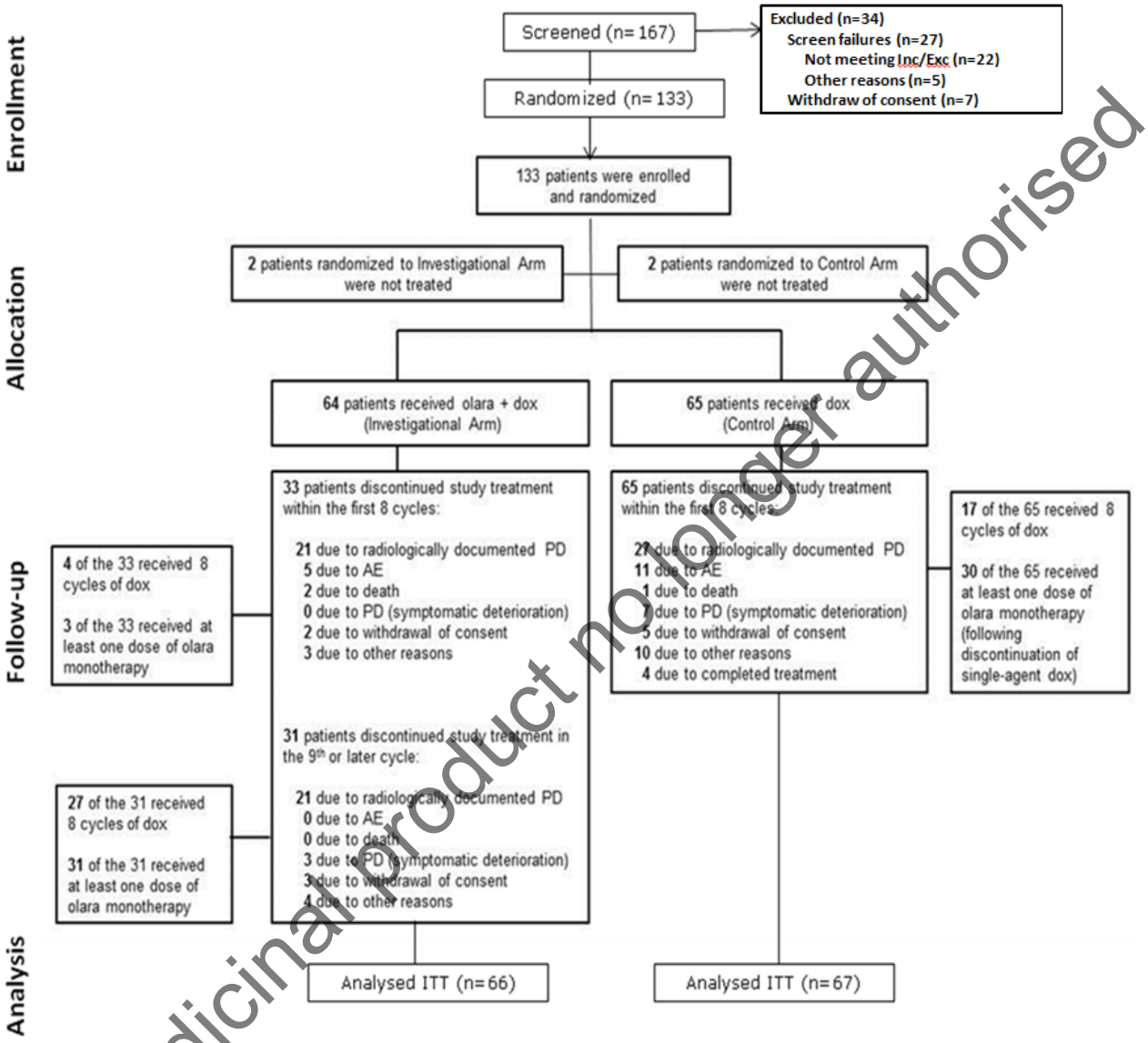
Abbreviations: IND = Investigational New Drug; NA = not applicable; OS = overall survival; PFS = progression-free survival; SAP = statistical analysis plan.

In addition, *post hoc* changes to planned statistical analysis were made to after the final PFS database lock:

- The analysis population for efficacy was changed from a randomized and treated population to all randomized patients (ITT, with the addition of the 4 randomized untreated patients).
- The original protocol and SAP presented 90% CIs for efficacy variables. In anticipation of regulatory submissions, 95% CIs were judged to be more appropriate and conventional for all efficacy parameters.
- A blinded independent review of radiologic assessments was conducted.
- Plans for subgroup analyses described per SAP were changed based on a review of literature (see Section 11.4.3.3.4).
- Subgroups for subgroup analyses are CRF-based unless otherwise noted.
- Additional post hoc sensitivity analyses were conducted to evaluate the robustness and internal consistency of the overall survival results to any potential impact of baseline and post-baseline covariates.
- An additional ad hoc exploratory sensitivity analysis was conducted with censoring rules that were the same as the primary analysis but patients were not censored for death or progression that occurred after 2 or more missed visits.

Results

Participant flow



Recruitment

Patients were randomized between May 2011 and January 2013.

This study was conducted at 17 investigative sites in the US, of which 16 sites treated patients.

At the data cut-off for OS final analysis (16 May 2015), there were 23 patients being followed for survival in the Investigational Arm and 8 patients in the Control Arm (the latter including 3 patients who received olaratumab monotherapy after discontinuation of doxorubicin).

Conduct of the study

There were 5 protocol amendments for Study JGDG as presented below:

Table 13: Substantive protocol amendments

Protocol Version *Approval Date*	Lilly Summary of Important Changes	Submission Date to IND (Sequence Number)
Version 1.0 *25 March 2010*	• Original protocol	Not submitted to any IND
Version 2.0 *14 July 2010*	• **Note:** Patient enrollment was initiated with this version of the protocol. • The protocol was amended to reflect a change in the olaratumab drug product used in the study; specifically, the drug product concentration changed from 5 mg/mL (250 mg/50 mL vial) to 10 mg/mL (500 mg/50 mL vial). Of note, this amendment was finalized prior to enrollment of any patients and therefore patients received only the 10-mg/mL formulation.	IND 100044 28 July 2010 Serial #0052
Version 3.0 *02 February 2012*	• The sample size of 120 was changed to 130 patients to better account for patients lost to follow-up who must be censored in the PFS analysis. There was no change to the assumed 50% improvement in PFS (that is, a PFS HR of 0.67), and no change to the number of events planned for the final PFS analysis. • Entry criteria were clarified (including the deletion of urinalysis for detection of proteinuria upon study entry because olaratumab was not found to effect renal function). • The language regarding dexrazoxane treatment was modified, stating that this treatment was optional (at the investigator's discretion) for those patients receiving doxorubicin. • Language was added stating that Control Arm patients who discontinued study therapy due to therapy-related toxicity or completed doxorubicin treatment and experienced stable disease (or better) could stay on study schedule and assessments until PD was documented and then receive olaratumab monotherapy. • Language regarding Control Arm patients who crossed over to olaratumab monotherapy was revised to emphasize that they must first discontinue doxorubicin due to disease progression.	IND100044 07 March 2012 Seq. #0160

Version 4.0 *17 July 2013*	• Prespecified a planned interim analysis to look at efficacy after a minimum of 80 PFS events had occurred, assigning a two-sided nominal alpha of 0.0001 to the interim analysis of PFS.	IND100044 30 July 2013 Seq. #0223 IND121500 21 February 2014 Seq. #0000
Version 5.0 *19 August 2014*	• Prespecified that a final analysis of OS data "will be conducted using a data cut-off date of 2 years after the last patient started treatment or after reaching approximately 91 deaths (that is, about 70% of the mITT population), whichever occurs later." • Indicated that an interim analysis of OS would be performed at the time of final PFS analysis, after a minimum of 91 OS events had been observed. • Evaluation of the association between PDGFRα expression and clinical outcomes changed from a secondary to an exploratory objective. • Radiographic tumor assessments after the data cut-off for primary analysis changed from every 6 weeks to every 12 weeks. • Clarified significance level for statistical testing of the efficacy analysis (efficacy analysis was powered for a one-sided log-rank test at the 0.1 significance level). A 2-sided p-value will also be computed. • Timing for the final PFS analysis was changed. The primary analysis was originally planned to be performed when at least 110 PFS events were observed. However, protocol-defined censoring rules for PFS required that PFS be censored at last radiographic assessment if death or disease progression was observed after 2 consecutive missed visits after last assessment. Similarly, any patient beginning a new systemic anticancer therapy prior to progression was also censored for PFS at the time of last assessment. Among the 129 randomized and treated patients, 20 were censored for one of these 2 reasons, such that 110 PFS events could not be attained for the primary analysis. Therefore, the statistical analysis plan and protocol were amended to define the data cutoff date of 15 August 2014 for the (final) primary analysis of PFS, by which time it was projected that at least 100 PFS events would be observed. Following data validation, it was confirmed that 103 investigator-determined PFS events had occurred prior to this cutoff date.	IND121500 20 August 2014 Seq. #0006
Version 6.0 *04 February 2015*	• Timeframe for allowing Control Arm patients to cross over to receive monotherapy with olaratumab was clarified. • A Continued Access Period was added for patients still on treatment when study completion occurs.	IND121500 03 April 2015 Seq. #0021

Abbreviations: HR = hazard ratio; IND = Investigational New Drug; OS = overall survival; mITT = modified intent-to-treat; PD = progressive disease; PDGFRα = platelet-derived growth factor receptor alpha; PFS = progression-free survival; Seq. = Sequence.

Baseline data

The baseline characteristics of patients in Study JGDG are summarised in the tables below.

Table 14: Demographic and Baseline Characteristics - Study JGDG Phase 2; ITT Population

	Number of Patients (%)	
	Investigational Arm N = 66	**Control Arm N = 67**
Sex		
Male	26 (39.4)	33 (49.3)
Female	40 (60.6)	34 (50.7)
Race		
White	55 (83.3)	60 (89.6)
Black	6 (9.1)	5 (7.5)
Asian	2 (3.0)	2 (3.0)
Native Hawaiian or Other Pacific Islander	1 (1.5)	0
Other	2 (3.0)	0
Age (years)		
Mean (SD)	56.8 (12.53)	58.3 (12.50)
Median	58.5	58.0
Minimum - Maximum	22 – 85	29 – 86
Age Group		
18 - <65	48 (72.7)	43 (64.2)
≥65	18 (27.3)	24 (35.8)
≥75	4 (6.1)	6 (9.0)
ECOG PS		
0	36 (54.5)	38 (56.7)
1	26 (39.4)	26 (38.8)
≥2	4 (6.1)	3 (4.5)

Abbreviation: ECOG PS = Eastern Cooperative Oncology Group Performance Status; ITT = intent-to-treat; N = number of randomized patients; SD = standard deviation.
Data cut-off date: 16 May 2015.

Table 15: Pretreatment Disease Characteristics (eCRF) Study JGDG Phase 2; ITT Population

	Number of Patients (%)	
	Investigational Arm N = 66	Control Arm N = 67
Duration of Disease (months)[a]		
Mean (SD)	31.9 (41.44)	34.7 (53.07)
Median	15.0	14.9
Minimum – Maximum	0.5 – 233.5	0.3 – 258.6
Grade		
Grade 1	7 (10.6)	8 (11.9)
Grade 2	5 (7.6)	7 (10.4)
Grade 3	29 (43.9)	29 (43.3)
Grade Cannot Be Assessed	6 (9.1)	5 (7.5)
Unknown	19 (28.8)	18 (26.9)
Histological Tumour Type (reclassified from eCRF)		
Angiosarcoma	4 (6.1)	3 (4.5)
Fibrosarcoma	1 (1.5)	0
Leiomyosarcoma	24 (36.4)	27 (40.3)
Liposarcoma	8 (12.1)	15 (22.4)
Neurofibrosarcoma	1 (1.5)	0
Synovial sarcoma	1 (1.5)	2 (3.0)
Undifferentiated Pleomorphic Sarcoma	10 (15.2)	14 (20.9)
Other		
Alveolar Soft Part Sarcoma	1 (1.5)	0
Chondrosarcoma Bone	0	2 (3.0)
Clear Cell Sarcoma	1 (1.5)	0
Endometrial Stromal Sarcoma	1 (1.5)	0
Epithelioid Sarcoma	2 (3.0)	0
Extraskeletal Chondrosarcoma	0	1 (1.5)
Extraskeletal Myxoid Chondrosarcoma	1 (1.5)	0
Fibromyxoid Sarcoma	1 (1.5)	1 (1.5)
Fibrosarcomatous Transformation in a Recurrent Dermatofibrosarcoma	1 (1.5)	0
Hemangiopericytoma	1 (1.5)	1 (1.5)
Malignant Glomus Tumour	1 (1.5)	0
Malignant Peripheral Nerve Sheath Tumour	1 (1.5)	0
Malignant Solitary Fibrous Tumour	1 (1.5)	0
Myxofibrosarcoma	1 (1.5)	0
Myxoid Chondrosarcoma	1 (1.5)	0
Myxoid Sarcoma	0	1 (1.5)
Soft Tissue Undifferentiated Round Cell Sarcoma Negative For Ews	1 (1.5)	0
Undifferentiated Neoplasm	1 (1.5)	0
Undifferentiated Uterine Sarcoma	1 (1.5)	0
Site of Metastatic Disease		
Lung	42 (63.6)	42 (62.7)
Liver	26 (39.4)	22 (32.8)
Soft Tissue	22 (33.3)	33 (49.3)
Lymph Nodes	16 (24.2)	21 (31.3)
Peritoneal	15 (22.7)	23 (34.3)
Bone	10 (15.2)	18 (26.9)
Pleural	10 (15.2)	9 (13.4)
Other[b]	8 (12.1)	16 (23.9)
Skin	3 (4.5)	0

Abbreviations: eCRF = electronic case report form; Ews = Ewing's Sarcoma; ITT = intent-to-treat; N = number of randomized patients; SD = standard deviation; STS = soft tissue sarcoma. Data cut-off date: 16 May 2015.

a Duration of disease is the time from date of histology/pathology confirmation of STS to date of informed consent.

b Other sites of metastatic disease included lung, liver, kidney, abdomen, pancreas, spleen, pelvic organs, small bowel, rectum, pelvis, chest, knee, retroperitoneal, other mesenteric masses, mediastinum, thyroid gland, adrenal gland.

Table 16: Prior Anticancer Therapies Received by Patients Study JGDG Phase 2; ITT Population

	Number of Patients (%)	
	Investigational Arm N = 66	Control Arm N = 67
Previous Surgery	55 (83.3)	57 (85.1)
Previous Radiotherapy	31 (47.0)	32 (47.8)
Prior Systemic Therapy[a]	38 (57.6)	37 (55.2)
Neoadjuvant	3 (4.5)	10 (14.9)
Adjuvant	17 (25.8)	10 (14.9)
Lines of Therapy[a]		
1st line[b]	14 (21.2)	12 (17.9)
2nd line[b]	8 (12.1)	7 (10.4)
3rd line[b]	2 (3.0)	1 (1.5)
4th line[b]	2 (3.0)	0
Regimen		
Gemcitabine/Docetaxel	25 (37.9)	27 (40.3)
Other	24 (36.4)	19 (28.4)

Abbreviations: ITT = intent-to-treat; N = number of randomized patients.
Data cut-off date: 16 May 2015.

a Patients may have received more than one type of therapy.

b If a patient received more than one line of therapy among 1st, 2nd, 3rd, and 4th line, the patient was counted in the highest line only.

Numbers analysed

Efficacy analyses were performed on the intention-to-treat (ITT) population. All 133 randomized patients in the Phase 2 portion, 66 in the Investigational Arm and 67 in the Control arm, were included in the ITT population. Four of these patients (2 in each arm) were randomized but did not receive treatment.

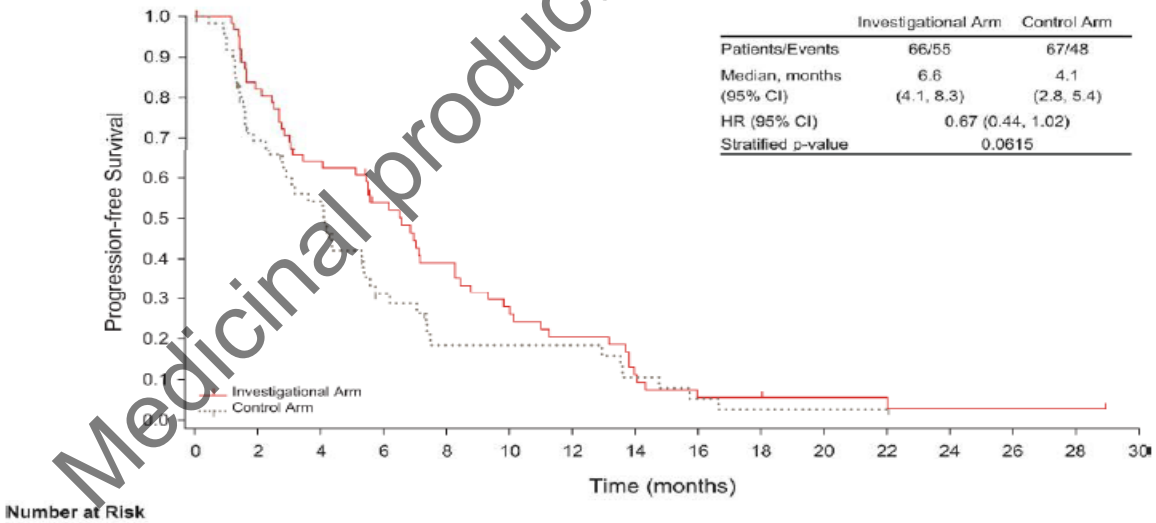
Outcomes and estimation

Primary endpoint: PFS

Table 17: Progression-Free Survival (Investigator Review) Study JGDG Phase 2; ITT Population.

	Investigational Arm N = 66	Control Arm N = 67
Number of Events, n (%)	55 (83.3)	48 (71.6)
Number Censored, n (%)	11 (16.7)	19 (28.4)
No Baseline Tumour Assessments	1 (1.5)	2 (3.0)
No Post-Baseline Tumour Assessments	2 (3.0)	2 (3.0)
Death or Progression After Two or More Missed Visits	1 (1.5)	3 (4.5)
Start of New Anticancer Therapy	5 (7.6)	5 (7.5)
No Documented Progression	2 (3.0)	6 (9.0)
Withdrew Consent	0	1 (1.5)
Median[a] (months)	6.6	4.1
95% CI[a]	(4.1, 8.3)	(2.8, 5.4)
Q25 - Q75[a]	2.7 – 10.2	1.6 – 7.4
3 months PFS Rate[a] (%)	69.0	59.9
95% CI[a]	(55.7, 78.9)	(45.9, 71.4)
6 months PFS Rate[a] (%)	53.9	31.1
95% CI[a]	(40.6, 65.4)	(18.9, 44.1)
Stratified Log-rank p-value[b,d]	0.0615	
Stratified Hazard Ratio[c,d]	0.672	
95% CI[c]	(0.442, 1.021)	
Unstratified Log-rank p-value[b,d]	0.1112	
Hazard Ratio[c,d]	0.730	
95% CI[c]	(0.494, 1.079)	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; PFS = progression-free survival; Q = quartile.
Data cut-off date: 15 August 2014.
a Estimated by the Kaplan-Meier method.
b Derived from a two–sided test.
c Hazard ratio is expressed as olaratumab + doxorubicin/doxorubicin and estimated from Cox model.
d Between olaratumab + doxorubicin arm and doxorubicin arm



Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; PFS = progression-free survival.
Source: Figure JGDG.14.1

Figure 7: Kaplan-Meier curve for PFS (investigator assessment) of Investigational Arm versus Control Arm (ITT population) - Study JGDG Phase 2

A blinded independent review of radiologic scans was conducted following the final PFS database lock to evaluate any potential systematic bias favoring either of the treatment arms with respect to PFS assessment.

Table 18: Progression-Free Survival (Independent Review) Study JGDG Phase 2; ITT Population.

	Investigational Arm N = 66	Control Arm N = 67
Number of Events, n (%)	37 (56.1)	34 (50.7)
Number Censored, n (%)	29 (43.9)	33 (49.3)
No Baseline Tumour Assessments	7 (10.6)	10 (14.9)
Death or Progression After Two or More Missed Visits	2 (3.0)	5 (7.5)
Start of New Anticancer Therapy	18 (27.3)	6 (9.0)
No Documented Progression	2 (3.0)	11 (16.4)
Withdrew Consent	0	1 (1.5)
Median[a] (months)	8.2	4.4
95% CI[a]	(5.5, 9.8)	(3.1, 7.4)
Q25 - Q75[a]	3.0 – 11.6	1.5 – 8.6
3 months PFS Rate[a] (%)	76.4	66.7
95% CI[a]	(62.8, 85.6)	(51.8, 77.9)
6 months PFS Rate[a] (%)	60.8	39.3
95% CI[a]	(45.8, 72.9)	(24.0, 54.2)
Stratified Log-rank p-value[b,d]	0.1208	
Stratified Hazard Ratio[c,d]	0.670	
95% CI[c]	(0.401, 1.117)	
Unstratified Log-rank p-value[b,d]	0.2157	
Hazard Ratio[c,d]	0.743	
95% CI[c]	(0.464, 1.190)	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; PFS = progression-free survival; Q = quartile.
Data cut-off date: 15 August 2014.
a Estimated by the Kaplan-Meier method.
b Derived from a two–sided test.
c Hazard ratio is expressed as olaratumab + doxorubicin/doxorubicin and estimated from Cox model.
d Between olaratumab + doxorubicin arm and doxorubicin arm.

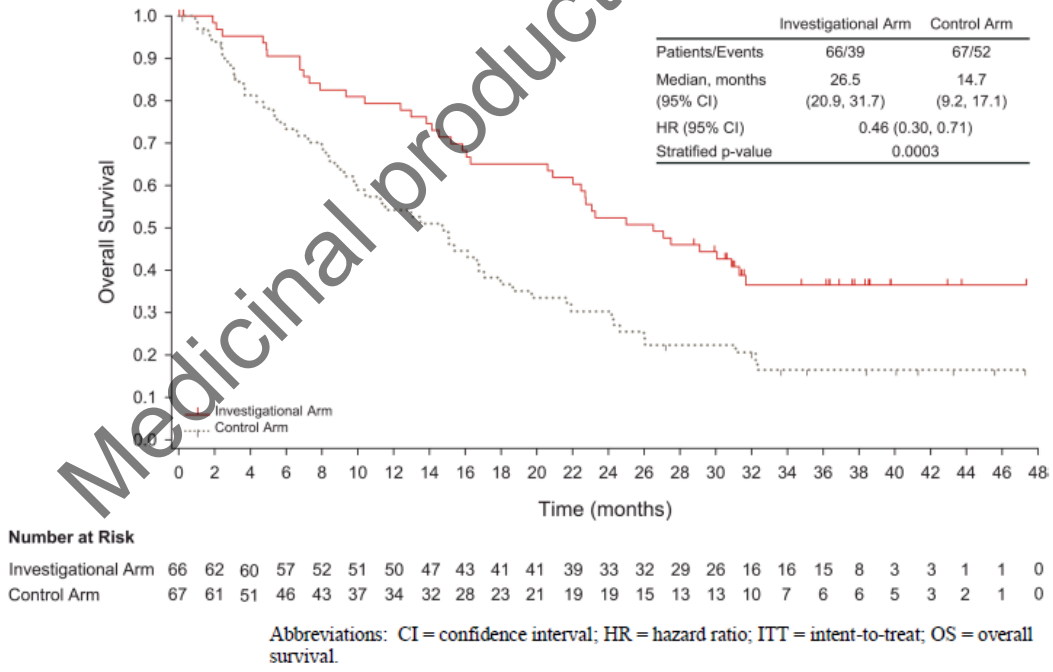
Secondary efficacy outcomes

OS:

Table 19: Overall Survival Study JGDG Phase 2; ITT Population

	Investigational Arm N = 66	Control Arm N = 67
Number of Deaths, n (%)	39 (59.1)	52 (77.6)
Number Censored, n (%)	27 (40.9)	15 (22.4)
Alive, n (%)	25 (37.9)	12 (17.9)
Lost to follow-up, n (%)	0	1 (1.5)
Withdrawal of Consent, n (%)	2 (3.0)	2 (3.0)
Median Survival (months)	26.5	14.7
95% CI[a]	(20.9, 31.7)	(9.2, 17.1)
Q25 - Q75[a]	13.8 – NE	5.5 – 26.0
3 months Survival Rate[a] (%)	95.2	87.6
95% CI[a]	(86.0, 98.4)	(76.8, 93.6)
6 months Survival Rate[a] (%)	90.5	73.8
95% CI[a]	(80.0, 95.6)	(60.6, 82.5)
Stratified Log-rank p-value[b,d]	0.0003	
Stratified Hazard Ratio[c,d]	0.463	
95% CI[c]	(0.301, 0.710)	
Unstratified Log-rank p-value[b,d]	0.0017	
Hazard Ratio[c,d]	0.517	
95% CI[c]	(0.341, 0.786)	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; NE = not evaluable; Q = quartile.
Data cut-off date: 16 May 2015.
[a] Estimated by the Kaplan-Meier method.
[b] Derived from a two–sided test.
[c] Hazard ratio is expressed as olaratumab + doxorubicin/doxorubicin and estimated from Cox model.
[d] Between olaratumab + doxorubicin arm and doxorubicin arm.



Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat; OS = overall survival.

Figure 8: Kaplan-Meier curves of Overall survival, Study JGDG Phase 2; ITT Population

An analysis of OS by the randomization factor of disease histology (LMS versus non -LMS) was pre-planned for Study JGDG.

Table 20: Overall Survival by Disease Histology per CRF - Study JGDG Phase 2; ITT Population

Leiomyosarcoma	Investigational Arm N = 24	Control Arm N = 27
Number of Events, n (%)	16 (66.7)	24 (88.9)
Number Censored, n (%)	8 (33.3)	3 (11.1)
Median[a] (months)	**28.3**	**13.2**
95% CI[a]	(20.6, 31.3)	(9.8, 21.7)
Unstratified Log-rank p-value[b,c]	0.0198	
Hazard Ratio[c]	0.473	
95% CI[c]	(0.248, 0.900)	
Non-Leiomyosarcoma	**Investigational Arm N = 42**	**Control Arm N = 40**
Number of Events, n (%)	23 (54.8)	28 (70.0)
Number Censored, n (%)	19 (45.2)	12 (30.0)
Median[a] (months)	**22.7**	**15.4**
95% CI[a]	(14.5, NE)	(6.6, 19.7)
Unstratified Log-rank p-value[b,c]	0.0348	
Hazard Ratio[c]	0.556	
95% CI[c]	(0.320, 0.967)	

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; NE = not evaluable.
Data cut-off date: 16 May 2015.
a. Estimated by the Kaplan-Meier method.
b. Hazard ratio is expressed as olaratumab + doxorubicin/doxorubicin and estimated from Cox model.
c. Between olaratumab + doxorubicin arm and doxorubicin arm.

ORR:

Table 21: Objective Response Rate - Study JGDG Phase 2; ITT Population

	Investigator Assessment			Independent Review		
	Inv. Arm N = 66	Control Arm N = 67	p-Value	Inv. Arm N = 66	Control Arm N = 67	p-Value
Best Overall Response, n (%)						
Complete response (CR)	2 (3.0)	1 (1.5)		3 (4.5)	1 (1.5)	
Partial response (PR)	10 (15.2)	7 (10.4)		9 (13.6)	4 (6.0)	
Stable disease (SD)	39 (59.1)	34 (50.7)		37 (56.1)	36 (53.7)	
Progressive disease (PD)	11 (16.7)	15 (22.4)		11 (16.7)	15 (22.4)	
Not evaluable (NE)	4 (6.1)	10 (14.9)		6 (9.1)	11 (16.4)	
Objective response rate (CR+PR), n (%)	**12 (18.2)**	**8 (11.9)**	0.3421[b,c]	**12 (18.2)**	**5 (7.5)**	0.0740[b,c]
95% CI[a]	9.8, 29.6	5.3, 22.2	0.3214[b,d]	9.8, 29.6	2.5, 16.6	0.0679[b,d]

Abbreviations: CI = confidence interval; CR = complete response; Inv = investigational; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category; NE = not evaluable; PD = progressive disease; ORR = objective response rate; PR = partial response; SD = stable disease. Data cut-off date: 15 August 2014.

a Estimated using binomial distribution.

b Between olaratumab + doxorubicin arm and doxorubicin arm.

c Derived from two-sided Fisher's exact test.

d Derived from two-sided Cochran-Mantel-Haenszel test adjusted by the stratification factor.

Ancillary analyses

- PDGFRα status

PDGFRα expression assessed by IHC was used for patient stratification to ensure both arms had equal representation of PDGFR-α expressing tumours. The IHC assay used for stratification (Assay 1) reported approximately 88% of evaluable cases positive for PDGFRα. However, after the trial was enrolled, further investigation into PDGFRα Assay 1 revealed that although the antibody used for stratification was quite sensitive for PDGFR-α, it had relatively poor specificity since it also recognized the β form of PDGFR. So, in the context of exploratory biomarker work to investigate PDGFRα and related ligands, an alternative PDGFRα IHC (Assay 2) was developed using a commercially available antibody highly sensitive and specific for PDGFRα.

Progression-free survival from the translational research (TR) population (that is, those patients with PDGFRα status determined by Assay 2 available) is shown in the table below.

Table 22: Progression-Free Survival by IHC PDGFRα Status and Treatment arms - Study JGDG TR Population (N=111)

	PDGFRα Positive		PDGFRα Negative	
	Investigational Arm N = 18	Control Arm N = 19	Investigational Arm N = 37	Control Arm N = 37
Patients with Events, n (%)	16 (88.89)	15 (78.95)	29 (78.38)	28 (75.68)
Patients Censored, n (%)	2 (11.11)	4 (21.05)	8 (21.62)	9 (24.32)
Median[a] (months)	**2.97**	**4.11**	**6.51**	**4.37**
95% CI[a]	(1.41, 8.77)	(1.54, 6.21)	(4.07, 8.44)	(1.64, 7.06)
Interaction p-value[b]	0.5924			
Hazard Ratio[c]	0.91		0.71	
95% CI[c]	(0.43, 1.92)		(0.42, 1.20)	

Abbreviations: CI = confidence interval; IHC = immunohistochemistry; ITT = intent-to-treat; N = number of randomized patients; n = number of patients in category.
Data cut-off date: 15 August 2014
a. Estimated by the Kaplan-Meier method.
b. Interaction p-value is based on the likelihood ratio test for the interaction term from the Cox model.
c. Hazard ratio is expressed as olaratumab + doxorubicin/doxorubicin and estimated from Cox model that includes marker status, treatment interaction between marker status and treatment, and stratification factors excluding marker status by assay 1.
Source: Table JGDG.14.54

- PFS sensitivity analyses

In order to show the robustness of the primary analysis of PFS, 4 sensitivity analyses were performed using different censoring/event definition scenarios (see table below).

Table 23: Sensitivity Analyses of Progression-Free Survival - Study JGDG Phase 2; ITT Population

Progression-free Survival	Stratified HR (95% CI)	p-Value
Primary Analysis	0.672 (0.442,1.021)	0.0615
Sensitivity Analysis 1[a]	0.623 (0.426,0.910)	0.0135
Sensitivity Analysis 2[b]	0.734 (0.497,1.085)	0.1208
Sensitivity Analysis 3[c]	0.631 (0.417,0.953)	0.0280
Ad Hoc Sensitivity Analysis 4[d]	0.664 (0.439,1.005)	0.0514

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat.

Data cut-off date: 15 August 2014.

a Sensitivity Analysis 1: If new anticancer treatment started before progression, the patient was considered to have disease progression at the date of the new cancer treatment; if death or progression occurred after 2 or more missed visits, the date of death or progression was used; and if lost to follow-up without progression, the patient was considered to have disease progression at the date of the last adequate assessment.

b Sensitivity Analysis 2: Used the actual reported date of progression or death regardless of missing assessments, treatment discontinuation or new anticancer treatment.

c Sensitivity Analysis 3: Added clinical progression (symptomatic deteriorations) as progressive events to the primary analysis.

d Ad Hoc Sensitivity Analysis 4: Censoring rules were the same as the primary analysis but patients were not censored if death or progression occurred after 2 or more missed visits.

- OS sensitivity analyses

In order to assess the impact of baseline characteristics on efficacy, a stratified Cox multivariate model of OS was performed, adjusted for specific factors considered potentially prognostic for OS on the basis of the literature and initial investigations of data from Study JGDG:

- liver metastases (presence at baseline vs. absence at baseline)
- ECOG PS (0 vs. 1 vs. 2)
- sex (females vs. males)
- age (< 65 years vs. ≥ 65 years)
- weight (above and below median weight)
- duration of disease since diagnosis (above and below median duration of disease)
- grade at diagnosis (1 vs. 2 vs. 3)
- albumin level (above and below median albumin level).

The OS HR for the treatment effect was 0.429 (95% CI: 0.267, 0.690), consistent with the stratified univariate OS HR of 0.463 observed in the main analysis.

Sensitivity analyses for OS were performed based on censoring at the date of starting new anticancer treatment.

Table 24: Sensitivity Analyses of Overall Survival Study JGDG Phase 2; ITT Population

Overall Survival	Stratified HR (95% CI)[b,c]	p-Value[a,c]
Primary Analysis	0.463 (0.301, 0.710)	0.0003
Sensitivity Analysis 1[d]	0.425 (0.193, 0.933)	0.0284
Sensitivity Analysis 2[e]	0.353 (0.192,0.647)	0.0005

Abbreviations: CI = confidence interval; HR = hazard ratio; ITT = intent-to-treat.
Note: This table includes treated patients from Phase 1b.
Data cut-off date: 16 May 2015.

a Derived from a two–sided test.

b Hazard ratio is expressed as olaratumab + doxorubicin/doxorubicin and estimated from Cox model.

c Between olaratumab + doxorubicin arm and doxorubicin arm.

d Sensitivity Analysis 1 was performed based on censoring at the date of starting new anticancer treatment.

e Sensitivity Analysis 2 was performed based on censoring at the date of starting selected post-study anticancer therapies (pazopanib, eribulin, gemcitabine + docetaxel, doxorubicin, and trabectedin)

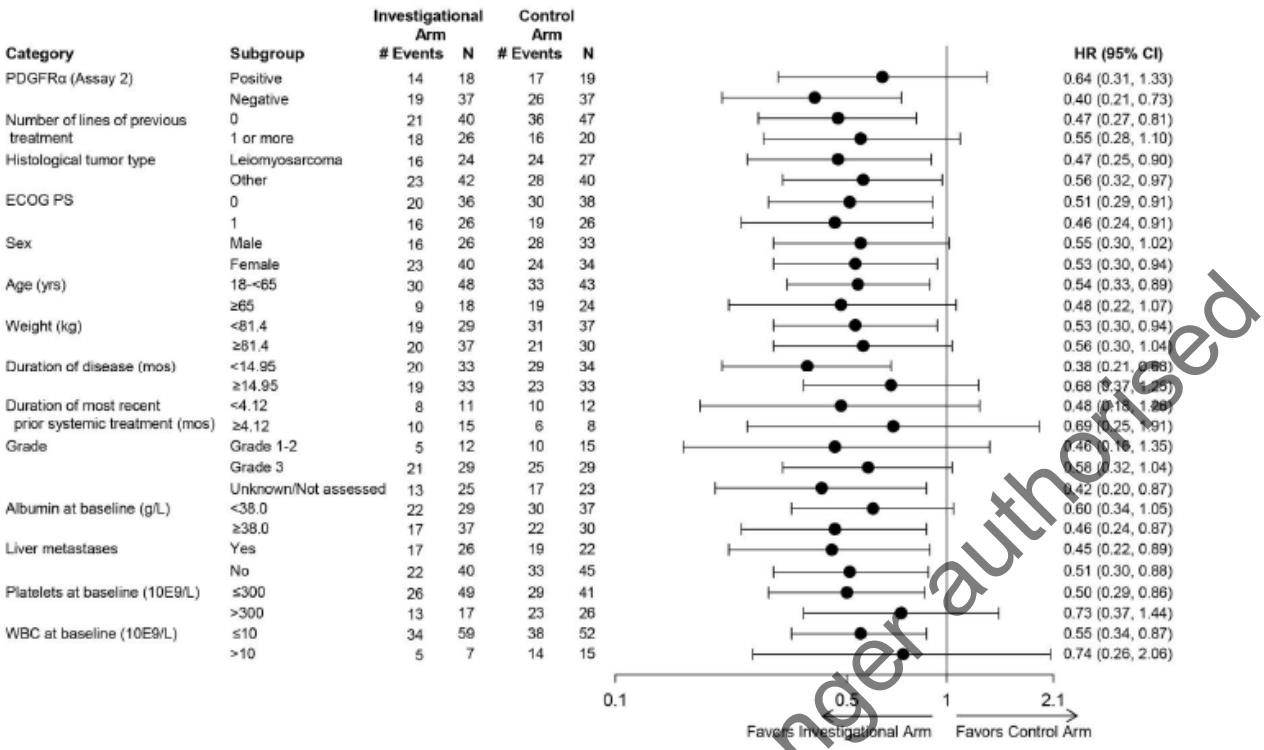
A *post hoc* sensitivity analysis to consider the impact of the number of cycles of therapy in OS has been provided (see table below).

Table 25: Overall Survival Results by Sensitivity Analysis Subgroups - Study JGDG Phase 2; ITT Population

	Olaratumab + Doxorubicin N = 66		Doxorubicin N = 67
Excluding patients discontinuing study treatment within 8 cycles due to AE or symptomatic PD			
Patients	61		49
OS Events	35		36
Median, months	26.8		16.1
Unstratified OS HR		0.55	
Unstratified log-rank p-value		0.012	
Excluding patients completing <4 cycles doxorubicin			
Patients	49		38
OS Events	24		28
Median, months	31.7		17.1
Unstratified OS HR		0.47	
Unstratified log-rank p-value		0.005	
Excluding patients completing <5 cycles doxorubicin			
Patients	41		31
OS Events	20		22
Median, months	31.7		17.5
Unstratified OS HR		0.51	
Unstratified log-rank p-value		0.027	
Excluding patients completing <6 cycles doxorubicin			
Patients	39		28
OS Events	18		19
Median, months	31.7		18.7
Unstratified OS HR		0.51	
Unstratified log-rank p-value		0.038	

Abbreviations: AE = adverse event; HR = hazard ratio; ITT = intent-to-treat; N = number of randomized patients; OS = overall survival; PD = progressive disease.
Data cut-off date: 16 May 2015.
Source: Table JGDG.14.37, Table JGDG.14.38, Table JGDG.14.39, Table JGDG.14.40.

OS (from the time of randomization) was similar among those patients on the Control Arm patients who received olaratumab monotherapy subsequent to discontinuation of doxorubicin and those patients who did not. The OS HR was 1.013 (p=.9660), indicating no evidence of a statistical difference in OS between these populations and underscoring that the use of olaratumab in the Control Arm did not adversely affect OS.



Abbreviations: CI = confidence interval; ECOG PS = Eastern Cooperative Oncology Group performance status; eCRF = electronic case report form; HR = hazard ratio; ITT = intent-to-treat; N = number of patients; OS = overall survival; PDGFRα = platelet-derived growth factor receptor alpha; WBC = white blood cells.

Figure 9: Forest plot of OS subgroup hazard ratios (with 95% confidence intervals) (ITT Population)

In addition, exploratory sensitivity analyses of PFS and OS were conducted which excluded patients never receiving study treatment or who discontinued during the first 8 cycles of study treatment for reasons other than radiographic progressive disease (PD), death, or completion of study treatment. Results of these analyses are presented in the following table.

Table 26: OS and PFS excluding patients discontinuing in the first 8 cycles for reasons other than radiographic PD, or completion of treatment – Phase 2, safety population (study JGDG)

	Investigational Arm N = 54	Control Arm N = 39
Number of PFS Events, n	50	35
Number PFS Censored, n	4	4
PFS Median[a] (months)	6.9	4.1
95% CI[a]	(3.4, 8.4)	(1.6, 5.4)
PFS Unstratified Log-rank p-value[b,d]	0.1963	
PFS Unstratified Hazard Ratio[c,d]	0.753	
95% CI[c]	(0.487, 1.162)	
Number of OS Events, n	33	30
Number OS Censored, n	21	9
OS Median[a] (months)	26.8	16.1
95% CI[a]	(20.9, NE)	(9.8, 21.7)
OS Unstratified Log-rank p-value[b,d]	0.0199	
OS Unstratified Hazard Ratio[c,d]	0.558	
95% CI[c]	(0.339, 0.918)	

Abbreviations: CI = confidence interval; N = number of randomised patients; n = number of patients in category; NE = not estimable; OS = overall survival; PD = progressive disease; PFS = progression-free survival.

a Estimated by the Kaplan-Meier method.
b Derived from a two–sided test.
c Hazard ratio is expressed as olaratumab + doxorubicin/doxorubicin and estimated from Cox model.
d Between olaratumab + doxorubicin arm and doxorubicin arm.

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 27: Summary of Efficacy for trial I5B-IE-JGDG (JGDG)

Title: A Phase 1b/2 Randomized Phase 2 Study Evaluating the Efficacy of Doxorubicin With or Without a Human Anti-PDGFRα Monoclonal Antibody (IMC-3G3) in the Treatment of Advanced Soft Tissue Sarcoma			
Study identifier	I5B-IE-JGDG (JGDG) / IMCL CP15-0806		
Design	This was an open-label, multicenter, Phase 1b/2 trial to evaluate the safety and efficacy of olaratumab (15 mg/kg administered on Days 1 and 8 of a 21-day cycle) in combination with doxorubicin (75 mg/m^2 administered on Day 1) in patients with advanced soft tissue sarcoma (STS). This treatment continued for up to 8 cycles at the investigator's discretion.		
	Duration of main phase:		In the Phase 1b portion and in both arms of the Phase 2 portion, doxorubicin was permitted to continue for a maximum of 8 cycles or until withdrawal criteria were met. Patients in the Phase 1b portion or the Investigational Arm of the Phase 2 portion could continue to receive olaratumab monotherapy after completion/discontinuation of doxorubicin until withdrawal criteria were met.
	Duration of Run-in phase:		Not applicable
	Duration of Extension phase:		Not applicable
Hypothesis	Superiority		
Treatments groups	Phase 1b Portion		N = 15 (ITT) • Olaratumab: 15 mg/kg (intravenous [I.V.]) on Days 1 and 8 of each 21-day cycle • Doxorubicin: 75 mg/m^2 (I.V.) on Day 1 of each 21-day cycle (maximum of 8 cycles)
	Investigational Arm		N = 66 (ITT) • Olaratumab: 15 mg/kg (intravenous [I.V.]) on Days 1 and 8 of each 21-day cycle • Doxorubicin: 75 mg/m^2 (I.V.) on Day 1 of each 21-day cycle (maximum of 8 cycles)
	Control Arm		N = 67 (ITT) • Doxorubicin: 75 mg/m^2 (I.V.) on Day 1 of each 21-day cycle (maximum of 8 cycles)
Endpoints and definitions	Primary endpoint	Progression-free survival (PFS)	Defined as the time from randomization until the first radiographic documentation of objective progression as defined by Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1, or death from any cause.
	Secondary endpoint	Overall Survival (OS)	Defined as the time from the date of randomization to the date of death from any cause.
	Secondary endpoint	Objective response rate (ORR)	Equal to the proportion of patients achieving a best overall response of partial response (PR) or complete response (CR), according to RECIST, from randomization until disease progression/recurrence.
	Secondary endpoint	Change in tumour size (CTS)	Maximum reduction from baseline per patient in the sum of target lesions.
Database lock	23 September 2014 (PFS); 19 June 2015 (OS)		

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (ITT)		
Descriptive statistics and estimate variability	Treatment group	Investigational Arm	Control Arm
	Number of subject	66	67
	PFS Median (months)	6.6	4.1
	95% CI	4.1, 8.3	2.8, 5.4
Effect estimate per comparison	Primary endpoint	Comparison groups	Investigational Arm / Control Arm
		Hazard Ratio	0.672
		95% CI	0.442, 1.021
		P-value	0.0615
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Investigational Arm	Control Arm
	Number of subject	66	67
	OS Median (months)	26.5	14.7
	95% CI	20.9, 31.7	9.2, 17.1
Effect estimate per comparison	Secondary endpoint (PFS)	Comparison groups	Investigational Arm / Control Arm
		Hazard Ratio	0.463
		95% CI	0.301, 0.710
		P-value	0.0003
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Investigational Arm	Control Arm
	Number of subject	66	67
	ORR (CR+PR) %	18.2	11.9
	95% CI	9.8, 29.6	5.3, 22.2
Effect estimate per comparison	Secondary Endpoint (ORR)	Comparison groups	Investigational Arm / Control Arm
		P-value	0.3421
Analysis description	**Secondary Analysis**		
Analysis population and time point description	Intent to treat		
Descriptive statistics and estimate variability	Treatment group	Investigational Arm	Control Arm
	Number of subject	66	67
	CTS % (mean)	10.3	8.2
Effect estimate per comparison	Secondary Endpoint (ORR)	Comparison groups	Investigational Arm / Control Arm
		P-value	0.7081

Analysis performed across trials (pooled analyses and meta-analysis)

No pooled analysis or meta-analysis has been submitted by the applicant.

Clinical studies in special populations

The efficacy data from study JGDG was analysed by age and gender and the results presented in the tables below.

Table 28: Subgroup analyses of PFS and OS by age (<65 years, ≥65 years); Study JGDG Phase 2 – ITT population

	Investigational Arm N=66		Control Arm N=67		Hazard Ratio[a]
	# Events / N	Median – months (95% CI[b])	# Events / N	Median – months (95% CI[b])	(95% CI[b])
Progression-Free Survival (Investigator Assessment)[c]					
Age<65 years	40/48	5.5 (2.8, 8.3)	31/43	4.1 (1.6, 5.4)	0.711 (0.442, 1.144)
Age ≥65 years	15/18	7.0 (3.0, 13.7)	17/24	4.4 (2.2,5.7)	0.563 (0.273, 1.162)
Overall Survival[d]					
Age<65 years	30/48	25.0 (16.7, 31.7)	33/43	15.4 (9.2, 18.7)	0.540 (0.328, 0.888)
Age ≥65 years	9/18	30.2 (6.8, NE)	19/24	10.4 (5.3, 21.9)	0.481 (0.216, 1.069)

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = number of randomized patients; NE = not estimable; OS = overall survival; PFS = progression-free survival.

a Expressed as olaratumab+doxorubicin/doxorubicin and estimated from Cox model.

b Estimate by the Kaplan-Meier method.

c Data cut-off date 15 August 2014.

d Data cut-off date 16 May 2015.

Table 29: Subgroup analyses of PFS and OS by gender (male, female); Study JGDG Phase 2 – ITT population

	Investigational Arm N=66		Control Arm N=67		Hazard Ratio[a]
	# Events / N	Median – months (95% CI[b])	# Events / N	Median – months (95% CI[b])	(95% CI[b])
Progression-Free Survival (Investigator Assessment)[c]					
Male	22/26	5.1 (2.4, 9.3)	26/33	4.1 (2.2, 5.6)	0.761 (0.428, 1.354)
Female	33/40	7.0 (5.5, 8.8)	22/34	4.1 (1.6, 12.9)	0.787 (0.456, 1.357)
Overall Survival[d]					
Male	16/26	22.0 (13.0, NE)	28/33	14.7 (8.0, 17.1)	0.551 (0.296, 1.025)
Female	23/40	27.3 (22.5, NE)	24/34	15.4 (8.9, 26.0)	0.527 (0.297, 0.936)

Abbreviations: CI = confidence interval; ITT = intent-to-treat; N = number of randomized patients; NE = not estimable; OS = overall survival; PFS = progression-free survival.

a Expressed as olaratumab+doxorubicin/doxorubicin and estimated from Cox model.

b Estimate by the Kaplan-Meier method.

c Data cut-off date 15 August 2014.

d Data cut-off date 16 May 2015.

Supportive study(ies)

No supportive studies have been submitted by the applicant.

2.5.3. Discussion on clinical efficacy

The current request for conditional marketing approval is based on a single open-label, randomized phase 1b/2 trial (study JGDG). It enrolled doxorubicin-naïve subjects with advanced STS not amenable to treatment with surgery or radiotherapy.

Design and conduct of clinical studies

The unblinded 1:1 randomized study was properly designed to reflect the universe of advanced STS facing palliative treatment with inclusion of a broad range of histotypes and an upper limit PS of 2 that reflects the real-life status of most individuals. It is to the credit of the trial's design that doxorubicin was chosen as the only treatment in the standard-arm, avoiding investigator-chosen schemes, even at the expense of recruitment rate. Maintenance of single-agent olaratumab was allowed in the experimental arm, while crossover to single-agent olaratumab was permitted in control arm upon progression.

PFS is considered an appropriate endpoint. The study was designed with a planned enrolment of 130 patients, assuming a 50% improvement in PFS, which is an ambitious target given the lack of significant improvement in the first-line treatment of STS for decades. Stratification took into account relevant data for the population included in the trial, even though the actual stratifications factors used when it comes to analysing the PFS were limited to number of lines of previous therapy (0 versus >0) and disease histology (LMS versus non-LMS).

Efficacy data and additional analyses

Baseline characteristics reflected those to be expected in the intended patient population to be treated with olaratumab. Histologies varied widely but over 60% of the cases were among the common subtypes of L-sarcomas and undifferentiated pleomorphic sarcoma. As expected early in the disease history, most subjects remained quite symptom-free (PS 0-1) in spite of significant numbers of grade 3 events (> 40%) with widespread disease not only to the lungs (around 60%), but also liver, soft-tissue and lymph nodes (over one third of the cases each).

Trial results were positive and they seem compelling from the clinical point of view. Treatment with olaratumab on top of doxorubicin nearly doubled PFS (8.2 vs 4.5 months; according to the IRC; 6.6 vs. 4.1 months, HR 0.672 [95% CI: 0.442, 1.021], p = 0.0615 according to investigator assessment). The improvement in OS was even more important. Olaratumab reduced the risk of death by 53.7% (HR = 0.463; p=0.0003), representing 80% longer median survival in the investigational arm (26.5 months vs. 14.7 months). In addition, Kaplan-Meier curves showed an unusual early separation and a persistence of the OS benefit over time. Although JGDG was a relatively small phase 1b/2 exploratory trial, the efficacy results observed, if confirmed within the context of the ongoing phase 3 trial JGDJ, represent a potential paradigm-shift in the treatment of advanced STS.

After adjusting for factors most likely to affect prognosis, olaratumab maintained its effect in the two groups of LMS and non-LMS. However, due to the high number of different sarcoma subtypes, the absence of a clear pattern according to the histology is not unexpected. It is not possible to exclude that the wide histological heterogeneity of the study could potentially have impacted on the overall survival results. However, the numbers are too small to make any sound conclusion.

Further analyses according to tumour load at baseline and baseline characteristics were provided during the procedure and did not show important discrepancies regarding the main results in terms of HR for both PFS and OS.

The Applicant was requested to evaluate the impact of the observed higher rate of early interruption of treatment for reason other than radiographically documented PD or death in the Control arm compared to the Investigational arm (50.7% vs 15.6%). Despite an improvement in the absolute median OS in the Control arm compared to the primary analysis (16.1 vs 14.7 months), suggesting that early interruption in the Control arm was related to a worse prognosis, the magnitude of benefit was maintained compared to the primary analyses (unstratified HRs 0.558 vs 0.517).

Post-study treatments varied between treatment arms, but none of the used regimens have been shown to increase the overall survival of patients. Moreover, two OS sensitivity analysis ruled out any eventual influence of post-study treatment on the primary OS analysis. In addition, post-hoc sensitivity analyses were performed to consider the impact of the number of cycles of therapy on OS. No discrepancies were found.

Potential baseline imbalances were also explored. A stratified Cox multivariate model of OS was performed, adjusted for specific factors considered potentially prognostic for OS on the basis of the literature. The OS HR for the treatment effect was 0.429 (95% CI: 0.267, 0.690), consistent with the stratified univariate OS HR of 0.463 observed in the main analysis. Further analyses according to tumour load at baseline and baseline characteristics, did not show important discrepancies regarding the main results in terms of HR for both PFS and OS.

The survival censoring is not considered informative, given that the vast majority are due to patients still alive. In addition, subgroups analyses do not reveal any signal of data driven by any subgroup.

The discrepancy between the PFS results and the outstanding survival outcome, could be also related to a major post-progression and off therapy effect. This possibility warrants further analyses with different approaches based on biomarkers and PFS2 results. Unfortunately, the Applicant was not able to provide the results of the exploratory biomarker analyses planned in the phase 2 study nor PFS2 data. Biomarker analyses and PFS2 are planned in the ongoing phase 3 JGDJ study, which could shed some light on that (See Annex II).

PDGFRα expression did not have any predictive value on response. Two IHC were sequentially used for PDGFRα expression studies. The first one was flawed with poor specificity and cross-reaction with irrelevant but similar receptors. A more precise assay was developed but equally failed to segregate responders from non-responders. The role of PDGFRα will be clarified in the confirmatory phase III trial, as it could have a profound impact on the clinical use of the drug and on its definitive regulatory status.

As with all therapeutic proteins, there is the potential for immunogenicity. Overall, a low incidence of both treatment emergent anti-drug antibodies and neutralising antibodies were detected in clinical trial samples.

Additional efficacy data needed in the context of a conditional MA

The survival advantage seen with olaratumab is not associated with a delay in tumour progression. Potential differences in some baseline characteristics (although the limited number of patients cannot allow drawing conclusions), the different histological subtypes included within the study and a (likely) off therapy effect could partly explain these results. These hypotheses require confirmation.

Because of the limited sample size, it is unlikely that further answers may be extrapolated from the phase 1b/2 study supporting this application, particularly in terms of subgroup analyses. Only the Phase 3 JGDJ

study will provide further clarification regarding the obtained and the missing data. It is reassuring that the enrolment of the phase 3 study is almost completed (as of 20 July 2016, the number of patients randomised is 505. Pre-planned enrolment was 460, with all sites closed to screening except in Japan and Taiwan to meet local regulatory requirements). Therefore, it is considered that recruitment won't be jeopardized by the time of EU launch, and the Applicant will likely be in a position to provide the results from the phase 3 study.

2.5.4. Conclusions on the clinical efficacy

According to the data from the phase II study JGDG, the use of combination of olaratumab and doxorubicin has shown an unexpected but clinically meaningful increase in OS in comparison to doxorubicin single agent (HR 0.463, 95% CI: 0.301- 0.710, p=0.0003; median gain of 11.8 months). This result seems to be reliable as supported by several sensitivity analyses. Nevertheless, this gain in life expectancy is not explained by the antitumor activity of the combination and PFS and ORR data do not show the same level of efficacy. A phase III randomized double-blind confirmatory study (JGDJ) is currently ongoing. Taking into account the high clinical relevance of the OS results obtained in a rare disease with limited effective treatment options and poor long-term survival, a conditional MA can be considered.

The CHMP considers the following measures necessary to address the missing efficacy data in the context of a conditional MA:

In order to further confirm the efficacy and safety of olaratumab in the treatment of patients with advanced soft tissue sarcoma, the MAH should submit the clinical study report of the phase III study JGDJ comparing doxorubicin plus olaratumab versus doxorubicin in patients with advanced or metastatic STS (including exploratory biomarker data) by 31 January 2020.

2.6. Clinical safety

Patient exposure

A total of 485 patients have received olaratumab in 9 Phase 1 and 2 clinical studies. The safety profile of olaratumab in combination with doxorubicin for the treatment of patients with advanced STS is principally derived from the Phase 2 portion of Study JGDG (n= 129, 64 patients in the investigational arm and 65 patients in the comparator arm).

Table 30: Patient exposure to olaratumab across the olaratumab studies◇

	Patients enrolled in the trial	Patients exposed to olaratumab		Patients exposed to the proposed dose range*
		In the Investigational Arm	Crossover in the Control Arm°	
Olaratumab + doxorubicin in STS				
JGDG (registration study)				
Phase 2 portion	133	64	30	94
Phase 1b portion	15	15		15
JGDI (phase 1, DDI Part A)	25	24#		0#
Olaratumab monotherapy in tumour types other than STS				

JGDC (phase 1, advanced cancer)	20	19		0
JGDF (phase 1, advanced cancer, Japan only)	17	16		6
JGDE (phase 2 randomized vs ramucirumab, GBM)	80	40		0
JGDH (phase 2 , GIST)	30	21		0
Olaratumab + chemotherapy (not doxorubicin) in tumour types other than STS				
JGDA (phase 2 randomized, ovarian cancer, olaratumab + liposomal doxorubicin)	125	62	28	0
JGDB (phase 2 randomized, NSCLC 1st line, olaratumab + carboplatin/paclitaxel)	137	67	18	0
JGDD (phase 2 randomized, prostate, olaratumab + mitoxantrone)	123	62	19	0

◇**Studies data cut-off**: Study JGDG: 16 May 2015; Study JGDI: 20 May 2015; Other studies: primary database lock dates on or before 23 July 2015
*****Olaratumab 15 mg/kg D1,8 every 3 weeks
° patients initially randomized to the control arm who received Olaratumab monotherapy subsequent to discontinuation of chemotherapy (Studies JGDA, JGDB, JGDD and JGDG)
Olaratumab 15 mg/kg D1,**10** on cycle 1, then D1,8 every 3 weeks

Table 31: Extent of Exposure to Olaratumab Study JGDG (Phase 2) - Safety Population

	Investigational Arm N = 64	Control Arm: Olaratumab Monotherapy after Doxorubicin[a] N = 30
Duration of Olaratumab Treatment (weeks)		
Mean (SD)	31.4 (26.71)	17.6 (31.25)
Median duration (weeks)	26.1	7.0
Range (weeks)	3.0 – 128.0	3.0 – 134.0
Number of Infusions, n		
Mean (SD)	19.4 (17.47)	10.6 (19.73)
Median	16.5	4.0
Range	1.0 - 83.0	1.0 – 81.0
Cumulative Dose Level (mg/kg)		
Mean (SD)	277.7 (256.27)	155.4 (284.74)
Median	230.1	61.0
Range	0.7 – 1217.1	0.2 – 1232.0
Relative Dose Intensity (%)		
Mean (SD)	83.0 (18.67)	79.0 (22.78)
Median	88.7	85.8
Range	2.4 – 101.9	0.6 – 96.8

Abbreviations: Investigational Arm = olaratumab plus doxorubicin; N = number of treated patients; n = number of patients in category; SD = standard deviation.
Note: Exposure to olaratumab in the Investigational Arm includes olaratumab monotherapy following discontinuation of doxorubicin after 8 cycles of combination therapy.
a Patients initially randomized to the Control Arm who received olaratumab monotherapy after discontinuation of doxorubicin.

Doxorubicin exposure was higher in the Investigational Arm: median number of cycles was 7 vs. 4 in the Investigational vs. Control Arm respectively.

Table 32: Extent of Exposure to Doxorubicin Study JGDG (Phase 2) - Safety Population

	Investigational Arm N = 64	Control Arm N = 65
Duration of Doxorubicin Treatment (weeks)		
Mean (SD)	17.6 (7.72)	13.6 (8.21)
Median duration (weeks)	21.3	12.3
Range (weeks)	3.0 – 29.0	3.0 – 25.4
Number of Infusions, n (%)		
Mean (SD)	5.7 (2.54)	4.4 (2.67)
Median	7.0	4.0
Range	1.0 – 8.0	1.0 – 8.0
Cumulative Dose Level (mg/m²)		
Mean (SD)	416.4 (185.01)	328.9 (203.50)

	Investigational Arm N = 64	Control Arm N = 65
Median	487.6	299.6
Range	73.9 – 617.0	74.9 – 751.3
Relative Dose Intensity (%)		
Mean (SD)	95.7 (10.93)	97.4 (8.65)
Median	99.1	99.0
Range	66.8 – 148.6	73.5 – 125.2

Abbreviations: N = number of treated patients; n = number of patients in category; SD = standard deviation.

Adverse events

Overall, the percentages of patients who experienced ≥1 TEAE (Investigational vs. Control Arm: 63 [98.4%] vs. 64 [98.5%]) and ≥1 treatment-emergent SAE (27 [42.2%] vs. 25 [38.5%]) were similar between treatment arms. There were more patients in the Investigational Arm that had TEAEs of Grade ≥3 compared with the Control Arm (51 [79.7%] vs. 45 [69.2%]).

Table 33: Overview of treatment-emergent adverse events – Safety population study JGDG (Phase 2)

Parameter[c]	Investigational Arm[a] N = 64 n (%)	Control Arm[a] N = 65 n (%)	Control Arm: Olaratumab Monotherapy after Doxorubicin[b] N = 30 n (%)
Patients with Any Adverse Event	**63 (98.4)**	**64 (98.5)**	**26 (86.7)**
Related to Any Study Drug	63 (98.4)	63 (96.9)	13 (43.3)
Related to Olaratumab	56 (87.5)	NA	11 (36.7)
Related to Chemotherapy	62 (96.9)	63 (96.9)	8 (26.7)
Patients with Any Treatment-Emergent SAE	**27 (42.2)**	**25 (38.5)**	**9 (30.0)**
Related to Any Study Drug	14 (21.9)	17 (26.2)	2 (6.7)
Related to Olaratumab	10 (15.6)	NA	2 (6.7)
Related to Chemotherapy	12 (18.8)	17 (26.2)	1 (3.3)
Patients with Any Grade ≥3 Adverse Event	**51 (79.7)**	**45 (69.2)**	**11 (36.7)**
Related to Any Study Drug	43 (67.2)	36 (55.4)	2 (6.7)
Related to Olaratumab	29 (45.3)	NA	2 (6.7)
Related to Chemotherapy	40 (62.5)	36 (55.4)	1 (3.3)
Patients with Any AE Leading to Discontinuation of Any Study Drug	**8 (12.5)**	**12 (18.5)**	**2 (6.7)**
Any AE Leading to Discontinuation of Olaratumab Only	1 (1.6)	NA	2 (6.7)
Any AE Leading to Discontinuation of Doxorubicin Only	3 (4.7)	12 (18.5)	0
Any AE Leading to Discontinuation of Both Olaratumab and Doxorubicin	4 (6.3)	0	0
Patients with Any AE with Outcome Death on Treatment	**0**	**5 (7.7)**	**2 (6.7)**
Related to Any Study Drug	0	2 (3.1)	1 (3.3)
Related to Olaratumab	0	NA	1 (3.3)
Related to Chemotherapy	0	2 (3.1)	1 (3.3)
Patients with Any AE with Outcome Death within 30 days of Last Dose	0	4 (6.2)	**2 (6.7)**
Related to Any Study Drug	0	2 (3.1)	1 (3.3)
Related to Olaratumab	0	NA	1 (3.3)
Related to Chemotherapy	0	2 (3.1)	1 (3.3)

Abbreviations: AE = adverse event; N = number of treated patients; n = number of patients in category; NA = not applicable; SAE = serious adverse event.
a The median number of doxorubicin infusions in the Investigational Arm was 7 and 4 in the Control Arm (Table 2.7.4.3).
b Patients initially randomized to the Control Arm who received olaratumab monotherapy after discontinuation of doxorubicin.
c Adverse event with missing or unknown relationship to study drug is counted as 'related'.

Summary of TEAEs occurring in ≥10% of patients in the pivotal study is presented below:

Table 34: Summary of TEAEs (any grade and grade ≥ 3) occurring in ≥ 10% in safety population, JGDG Study (Phase 2)

Adverse Event Term	Investigational Arm[a] N = 64 n (%)		Control Arm[a] N = 65 n (%)		Control Arm: Olaratumab Monotherapy after Doxorubicin[b] N = 30 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with any AE	**63 (98.4)**	**51 (79.7)**	**64 (98.5)**	**45 (69.2)**	**26 (86.7)**	**11 (36.7)**
Nausea	47 (73.4)	1 (1.6)	34 (52.3)	2 (3.1)	6 (20.0)	1 (3.3)
Fatigue[c]	44 (68.8)	6 (9.4)	45 (69.2)	2 (3.1)	6 (20.0)	2 (6.7)
Musculoskeletal Pain[d]	41 (64.1)	5 (7.8)	16 (24.6)	1 (1.5)	7 (23.3)	2 (6.7)
Neutropenia[e]	38 (59.4)	35 (54.7)	25 (38.5)	22 (33.8)	0	0
Mucositis[f]	34 (53.1)	2 (3.1)	23 (35.4)	3 (4.6)	2 (6.7)	0
Alopecia	33 (51.6)	0	26 (40.0)	0	2 (6.7)	0
Vomiting	29 (45.3)	0	12 (18.5)	0	5 (16.7)	0
Infections and Infestations[g]	27 (42.2)	5 (7.8)	27 (41.5)	7 (10.8)	6 (20.0)	1 (3.3)
Anaemia[h]	26 (40.6)	8 (12.5)	24 (36.9)	6 (9.2)	5 (16.7)	1 (3.3)
Constipation	22 (34.4)	0	21 (32.3)	1 (1.5)	3 (10.0)	0
Diarrhoea	22 (34.4)	2 (3.1)	15 (23.1)	0	5 (16.7)	0
Decreased Appetite	20 (31.3)	1 (1.6)	13 (20.0)	0	3 (10.0)	2 (6.7)
Abdominal Pain[i]	15 (23.4)	2 (3.1)	9 (13.8)	0	3 (10.0)	0
Pyrexia	15 (23.4)	0	12 (18.5)	0	3 (10.0)	0
Thrombocytopenia[j]	16 (25.0)	7 (10.9)	14 (21.5)	5 (7.7)	0	0
Cough	14 (21.9)	0	12 (18.5)	0	3 (10.0)	0
Neuropathy[k]	14 (21.9)	0	7 (10.8)	0	2 (6.7)	0
Headache	13 (20.3)	0	6 (9.2)	0	1 (3.3)	0
Dyspnoea	11 (17.2)	0	12 (18.5)	1 (1.5)	1 (3.3)	1 (3.3)
Hypokalaemia[l]	9 (14.1)	2 (3.1)	6 (9.2)	3 (4.6)	1 (3.3)	1 (3.3)
Lymphopenia[m]	8 (12.5)	5 (7.8)	3 (4.6)	1 (1.5)	0	0
Febrile Neutropenia	8 (12.5)	8 (12.5)	9 (13.8)	9 (13.8)	0	0
Insomnia	8 (12.5)	0	6 (9.2)	0	2 (6.7)	0
Non-cardiac Chest Pain	8 (12.5)	0	4 (6.2)	0	1 (3.3)	0
Anxiety	7 (10.9)	0	2 (3.1)	0	0	0
Dehydration	7 (10.9)	1 (1.6)	6 (9.2)	0	2 (6.7)	1 (3.3)
Dry Eye	7 (10.9)	0	2 (3.1)	0	0	0
Dry Mouth	7 (10.9)	1 (1.6)	6 (9.2)	0	1 (3.3)	0
Rash[n]	7 (10.9)	0	5 (7.7)	1 (1.5)	5 (16.7)	0
Hypomagnesaemia[o]	7 (10.9)	0	1 (1.5)	0	1 (3.3)	0
Weight Decreased	7 (10.9)	0	7 (10.8)	0	2 (6.7)	0
Dizziness	6 (9.4)	0	10 (15.4)	0	5 (16.7)	0
Chills	4 (6.3)	0	2 (3.1)	0	3 (10.0)	0
Adverse Events of Special Interest[p]						
Cardiac Dysfunction	15 (23.4)	1 (1.6)	11 (16.9)	0	4 (13.3)	0
Cardiac Arrhythmias	10 (15.6)	0	10 (15.4)	1 (1.5)	5 (16.7)	1 (3.3)
Infusion-related Reactions	8 (12.5)	2 (3.1)	0	0	3 (10.0)	1 (3.3)

Abbreviations: AE = adverse event; AESI = adverse event of special interest; IRR = infusion-related reaction; MedDRA = Medical Dictionary for Regulatory Activities; N = number of treated patients; n = number of patients in category; TEAE = treatment-emergent adverse event.

Note: Refer to Table APP.2.7.4.7.5.1 and Table APP.2.7.4.7.5.2 for the full list of PTs included in each consolidated TEAE term and AESI.

Note: TEAEs with grade missing are counted in 'Any Grades'.

Note: At each level of summarization, a patient is counted once according to the TEAE with worst grade.

Note: Consolidated TEAE categories and AESIs are italicized. For the list of preferred terms that were reported in Study JGDG, refer to Table JGDG.14.64, Table 2.7.4.11 and Table JGDG.14.115.

a The median number of doxorubicin infusions in the Investigational Arm was 7 and 4 in the Control Arm (Table 2.7.4.3).

b Patients initially randomized to the Control Arm who received olaratumab monotherapy after discontinuation of doxorubicin.

c Preferred terms reported were fatigue and asthenia.

d Preferred terms reported were arthralgia, back pain, bone pain, flank pain, groin pain, muscle spasms, musculoskeletal chest pain, musculoskeletal pain, myalgia, neck pain, and pain in extremity.

e Preferred terms reported were neutropenia, leukopenia, neutrophil count decreased, and white blood cell count decreased.

f Preferred terms reported were mucosal inflammation, oropharyngeal pain, and stomatitis.

g Includes all preferred terms within the MedDRA™ system organ class of Infections and Infestations.

h Preferred terms reported were anemia and hemoglobin decreased.

i Preferred terms reported were abdominal pain upper, abdominal pain, and abdominal pain lower.

j Preferred terms reported were thrombocytopenia and platelet count decreased.

k Preferred terms reported were neuropathy peripheral, paresthesia, peripheral sensory neuropathy, and hypoesthesia.

l Preferred term reported was hypokalemia.

m Preferred terms reported were lymphocyte count decreased and lymphopenia.

n Preferred terms reported were rash, rash papular, dermatitis, dermatitis acneiform, rash pustular, rash macular, and rash pruritic.

o Preferred terms reported were hypomagnesemia and magnesium deficiency.

p Preferred terms reported for *IRRs* (from the core IRR analysis based on 48 preferred terms [prior to medical adjudication]) are in Table JGDG.12.30. For the comprehensive incidence of *IRRs* based on the medically adjudicated core and post-hoc IRR analyses, see Table 2.7.4.37. Preferred terms reported for *cardiac arrhythmias* are in Table 2.7.4.43 and Table JGDG.14.115, and in Table 2.7.4.45 and Table JGDG.14.115for *cardiac dysfunction*.

Notable AEs

Notable patients were defined as those patients who met 1 or more of the following criteria: Discontinued study treatment due to any AE; Experienced death while on any study treatment or within 30 days of last study dose; Experienced suspected unexpected serious adverse reactions; Discontinued any study treatment due to reasons other than AE or progressive disease (PD); Discontinued the study due to lost to follow-up; Experienced AESIs.

Gastrointestinal Disorders

It was observed that, in the Investigational Arm compared with the Control Arm, a higher incidence of nausea (47 [73.4%] vs. 34 [52.3%]), *mucositis* (34 [53.1%] vs. 23 [35.4%]), vomiting (29 [45.3%] vs. 12 [18.5%]), and diarrhea (22 [34.4%] vs. 15 [23.1%]) were observed. These events are generally considered toxicities associated with doxorubicin; they were monitorable and manageable, predominantly Grade ≤2, and did not lead to a higher incidence of treatment discontinuation.

Neutropenia/Febrile Neutropenia/Infection

In the Phase 2 portion of Study JGDG, the incidence of any-grade neutropenia (consolidated term) was higher in the Investigational Arm than in the Control Arm (38 [59.4%] vs. 25 [38.5%], respectively). The incidence of Grade 3 neutropenia was also higher in the Investigational Arm compared with the Control Arm (12 [18.8%] vs. 5 [7.7%], respectively); a higher rate was also observed in the Investigational Arm with Grade ≥4 neutropenia (23 [35.9%] vs. 17 [26.2%], respectively).

As with the AE reports, the laboratory results also demonstrate a similar trend in that there was a higher rate of decreased neutrophils shifts from Grade 0 at baseline to Grade 3 or 4 while on study observed in the Investigational Arm than in the Control Arm.

In order to assess any potential association of neutropenia with infectious complications, an additional analysis was performed. The rate of severe infection was similar between the treatment arms. Despite the higher rate of neutropenia in the Investigational Arm versus the Control Arm, the combination of olaratumab and doxorubicin did not result in an increased incidence of febrile neutropenia (12.5% in the olaratumab plus doxorubicin arm and 13.8 % in the doxorubicin alone arm) or infections. In addition, no increase in the number of treatment discontinuations or deaths was observed in the Investigational Arm as a consequence of the higher rate of neutropenia.

Table 35: Treatment-emergent severe infections and neutropenic infection – Safety population – Study JGDG (Phase 2)

	Investigational Arm N = 64 n (%)	Control Arm N = 65 n (%)
Severe Infection	13 (20.3)	14 (21.5)
Neutropenic Infection	8 (12.5)	11 (16.9)
Non-neutropenic Infection	5 (7.8)	3 (4.6)

Abbreviations: N = number of treated patients; n = number of patients in category.

The use of G-CSF for the treatment of neutropenia was higher in the Investigational Arm 35 [(54.7%]) compared with the Control Arm (24 [36.9%]), consistent with the higher incidence of neutropenia on the Investigational Arm.

Anaemia

The incidence of anaemia was similar in both treatment arms (26 [40.6%] in the Investigational Arm vs. 24 [36.9%] in the Control Arm) and consisted mainly of Grade 1 and 2 events. There were not differences between the treatment arms in the rate of shifts in low haemoglobin while on study. There were no Grade 4 anaemia events by laboratory assessment.

Transfusions were the most frequent procedures performed on both treatment arms, primarily red blood cell transfusions for the treatment of anaemia, and its use was similar between treatment arms (17.2% [Investigational Arm] vs. 13.8% [Control Arm]).

Thrombocytopenia

The incidence of thrombocytopenia was similar in both arms (16 [25.0%] in the Investigational Arm vs. 14 [21.5%] in the Control Arm) and consisted mainly of Grade 1 and 2 events (Grade ≥4 events were also evenly distributed between both treatment arms: 2 [3.1%] in each arm).

There was no difference between the treatment arms in the rate of shifts in low platelets while on study. One patient (1.5%) on the Control Arm received platelet transfusion for the treatment of thrombocytopenia.

Musculoskeletal Pain

In Study JGDG, an imbalance was seen between the Investigational Arm and Control Arm in the SOC of Musculoskeletal and Connective Tissue Disorders and also in individual PTs within this SOC. This includes AEs pertaining to pain in relation to various anatomical structures such as muscles, joints, and bone.

The incidence of musculoskeletal pain (any grade) was higher in the Investigational Arm (41 [64.1%]) as compared to the Control Arm (16 [24.6%]). The majority of these events were Grade 1 or 2. The incidence of Grade ≥3 musculoskeletal pain was higher in the Investigational Arm (5 [7.8%]) as compared to the Control Arm (1 [1.5%]). In the majority of patients the pain was related to the patients' underlying cancer or metastases or pre-existing or concomitant conditions. The majority of these events occurred in the first 4 cycles. The pain can last from few days to up to 200 days. In some patients there was a recurrence of pain .The pain did not worsen with time or during recurrence. Moreover, the majority of Grade 2-3 events occurred within the first 2 cycles.

Table 36: Summary of treatment-emergent adverse events of consolidated term musculoskeletal pain – Safety population Study JGDG (Phase 2)

	Investigational Arm N = 64 n (%)		Control Arm N = 65 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Musculoskeletal Pain	41 (64.1)	5 (7.8)	16 (24.6)	1 (1.5)
Pain in Extremity	15 (23.4)	2 (3.1)	1 (1.5)	0
Back Pain	12 (18.8)	2 (3.1)	6 (9.2)	0
Muscle Spasms	10 (15.6)	0	1 (1.5)	0
Arthralgia	8 (12.5)	0	2 (3.1)	0
Musculoskeletal Chest Pain	8 (12.5)	1 (1.6)	2 (3.1)	0
Myalgia	6 (9.4)	0	2 (3.1)	0
Bone Pain	5 (7.8)	0	1 (1.5)	0
Musculoskeletal Pain	4 (6.3)	0	2 (3.1)	1 (1.5)
Flank Pain	2 (3.1)	0	1 (1.5)	0
Groin Pain	2 (3.1)	0	0	0
Neck Pain	1 (1.6)	0	0	0

Abbreviations: N = number of treated patients; n = number of patients in category.

Pain in Extremity

Pain in extremity (any grade) was reported as a TEAE in 15 patients (23.4%) in the Investigational Arm versus 1 patient (1.5%) in the Control Arm. Grade ≥3 events of pain in extremity were reported in 2 patients in the Investigational Arm (3.1%) and none in Control Arm.

Table 37: Adverse events of pain in extremity - Safety population Study JGDG (Phase 2)

n	Grades	Lilly Assessment
Investigational Arm		
6	1 (n=5) 3 (n=1)	Related to underlying disease
2	1 (n=2)	Related to radiculopathy secondary to spinal metastases
1	3	Related to cellulitis
1	2	Related to DVT of leg
1	1	Related to peripheral neuropathy (investigator assessed as related to doxorubicin)
1	1	Related to generalized musculoskeletal pain, muscle spasms and pre-existing disc herniation
3	1	The investigator assessed these events as not related to investigational drug. Without further information, this AE is possibly drug related.
Control Arm		
1	1	Related to underlying tumor

Abbreviations: AE = adverse event; DVT = deep vein thrombosis; n = number of patients in category.

A total of 8 of 15 (53%) patients in the Investigational Arm and 1 of 1 (100%) patient in the Control Arm had the AE pain in extremity assessed by the Sponsor as related to underlying tumour or metastases. Of the remaining 7 patients in the Investigational Arm, pain in extremity was assessed as related to an AE for 4 patients (cellulitis [n=1], deep vein thrombosis [DVT] of leg [n=1], peripheral neuropathy [n=1], and generalized muscle pain and muscle spasms [n=1]). For 3 patients, further information was not available, and the Sponsor assessed these as possibly drug related. Most AEs were Grade 1 or 2.

Adverse Events of Special Interest

Adverse events of special interest have been defined by the Sponsor as follows:

- Combination of olaratumab and doxorubicin (from Studies JGDG and JGDI)
    - IRRs
    - Cardiac arrhythmias
    - Cardiac dysfunction
- Olaratumab only (from all 9 studies)
    - IRRs
- Doxorubicin (from Studies JGDG and JGDI)
    - Cardiac arrhythmias
    - Cardiac dysfunction

Infusion-Related Reactions

As a monoclonal antibody, olaratumab is associated with the risk of *IRRs*. Accordingly, *IRRs* were assessed as an AESI across all studies in patients who received at least 1 dose of olaratumab. A predetermined list of 48

PTs constituting the broad concept of IRR was used in the core analysis of IRRs across the 9 studies. An additional post-hoc analysis using an additional 9 PTs was performed at the request of FDA. The additional PTs included in this post-hoc analysis were pyrexia, chills, flushing, hypotension, dyspnoea, back pain, and abdominal pain (abdominal pain, abdominal pain lower and abdominal pain upper). A summary table of IRRs across all studies testing olaratumab is presented below:

Table 38: Overall Assessment of Infusion-Related Reactions across the olaratumab Clinical Development Program (9 studies), Safety Population

	IRR due to Olaratumab				IRR due to Chemotherapy	
	Olaratumab-Containing Arm[a,b]		Control Arm: Olaratumab Monotherapy after Chemotherapy[c]		Control Arm	
Study	Any Gr n (%)	Gr ≥3 n (%)	Any Gr n (%)	Gr ≥3 n (%)	Any Gr n (%)	Gr ≥3 n (%)
Study JGDG (Phase 1b portion)	N = 15					
Core IRR analysis (48 PTs)	2 (13.3)	0				
Post-hoc IRR analysis (9 PTs)	0	0				
Total for JGDG Phase 1b	**2 (13.3)**	**0**				
Study JGDG[d] (Phase 2 portion)	N = 64		N = 30		N = 65	
Core IRR analysis (48 PTs)	6 (9.4)	2 (3.1)	4 (13.3)[e]	2 (6.7)[e]	0	0
Post-hoc IRR analysis (9 PTs)	3 (4.7)	0	3 (10.0)	0	2 (3.1)	0
Total Patients in Study JGDG Phase 2[e]	**8 (12.5)**	**2 (3.1)**	**6 (20.0)**	**2 (6.7)**	**2 (3.1)**	**0**
Study JGDI	N = 24					
Core IRR analysis (48 PTs)	2 (8.3)	1 (4.2)				
Post-hoc IRR analysis (9 PTs)	1 (4.2)	0				
Total Patients in Study JGDI	**3 (12.5)**	**1 (4.2)**				
Study JGDA[d]	N = 62		N = 28		N = 61	
Core IRR analysis (48 PTs)	4 (6.5)	0	1 (3.6)	0	2 (3.3)	0
Post-hoc IRR analysis (9 PTs)	2 (3.2)	0	2 (7.1)	0	1 (1.7)	0
Total Patients in Study JGDA	**6 (9.7)**	**0**	**3 (10.7)**	**0**	**3 (4.9)**	**0**
Study JGDB[d]	N = 67		N = 18		N = 64	
Core IRR analysis (48 PTs)	12 (17.9)	1 (1.5)	2 (11.1)	1 (5.6)	1 (1.6)	0
Post-hoc IRR analysis (9 PTs)	5 (7.5)	0	0	0	4 (6.3)	1 (1.6)
Total Patients in Study JGDB	**17 (25.4)**	**1 (1.5)**	**2 (11.1)**	**1 (5.6)**	**5 (7.8)**	**1 (1.6)**
Study JGDD[d]	N = 62		N = 19		N = 59	
Core IRR analysis (48 PTs)	4 (6.5)	3 (4.8)	3 (15.8)	1 (5.3)	0	0
Post-hoc IRR analysis (9 PTs)	2 (3.2)	0	0	0	0	0
Total Patients in Study JGDD	**6 (9.7)**	**3 (4.8)**	**3 (15.8)**	**1 (5.3)**	**0**	**0**
Study JGDC[f]	N = 19					
Core IRR analysis (48 PTs)	3 (15.8)	0				
Post-hoc IRR analysis (9 PTs)	2 (10.5)	0				
Total Patients in Study JGDC	**5 (26.3)**	**0**				
Study JGDF[f]	N = 16					
Core IRR analysis (48 PTs)	0	0				
Post-hoc IRR analysis (9 PTs)	0	0				
Total Patients in Study JGDF	**0**	**0**				
Study JGDE[f]	N = 40					
Core IRR analysis (48 PTs)	4 (10.0)	0				
Post-hoc IRR analysis (9 PTs)	1 (2.5)	0				
Total Patients in Study JGDE	**4 (10.0)**	**0**				
Study JGDH[f]	N = 21					
Core IRR analysis (48 PTs)	4 (19.0)	0				
Post-hoc IRR analysis (9 PTs)	3 (14.3)	0				
Total Patients in Study JGDH	**5 (23.8)**	**0**				
Total number of patients	**56 (14.4)**	**7 (1.8)**	**14 (14.7)**	**4 (4.2)**	**10 (4.0)**	**1 (0.4)**

Abbreviations: AE = adverse event; Gr = grade; IRR = infusion-related reaction; N = number of treated patients; n = number of patients in category; PT = preferred term.

a As part of the Lilly adjudication process, patients receiving olaratumab plus chemotherapy who had an *IRR* that resulted in the interruption of the chemotherapy were considered to have an *IRR* due to chemotherapy and unlikely related to olaratumab. The overall frequencies for olaratumab *IRRs* provided in the Olaratumab-Containing Arm exclude these chemotherapy-related *IRRs*. This only affected 3 patients in Study JGDB and 2 patients in Study JGDA. There were no infusion interruptions of doxorubicin in patients receiving olaratumab plus doxorubicin in Study JGDG.

b The Olaratumab-Containing Arm contains olaratumab-treated patients in the Investigational Arms of randomized studies or olaratumab-treated patients in single-arm monotherapy or combination studies.

c Patients initially randomized to the Control Arm who received olaratumab monotherapy after discontinuation of chemotherapy.

d Randomized studies.

e The total IRR count for the JGDG Investigational Arm includes 1 patient who was initially adjudicated as having an IRR based on AE details added from the post-hoc IRR analysis. Following completion of summary submission documents and datasets, re-review and quality check of this patient's complete narrative determined that this patient did not meet the criteria for IRR based upon all available AE information. This correction is reflected in the final narrative assessment provided. The discrepancy between IRR rate in the datasets/tabulations and the supporting final narrative statements resulted in the over-reporting of this 1 patient as having an IRR in Study JGDG.

f Olaratumab monotherapy studies.

IRRs were reported in 12.5 % of patients. The majority of IRRs occurred during or following the first olaratumab infusion. Symptoms of IRRs included flushing, shortness of breath, bronchospasm, or fever/chills, and in some cases manifested as severe hypotension, anaphylactic shock, or fatal cardiac arrest. Severe IRRs, also including a fatal case were reported in 3.1 % of patients and mainly presented with shortness of breath, loss of consciousness and hypotension. All severe IRRs occurred during or immediately after the first administration of olaratumab (see sections 4.4 and 4.8 of the SmPC).

Medical intervention employed to manage *IRRs* included: infusion rate decreased in 21 (30.0%) patients, infusion interruption in 49 (70.0%) patients, antihistamines in 43 (61.7%) patients, corticosteroids in 26 (37.1%) patients, and other treatment in 29 (41.4%) patients.

Patients with a Grade ≥3 *IRR*s were immediately and permanently discontinued from olaratumab, in accordance with study protocols. In the 11 patients with Grade ≥3 *IRRs* due to olaratumab, 9 were treated with antihistamines, 8 were treated with corticosteroids, and 10 received additional/other treatment.

Overall, across all studies (n=485), among the 70 patients who had an initial *IRR* grade 1 and 2 due to olaratumab, 59 (84.3%) were rechallenged and 12 (20.3%) of those patients had another *IRRs* (either Grade 1 or 2 in severity).

Cardiac Arrhythmias

In Study JGDG (randomized Phase 2 portion), the rate of cardiac arrhythmias was similar in both arms (15.6 % in the Investigational Arm and 15.4 % in the Control Arm); the majority of these events were Grade 1-2 events of bradycardia or tachycardia. There were no AEs of serious (Grade ≥3) arrhythmia in the Investigational Arm.

Cardiac Dysfunction

In Study JGDG (randomized Phase 2 portion), following medical review of the data the overall incidence of cardiac dysfunction was considered to be similar between the 2 treatments arms. The majority of the events were Grade 1 and 2, with ejection fraction decreased reported most frequently. These findings are in the context of higher cumulative doxorubicin drug exposure in the Investigational Arm compared to the Control Arm.

Table 39: AESI of *Cardiac Dysfunction*, Safety Population, Study JGDG (Phase 1b and Phase 2)

	Phase 1b		Phase 2			
	Olaratumab + Doxorubicin N = 15 n (%)		Investigational Arm N = 64 n (%)		Control Arm N = 65 n (%)	
AESI Category	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac Dysfunction	**2 (13.3)**	**1 (6.7)**	**15 (23.4)**	**1 (1.6)**	**11 (16.9)**	**0**
Oedema Peripheral	1 (6.7)	0	10 (15.6)	0	7 (10.8)	0
Ejection Fraction Decreased	1 (6.7)	0	5 (7.8)	1 (1.6)	4 (6.2)	0
Cardiac Failure Congestive	0	0	1 (1.6)	1 (1.6)	0	0
Hepatojugular Reflux	0	0	1 (1.6)	0	0	0
Jugular Vein Distension	0	0	1 (1.6)	0	0	0
Left Ventricular Dysfunction	1 (6.7)	1 (6.7)	1 (1.6)	0	0	0
***Cardiac Dysfunction* (excluding peripheral edema)[a]**	2 (13.3)	1 (6.7)	5 (7.8)	1 (1.6)	4 (6.2)	0

Abbreviations: AESI = adverse event of special interest; N = number of treated patients; n = number of patients in category.
Note: Patients with more than one cardiac dysfunction adverse event may be counted more than once.
Note: Only those preferred terms that were reported are listed in table. Refer to Table APP.2.7.4.7.5.2 for the full list of preferred terms included in the AESI of *cardiac dysfunction*.
a In the Phase 2 portion, the overall rate of *cardiac dysfunction* excluding events of peripheral edema was 7%.
Source: taesi, lae.

An analysis of the peripheral oedema events has been conducted. The Applicant stated that peripheral oedema can be caused by a number of factors in this population, such as immobility, DVT, renal insufficiency, hepatic dysfunction due to tumour metastases, underlying tumour causing lymphatic or venous obstruction, or hypoalbuminemia. This analysis included reviewing cardiac function assessments (ECHO/MUGA scans) and specifically looking at any additional AEs within the cardiac failure SMQ. Ten patients in the Investigational Arm and 7 patients in the Control Arm experienced peripheral oedema. None of the reported AEs suggested cardiac dysfunction or a significant deterioration in left ventricular function, except for one patient in the Control Arm in whom peripheral oedema was associated with a fall in LVEF (35%, baseline was 65%) but oedema was considered likely multifactorial.

Haemorrhagic events

During the procedure, the applicant was requested to examine all the haemorrhagic events across the development programme of olaratumab. The majority of haemorrhagic AEs reported were considered unrelated to study drugs and they were mainly G1-2. Haemorrhagic events considered by investigator as related to any study drug were reported in 14/294 (4.8%) patients treated with olaratumab in association with chemotherapy, in 3/96 (3.1%) patients in the monotherapy studies, and in 0/95 patients treated with olaratumab monotherapy at crossover. Among them, there were three Grade ≥3 events: two (one fatal ICH and one GI haemorrhage G4) in the combination studies, both having plausible confounding factors. One event (an intrahepatic bleeding due to tumour rupture) was reported in the monotherapy studies, for which the causal relation with olaratumab could not be excluded.

Adverse Drug Reaction (ADR)

The Applicant used the following analytical criteria to conduct an initial screen of the AE data in Study JGDG (randomized Phase 2 portion), where “incidence” is the percentage of patients experiencing the event. Events meeting either of these criteria in Study JGDG were evaluated as potential ADRs for olaratumab:

- The two-sided p-value is <0.10 (with the incidence higher in the Investigational Arm than in the Control Arm) and the risk ratio is >1 (Investigational Arm vs. Control Arm).

- The two-sided p-value is ≥0.10 (comparing the Investigational Arm with the Control Arm), the olaratumab plus doxorubicin incidence is ≥1% (not rounded up), the risk ratio is ≥2 (Investigational Arm vs. Control Arm), and the absolute count among olaratumab-treated patients is at least 4.

- The incidence in the Investigational Arm is ≥10% (not rounded up) and the risk ratio is ≥1 (Investigational Arm vs. Control Arm).

The table resulting from this analysis is reported below:

Table 40: Adverse reactions occurring in patients receiving olaratumab plus doxorubicin for Soft Tissue Sarcoma (Phase 2)

MedDRA System Organ Class Event	Investigational Arm N = 64		Control Arm N = 65	
	All Grades (%)	Grade ≥3 (%)	All Grades (%)	Grade ≥3 (%)
Blood and Lymphatic System Disorders				
Neutropenia[a]	59.4	54.7	38.5	33.8
Gastrointestinal Disorders				
Diarrhoea	34.4	3.1	23.1	0
Mucositis[b]	53.1	3.1	35.4	4.6
Nausea	73.4	1.6	52.3	3.1
Vomiting	45.3	0	18.5	0
General Disorders and Administrative Site Conditions				
Infusion-Related Reactions[c]	12.5	3.1	3.1	0
Musculoskeletal and Connective Tissue Disorders				
Musculoskeletal Pain[d]	64.1	7.8	24.6	1.5
Nervous System Disorders				
Headache	20.3	0	9.2	0

Abbreviations: AESI = adverse event of special interest; MedDRA = Medical Dictionary for Regulatory Activities (Version 17.1); N = number of treated patients.

a Preferred terms reported were leukopenia, neutropenia, neutrophil count decreased, and white blood cell count decreased.

b Preferred terms reported were mucosal inflammation, oropharyngeal pain, and stomatitis.

c The AESI infusion-related reactions is a composite term based on an assessment of 57 preferred terms.

d Preferred terms reported were arthralgia, back pain, bone pain, flank pain, groin pain, musculoskeletal chest pain, musculoskeletal pain, myalgia, muscle spasms, neck pain, and pain in extremity.

Safety data from supportive studies

Supportive safety evaluations of 39 patients treated with olaratumab + doxorubicin in STS within the phase 1b portion of study JGDG and the phase 1 study JGDI have been provided. Overall, JGDG phase 1b showed a similar safety profile compared to the phase 2. In JGDI the frequency of each AE seems lower compared to the phase 2 portion of study JGDG. However the data from this study is very limited due to the short follow up and the short median duration of treatment.

Supportive safety evaluations of 94 patients treated with olaratumab monotherapy within the nonrandomized single-agent Phase 1 and Phase 2 studies (Studies JGDC, JGDF, JGDE [olaratumab arm only], and JGDH) have been provided. Overall, more frequently reported TEAEs related to olaratumab across these four studies where fatigue, IRRs, rash, proteinuria, hypertension, nausea. Grade 3 TEAEs related to olaratumab reported were (1 patient each): lymphopenia, hypertension, AST increase, abnormal hepatic function, syncope. Lymphopenia has been recorded. No Neutropenia events were reported with olaratumab monotherapy, which was the most frequent event in the combination olaratumab + doxorubicin instead. Neutropenia does not appear to be an AE typically associated to olaratumab.

In JGDF study (phase I, advanced cancer, Japan only), a Grade 3 tumour haemorrhage related to olaratumab has been reported as treatment emergent-SAE. In JGDC study (phase I, advanced cancer) a Grade 2 tumour haemorrhage has been reported as treatment emergent-SAE, for which the Applicant stated that the tumour haemorrhage occurred the same day as when image revealed new liver lesions demonstrating PD. In study

JGDE (phase II, olaratumab vs ramucirumab, glioblastoma), a Grade 2 intracranial haemorrhage (ICH) has been reported as treatment emergent-SAE. A possible relationship between the event of ICH and study drug cannot be excluded, based on the possibility that haemorrhage into an area of tumour necrosis occurred; however, the patient was also receiving aspirin and enoxaparin, which may confound the association. In addition, the underlying disease in this patient population could represent a confounding factor for the event of ICH.

Further, across the three studies JGDA, JGDB and JGDD, a total of 65 patients received olaratumab monotherapy in the Control Arms after discontinuation of respective chemotherapy. Overall, the most common drug-related TEAE reported in this population were gastrointestinal disorders (nausea, vomiting, constipation, stomatitis), fatigue, IRR, nervous system disorders (dizziness, peripheral neuropathy, headache), musculoskeletal disorder, anaemia.

Supportive safety evaluations of 191 patients treated with olaratumab + chemotherapy (other than doxorubicin) in the randomized Phase 2 studies (Studies JGDA, JGDB, JGDD) in non-STS tumour type have been provided. Overall, the most common TEAE reported (regardless the causality) in the combination arms of these three studies were fatigue, nausea, constipation, neuropathy, alopecia, neutropenia, anemia. One case of grade 3 gastrointestinal haemorrhage has been reported in JGDB study (phase 2, NSCLC 1° line, carboplatin + paclitaxel + olaratumab). Per investigator, acetylsalicylic acid and chronic steroid use were potential causes of the events, however carboplatin, paclitaxel, and olaratumab also could not be ruled out as possible contributors. No tumour haemorrhage has been reported in the JGDG study. In JGDG Study, 3 cases of grade 3 gastrointestinal haemorrhages and one case of grade 3 hepatic haemorrhage were recorded; however all these events were considered not related to olaratumab.

Serious adverse event/deaths/other significant events

Serious adverse events (SAEs)

Treatment emergent SAEs (TE-SAE) occurred in the pivotal study are summarized in the following tables:

Table 41: Summary of TE-SAE, safety population, JGDG Study (Phase 2)

Parameter[c]	Investigational Arm[a] N = 64 n (%)	Control Arm[a] N = 65 n (%)	Control Arm: Olaratumab Monotherapy after Doxorubicin[b] N = 30 n (%)
Patients with Any Treatment-Emergent SAE	**27 (42.2)**	**25 (38.5)**	**9 (30.0)**
Related to Any Study Drug	14 (21.9)	17 (26.2)	2 (6.7)
Related to Olaratumab	10 (15.6)	NA	2 (6.7)
Related to Chemotherapy	12 (18.8)	17 (26.2)	1 (3.3)

Only SAE occurring in ≥2 patients were reported below:

Table 42: TE-SAEs occurring in ≥ 2 Patients in Either Treatment Arm with Grade ≥ 3 Event, safety population, JGDG Study (Phase 2)

Adverse Event Term	Investigational Arm N = 64 n (%)		Control Arm N = 65 n (%)		Control Arm: Olaratumab Monotherapy following Doxorubicin[a] N = 30 n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Patients with any SAE	**27 (42.2)**	**27 (42.2)**	**25 (38.5)**	**22 (33.8)**	**9 (30.0)**	**9 (30.0)**
Febrile Neutropenia	8 (12.5)	8 (12.5)	8 (12.3)	8 (12.3)	0	0
Musculoskeletal Pain[b]	3 (4.7)	3 (4.7)	1 (1.5)	0	2 (6.7)	2 (6.7)
Neutropenia[c]	3 (4.7)	3 (4.7)	3 (4.6)	3 (4.6)	0	0
Abdominal Pain[d]	2 (3.1)	2 (3.1)	1 (1.5)	0	0	0
Urinary Tract Infection	1 (1.6)	1 (1.6)	3 (4.6)	3 (4.6)	0	0
Thrombocytopenia[e]	0	0	2 (3.1)	2 (3.1)	0	0
Adverse Events of Special Interest[f,g]						
Infusion-related Reactions	2 (3.1)	2 (3.1)	0	0	1 (3.3)	1 (3.3)
Cardiac Arrhythmias[h]	1 (1.6)	0	1 (1.5)	1 (1.5)	1 (3.3)	1 (3.3)

Summary of Treatment-Emergent Serious Adverse Events Occurring in ≥2 Patients in Either Treatment Arm with Grade ≥3 Event
Safety Population (concluded)
Study JGDG (Phase 2)

Abbreviations: AESI = adverse event of special interest; IRR = infusion-related reaction; N = number of treated patients; n = number of patients in category; PT = preferred term; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Note: Refer to Table APP.2.7.4.7.5.1 and Table APP.2.7.4.7.5.2 for the full list of PTs included in each consolidated TEAE term and AESI.

Note: TEAEs with grade missing are counted in 'All Grades'.

Note: At each level of summarization, a patient is counted once according to the TEAE with worst grade.

Note: Consolidated TEAE categories and AESIs are italicized. For the list of preferred terms that were reported in Study JGDG, refer to Table JGDG.14.92, Table JGDG.14.93, and Table APP.2.7.4.7.5.3.

a Patients initially randomized to the Control Arm who received olaratumab monotherapy after discontinuation of doxorubicin.

b Preferred terms reported were back pain, pain in extremity, and musculoskeletal chest pain.

c Preferred terms reported were neutropenia and white blood cell count decreased.

d Preferred terms reported were abdominal pain and abdominal pain upper.

e Preferred term reported was thrombocytopenia.

f Analyses are based on the integrated safety database.

g Preferred term reported for *IRRs* (from the core IRR analysis based on 48 preferred terms [prior to medical adjudication]) were hypersensitivity reaction and IRR. For the comprehensive incidence of IRRs based on the medically adjudicated core and post-hoc analyses, see Table 2.7.4.37. Preferred terms reported for *cardiac arrhythmias* were sinus bradycardia, syncope and cardiac arrest. No serious events of *cardiac dysfunction* were reported.

h Occurred in <2 patients with Grade ≥3 event but are included in this table as they are considered clinically important.

Source: tsae, tsaecon, tsaecon_mpain_withpex, lissaesi.r1, lissasof.r1, lissaeof.r2.

Deaths

Deaths occurred in the pivotal study are summarized in the following Table:

Table 43: summary of primary cause of death as reported by the investigator, safety population, JGDG Study (Phase 2)

Reasons for Death	Investigational Arm N = 64 n (%)	Control Arm N = 65 n (%)	Control Arm: Olaratumab Monotherapy following Doxorubicin[a,b] N=30 n (%)
All Deaths	**39 (60.9)**	**51 (78.5)**	**23 (76.7)**
Disease Progression	38 (59.4)	44 (67.7)	22 (73.3)
Adverse Event	0	6 (9.2)	1 (3.3)
Other	1 (1.6)	1 (1.5)	0
Deaths on Study or within 30 Days of Last Dose	**3 (4.7)**	**7 (10.8)**	**2 (6.7)**
Disease Progression	3 (4.7)	2 (3.1)	1 (3.3)
Adverse Event	0	5 (7.7)	1 (3.3)[c]
Other	0	0	0

Abbreviations: AE = adverse event; N = number of treated patients; n = number of patients in category.
Note: Deaths in Control Arm include those occurred during both the doxorubicin treatment period and subsequent olaratumab monotherapy phase.
a Patients initially randomized to the Control Arm who received olaratumab monotherapy after discontinuation of doxorubicin.
b Patients with any AE with outcome death represents a subset of the data in the Control Arm column.
c One patient in the Control Arm, who subsequently received olaratumab monotherapy, had a fatal AE (preferred term: cardiac arrest) potentially associated with olaratumab infusion.

Table 44: TEAE with an outcome of death on study or within 30 days of last dose by SOC and PT (regardless the causality), safety population, JGDG Study (Phase 2)

System Organ Class Preferred Term	Investigational Arm N = 64 n (%)	Control Arm N = 65 n (%)	Control Arm: Olaratumab Monotherapy following Doxorubicin[a] N = 30 n (%)
Deaths due to Adverse Event	**0**	**5 (7.7)**	**1 (3.3)**
Cardiac Disorders			
Cardiac Arrest	0	1 (1.5)	1 (3.3)
Infection and Infestations			
Sepsis	0	1 (1.5)	0
Septic shock	0	1 (1.5)	0
Respiratory, Thoracic, and Mediastinal Disorders			
Pneumonia aspiration	0	1 (1.5)	0
Respiratory failure	0	1 (1.5)	0

Abbreviations: N = number of treated patients; n = number of patients in category.
Note: Deaths in Control Arm include those occurred during both the doxorubicin treatment period and subsequent olaratumab monotherapy phase.
a Patients initially randomized to the Control Arm who received olaratumab monotherapy after discontinuation of doxorubicin.

A total of 10 deaths occurred during study therapy or within 30 days after the last dose of study therapy, 3 in the Investigational Arm and 7 in the Control Arm. In the Investigational Arm, all the 3 deaths reported were related to disease progression. In the Control Arm, among the 7 deaths reported, 2 were considered due to disease progression. The other 5 deaths were considered related to AEs, including 2 doxorubicin-related (sepsis and septic shock). Cardiac arrest occurred in a patient in the Control Arm who crossover to Olaratumab.

In the phase 1b portion of JGDG, there was one death due to AE, which was considered not related to any study drug by investigator. The Applicant agrees with the investigator's opinion that the cause of death was not known.

In the additional phase 2 randomized studies in other solid tumours (JGDA, JGDB, and JGDD), the following deaths possibly related to olaratumab were reported: in the Investigational Arm of JGDA study, one patient (1.6%) died due to AE (intracranial haemorrhage, ICH) >30 days after last dose of study therapy and was assessed as possibly related to olaratumab. The AE of ICH was confounded by recent history of head trauma, and the Applicant's assessment of relationship of the event with olaratumab is indeterminate. In the Investigational arm of JGDB study, one patient died on C1D8 (8 days after carboplatin/paclitaxel/olaratumab), cause of death were related to underlying NSCLC, septic shock secondary to pneumonia and febrile neutropenia. The AE of febrile neutropenia and sepsis were considered related to carboplatin, paclitaxel and olaratumab. In JGDD study, one patient in the control arm who received olaratumab monotherapy after progression, died due to cardiac arrest seven days after the last dose of olaratumab. The Applicant agrees with the investigator for the cause of death, cardiac arrest, being related to disease progression and concomitant overall deterioration, but also recognizes a possible role of pyelonephritis and bronchopneumonia.

In the supportive studies with olaratumab monotherapy, no deaths related to olaratumab were reported.

Laboratory findings

Laboratory shifts for decreased haemoglobin and platelet count in the pivotal study are presented below:

Table 45: laboratory toxicity (low haemoglobin) shift from baseline to worst grade on-study based on CTC grade, Study JGDG, phase 2 safety population

Baseline Grade	Investigational Arm N = 64							Control Arm N = 65						
	Worst Postbaseline CTC Grade							Worst Postbaseline CTC Grade						
	n	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	Missing	n	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	Missing
Gr 0	36 (56.3)	2 (3.1)	19 (29.7)	14 (21.9)	0	0	1 (1.6)	33 (50.8)	3 (4.6)	16 (24.6)	12 (18.5)	0	0	2 (3.1)
Gr 1	24 (37.5)	0	7 (10.9)	13 (20.3)	4 (6.3)	0	0	26 (40.0)	0	8 (12.3)	15 (23.1)	2 (3.1)	0	1 (1.5)
Gr 2	4 (6.3)	0	0	2 (3.1)	2 (3.1)	0	0	6 (9.2)	0	0	3 (4.6)	3 (4.6)	0	0
Gr 3	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gr 4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	64	2 (3.1)	26 (40.6)	29 (45.3)	6 (9.4)	0	1 (1.6)	65	3 (4.6)	24 (36.9)	30 (46.2)	5 (7.7)	0	3 (4.6)

Abbreviations: CTC = Common Terminology Criteria; Gr = grade; N = number of treated patients; n = number of patients in category.
Data cut-off date: 16 May 2015.

Table 46: laboratory toxicity (low platelet) shift from baseline to worst grade on-study based on CTC grade, Study JGDG, phase 2 safety population

Baseline Grade	Investigational Arm N = 64							Control Arm N = 65						
	Worst Postbaseline CTC Grade							Worst Postbaseline CTC Grade						
	n	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	Missing	n	Gr 0	Gr 1	Gr 2	Gr 3	Gr 4	Missing
Gr 0	60 (93.8)	21 (32.8)	28 (43.8)	6 (9.4)	3 (4.7)	1 (1.6)	1 (1.6)	63 (96.9)	34 (52.3)	17 (26.2)	3 (4.6)	4 (6.2)	2 (3.1)	3 (4.6)
Gr 1	4 (6.3)	0	2 (3.1)	2 (3.1)	0	0	0	2 (3.1)	0	1 (1.5)	0	0	1 (1.5)	0
Gr 2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gr 3	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Gr 4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Missing	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total	64	21 (32.8)	30 (46.9)	8 (12.5)	3 (4.7)	1 (1.6)	1 (1.6)	65	34 (52.3)	18 (27.7)	3 (4.6)	4 (6.2)	3 (4.6)	3 (4.6)

Abbreviations: CTC = Common Terminology Criteria; Gr = grade; N = number of treated patients; n = number of patients in category.
Data cut-off date: 16 May 2015.

Immunological events

Of the 109 patients exposed to olaratumab, 85 patients were considered evaluable for the presence/absence of ADA. Treatment-emergent ADA were identified in 5 (5.9%) of the 85 evaluable patients, with titers ranging from 1:40 to 1:80. All 5 treatment-emergent ADA-positive subjects also had detectable neutralizing antibodies. All *IRRs* (n=2) associated with treatment-emergent ADA were Grade 2 and did not lead to treatment discontinuation.

The treatment-emergent ADA data from the 8 supportive studies are consistent with the data from Study JGDG.

Safety in special populations

Additional analyses summarizing TEAEs by subgroups, including histology (LMS, non-LMS), age (<65, ≥65, ≥65 to <75, ≥75 to <85, and ≥85 years), sex (male, female), and race (White, Non-White), were performed.

Histology (Leiomyosarcoma vs. Non-Leiomyosarcoma)

The safety profile of olaratumab in combination with doxorubicin was consistent across LMS and non-LMS (other) disease histology, and with that of the overall study population. Given the small number of patients within the other STS subtype populations, comparative safety analyses within this group could not be performed.

Age

Overall, the rate of AEs in terms of SOC and individual PT for the 65-74 years and 74-84 years age groups was similar to that of the <65 years age group. Of note, there was only 1 patient in the Phase 2 portion of Study JGDG age >85 years; this patient is not included in the subgroup analyses shown in Table 33 and Table 34.

There was a trend for a higher rate of AEs in both the 65-74 years and 74-84 years age groups as compared to the <65 years age group for the haematological toxicities (SOC of Blood and Lymphatic System Disorders and individual PTs). However, this trend was seen in both the investigational and the control arms, indicating possible susceptibility of the elderly population to the bone marrow suppressive effects of doxorubicin.

Table 47: Treatment-emergent adverse events by system organ class, preferred term and age group – Phase 2, safety population (study JGDG)

System Organ Class[b] Preferred Term[c] n (%)	All Patients		Age <65		Age ≥65 and <75		Age ≥75 and <85[a]	
	Ola+Dox N=64	Dox N=65	Ola+Dox N=47	Dox N=41	Ola+Dox N=14	Dox N=18	Ola+Dox N=3	Dox N=5
Gastrointestinal Disorders	**56 (87.5)**	**54 (83.1)**	**43 (91.5)**	**34 (82.9)**	**11 (78.6)**	**15 (83.3)**	**2 (66.7)**	**4 (80.0)**
Nausea	47 (73.4)	34 (52.3)	37 (78.7)	24 (58.5)	8 (57.1)	10 (55.6)	2 (66.7)	0
Vomiting	29 (45.3)	12 (18.5)	23 (48.9)	8 (19.5)	5 (35.7)	4 (22.2)	1 (33.3)	0
Constipation	22 (34.4)	21 (32.3)	16 (34.0)	15 (36.6)	5 (35.7)	5 (27.8)	1 (33.3)	1 (20.0)
Diarrhoea	22 (34.4)	15 (23.1)	19 (40.4)	8 (19.5)	2 (14.3)	4 (22.2)	1 (33.3)	3 (60.0)
Stomatitis	11 (17.2)	10 (15.4)	9 (19.1)	5 (12.2)	2 (14.3)	5 (27.8)	0	0
Abdominal Pain Upper	8 (12.5)	2 (3.1)	6 (12.8)	1 (2.4)	1 (7.1)	1 (5.6)	1 (33.3)	0
Dry Mouth	7 (10.9)	6 (9.2)	4 (8.5)	3 (7.3)	3 (21.4)	2 (11.1)	0	1 (20.0)
General Disorders & Administration Site Conditions	**55 (85.9)**	**56 (86.2)**	**42 (89.4)**	**36 (87.8)**	**11 (78.6)**	**15 (83.3)**	**2 (66.7)**	**4 (80.0)**
Fatigue	44 (68.8)	45 (69.2)	34 (72.3)	28 (68.3)	8 (57.1)	14 (77.8)	2 (66.7)	2 (40.0)
Mucosal Inflammation	17 (26.6)	12 (18.5)	13 (27.7)	10 (24.4)	3 (21.4)	2 (11.1)	1 (33.3)	0
Pyrexia	15 (23.4)	12 (18.5)	13 (27.7)	4 (9.8)	2 (14.3)	5 (27.8)	0	3 (60.0)
Oedema Peripheral	10 (15.6)	7 (10.8)	6 (12.8)	6 (14.6)	3 (21.4)	0	1 (33.3)	1 (20.0)
Non-Cardiac Chest Pain	8 (12.5)	4 (6.2)	7 (14.9)	3 (7.3)	1 (7.1)	0	0	1 (20.0)
Blood and Lymphatic System Disorders	**45 (70.3)**	**41 (63.1)**	**31 (66.0)**	**22 (53.7)**	**12 (85.7)**	**14 (77.8)**	**2 (66.7)**	**4 (80.0)**
Neutropenia	29 (45.3)	15 (23.1)	20 (42.6)	8 (19.5)	7 (50.0)	5 (27.8)	2 (66.7)	1 (20.0)
Anaemia	26 (40.6)	24 (36.9)	16 (34.0)	12 (29.3)	8 (57.1)	9 (50.0)	2 (66.7)	3 (60.0)
Leukopenia	16 (25.0)	5 (7.7)	13 (27.7)	2 (4.9)	3 (21.4)	2 (11.1)	0	0
Thrombocytopenia	14 (21.9)	12 (18.5)	6 (12.8)	7 (17.1)	6 (42.9)	3 (16.7)	2 (66.7)	1 (20.0)
Febrile Neutropenia	8 (12.5)	9 (13.8)	5 (10.6)	6 (14.6)	2 (14.3)	3 (16.7)	1 (33.3)	0
Skin and Subcutaneous Tissue Disorders	**44 (68.8)**	**31 (47.7)**	**32 (68.1)**	**23 (56.1)**	**10 (71.4)**	**6 (33.3)**	**2 (66.7)**	**2 (40.0)**
Alopecia	33 (51.6)	26 (40.0)	24 (51.1)	18 (43.9)	7 (50.0)	6 (33.3)	2 (66.7)	2 (40.0)
Respiratory, Thoracic, and Mediastinal Disorders	**43 (67.2)**	**31 (47.7)**	**33 (70.2)**	**20 (48.8)**	**9 (64.3)**	**8 (44.4)**	**1 (33.3)**	**2 (40.0)**
Cough	14 (21.9)	12 (18.5)	12 (25.5)	7 (17.1)	2 (14.3)	3 (16.7)	0	1 (20.0)
Oropharyngeal Pain	12 (18.8)	3 (4.6)	9 (19.1)	3 (7.3)	3 (21.4)	0	0	0
Dyspnoea	11 (17.2)	12 (18.5)	8 (17.0)	7 (17.1)	2 (14.3)	3 (16.7)	1 (33.3)	1 (20.0)
Musculoskeletal and Connective Tissue Disorders	**42 (65.6)**	**17 (26.2)**	**30 (63.8)**	**13 (31.7)**	**10 (71.4)**	**2 (11.1)**	**2 (66.7)**	**2 (40.0)**
Pain in Extremity	15 (23.4)	1 (1.5)	12 (25.5)	0	3 (21.4)	1 (5.6)	0	0
Back Pain	12 (18.8)	6 (9.2)	7 (14.9)	4 (9.8)	4 (28.6)	0	1 (33.3)	2 (40.0)
Muscle Spasms	10 (15.6)	1 (1.5)	6 (12.8)	1 (2.4)	4 (28.6)	0	0	0
Arthralgia	8 (12.5)	2 (3.1)	5 (10.6)	2 (4.9)	3 (21.4)	0	0	0
Musculoskeletal Chest Pain	8 (12.5)	2 (3.1)	7 (14.9)	2 (4.9)	1 (7.1)	0	0	0
Investigations	**33 (51.6)**	**25 (38.5)**	**20 (42.6)**	**16 (39.0)**	**12 (85.7)**	**6 (33.3)**	**1 (33.3)**	**3 (60.0)**
Neutrophil Count Decreased	12 (18.8)	9 (13.8)	5 (10.6)	6 (14.6)	7 (50.0)	2 (11.1)	0	1 (20.0)
WBC Count Decreased	12 (18.8)	7 (10.8)	4 (8.5)	3 (7.3)	7 (50.0)	3 (16.7)	1 (33.3)	1 (20.0)
Weight Decreased	7 (10.9)	7 (10.8)	4 (8.5)	5 (12.2)	3 (21.4)	1 (5.6)	0	1 (20.0)
Metabolism and Nutrition Disorders	**33 (51.6)**	**29 (44.6)**	**23 (48.9)**	**19 (46.3)**	**8 (57.1)**	**7 (38.9)**	**2 (66.7)**	**3 (60.0)**
Decreased Appetite	20 (31.3)	13 (20.0)	13 (27.7)	9 (22.0)	5 (35.7)	3 (16.7)	2 (66.7)	1 (20.0)
Hypokalaemia	9 (14.1)	6 (9.2)	6 (12.8)	4 (9.8)	2 (14.3)	1 (5.6)	1 (33.3)	1 (20.0)
Dehydration	7 (10.9)	6 (9.2)	6 (12.8)	6 (14.6)	0	0	1 (33.3)	0
Nervous System Disorders	**31 (48.4)**	**26 (40.0)**	**21 (44.7)**	**18 (43.9)**	**8 (57.1)**	**7 (38.9)**	**2 (66.7)**	**1 (20.0)**
Headache	13 (20.3)	6 (9.2)	9 (19.1)	3 (7.3)	3 (21.4)	2 (11.1)	1 (33.3)	1 (20.0)
Neuropathy Peripheral	8 (12.5)	5 (7.7)	7 (14.9)	3 (7.3)	1 (7.1)	2 (11.1)	0	0
Infections and Infestations	**27 (42.2)**	**27 (41.5)**	**18 (38.3)**	**16 (39.0)**	**7 (50.0)**	**7 (38.9)**	**2 (66.7)**	**4 (80.0)**
Upper Respiratory Tract Infection	8 (12.5)	4 (6.2)	5 (10.6)	2 (4.9)	2 (14.3)	1 (5.6)	1 (33.3)	1 (20.0)
Psychiatric Disorders	**18 (28.1)**	**12 (18.5)**	**13 (27.7)**	**8 (19.5)**	**4 (28.6)**	**3 (16.7)**	**1 (33.3)**	**1 (20.0)**
Insomnia	8 (12.5)	6 (9.2)	7 (14.9)	3 (7.3)	1 (7.1)	3 (16.7)	0	0
Anxiety	7 (10.9)	2 (3.1)	5 (10.6)	2 (4.9)	1 (7.1)	0	1 (33.3)	0
Eye Disorders	**15 (23.4)**	**3 (4.6)**	**8 (17.0)**	**1 (2.4)**	**6 (42.9)**	**1 (5.6)**	**1 (33.3)**	**1 (20.0)**
Dry Eye	7 (10.9)	2 (3.1)	3 (6.4)	1 (2.4)	3 (21.4)	0	1 (33.3)	1 (20.0)
Vascular Disorders	**11 (17.2)**	**13 (20.0)**	**6 (12.8)**	**7 (17.1)**	**5 (35.7)**	**4 (22.2)**	**0**	**1 (20.0)**
Cardiac Disorders	**10 (15.6)**	**9 (13.8)**	**7 (14.9)**	**8 (19.5)**	**2 (14.3)**	**1 (5.6)**	**1 (33.3)**	**0**
Injury, Poisoning, and Procedural Complications	**9 (14.1)**	**4 (6.2)**	**6 (12.8)**	**4 (9.8)**	**3 (21.4)**	**0**	**0**	**0**
Renal and Urinary Disorders	**9 (14.1)**	**8 (12.3)**	**5 (10.6)**	**4 (9.8)**	**2 (14.3)**	**3 (16.7)**	**2 (66.7)**	**1 (20.0)**
Ear and Labyrinth Disorders	**7 (10.9)**	**3 (4.6)**	**3 (6.4)**	**1 (2.4)**	**3 (21.4)**	**1 (5.6)**	**1 (33.3)**	**1 (20.0)**

Abbreviations: Dox = doxorubicin; N = number of patients in category; n = number of patients in subcategory; Ola = olaratumab; WBC = white blood cell.

[a] Only one treated patient (randomized to the Control Arm) was age >85 years; this patient is not included in the age subgroup analysis shown in this table.

[b] Includes only System Organ Classes for which an adverse event was reported for at least 10% of patients in the Phase 2 Investigational Arm overall.

[c] Includes only Preferred Terms for which an event was reported for at least 10% of patients in the Phase 2 Investigational Arm overall.

Table 48: Study-drug related treatment-emergent adverse events by system organ class, preferred term and age group – Phase 2, safety population (study JGDG)

System Organ Class[b] Preferred Term[c] n (%)	All Patients		Age <65		Age ≥65 and <75		Age ≥75 and <85[a]	
	Ola+Dox N=64	Dox N=65	Ola+Dox N=47	Dox N=41	Ola+Dox N=14	Dox N=18	Ola+Dox N=3	Dox N=5
Gastrointestinal Disorders	**49 (76.6)**	**47 (72.3)**	**39 (83.0)**	**29 (70.7)**	**8 (57.1)**	**13 (72.2)**	**2 (66.7)**	**4 (80.0)**
Nausea	43 (67.2)	30 (46.2)	34 (72.3)	20 (48.8)	7 (50.0)	10 (55.6)	2 (66.7)	0
Vomiting	22 (34.4)	10 (15.4)	17 (36.2)	6 (14.6)	4 (28.6)	4 (22.2)	1 (33.3)	0
Diarrhoea	15 (23.4)	10 (15.4)	12 (25.5)	5 (12.2)	2 (14.3)	3 (16.7)	1 (33.3)	2 (40.0)
Constipation	10 (15.6)	11 (16.9)	7 (14.9)	8 (19.5)	3 (21.4)	3 (16.7)	0	0
Stomatitis	10 (15.6)	9 (13.8)	9 (19.1)	4 (9.8)	1 (7.1)	5 (27.8)	0	0
General Disorders & Administration Site Conditions	**48 (75.0)**	**45 (69.2)**	**37 (78.7)**	**28 (68.3)**	**9 (64.3)**	**13 (72.2)**	**2 (66.7)**	**4 (80.0)**
Fatigue	41 (64.1)	39 (60.0)	31 (66.0)	25 (61.0)	8 (57.1)	12 (66.7)	2 (66.7)	2 (40.0)
Mucosal Inflammation	17 (26.6)	12 (18.5)	13 (27.7)	10 (24.4)	3 (21.4)	2 (11.1)	1 (33.3)	0
Blood and Lymphatic System Disorders	**44 (68.8)**	**39 (60.0)**	**30 (63.8)**	**22 (53.7)**	**12 (85.7)**	**13 (72.2)**	**2 (66.7)**	**3 (60.0)**
Neutropenia	28 (43.8)	15 (23.1)	20 (42.6)	8 (19.5)	6 (42.9)	5 (27.8)	2 (66.7)	1 (20.0)
Anaemia	22 (34.4)	22 (33.8)	13 (27.7)	11 (26.8)	7 (50.0)	9 (50.0)	2 (66.7)	2 (40.0)
Leukopenia	16 (25.0)	5 (7.7)	13 (27.7)	2 (4.9)	3 (21.4)	2 (11.1)	0	0
Thrombocytopenia	13 (20.3)	12 (18.5)	6 (12.8)	7 (17.1)	5 (35.7)	3 (16.7)	2 (66.7)	1 (20.0)
Febrile Neutropenia	8 (12.5)	9 (13.8)	5 (10.6)	6 (14.6)	2 (14.3)	3 (16.7)	1 (33.3)	0
Skin and Subcutaneous Tissue Disorders	**40 (62.5)**	**28 (43.1)**	**29 (61.7)**	**20 (48.8)**	**9 (64.3)**	**6 (33.3)**	**2 (66.7)**	**2 (40.0)**
Alopecia	30 (46.9)	26 (40.0)	21 (44.7)	18 (43.9)	7 (50.0)	6 (33.3)	2 (66.7)	2 (40.0)
Investigations	**25 (39.1)**	**17 (26.2)**	**14 (29.8)**	**9 (22.0)**	**10 (71.4)**	**6 (33.3)**	**1 (33.3)**	**2 (40.0)**
Neutrophil Count Decreased	12 (18.8)	9 (13.8)	5 (10.6)	6 (14.6)	7 (50.0)	2 (11.1)	0	1 (20.0)
WBC Count Decreased	12 (18.8)	7 (10.8)	4 (8.5)	3 (7.3)	7 (50.0)	3 (16.7)	1 (33.3)	1 (20.0)
Metabolism and Nutrition Disorders	**24 (37.5)**	**16 (24.6)**	**16 (34.0)**	**13 (31.7)**	**6 (42.9)**	**2 (11.1)**	**2 (66.7)**	**1 (20.0)**
Decreased Appetite	17 (26.6)	6 (9.2)	10 (21.3)	4 (9.8)	5 (35.7)	2 (11.1)	2 (66.7)	0
Nervous System Disorders	**20 (31.3)**	**12 (18.5)**	**12 (25.5)**	**8 (19.5)**	**7 (50.0)**	**3 (16.7)**	**1 (33.3)**	**1 (20.0)**
Respiratory, Thoracic, and Mediastinal Disorders	**20 (31.3)**	**12 (18.5)**	**16 (34.0)**	**7 (17.1)**	**4 (28.6)**	**4 (22.2)**	**0**	**1 (20.0)**
Infections and Infestations	**12 (18.8)**	**14 (21.5)**	**9 (19.1)**	**7 (17.1)**	**2 (14.3)**	**4 (22.2)**	**1 (33.3)**	**3 (60.0)**
Musculoskeletal and Connective Tissue Disorders	**11 (17.2)**	**6 (9.2)**	**8 (17.0)**	**6 (14.6)**	**3 (21.4)**	**0**	**0**	**0**
Eye Disorders	**7 (10.9)**	**2 (3.1)**	**4 (8.5)**	**1 (2.4)**	**2 (14.3)**	**0**	**1 (33.3)**	**1 (20.0)**

Abbreviations: Dox = doxorubicin; N = number of patients in category; n = number of patients in subcategory; Ola = olaratumab; WBC = white blood cell.

[a] Only one treated patient (randomized to the Control Arm) was age >85 years; this patient is not included in the age subgroup analysis shown in this table.

[b] Includes only System Organ Classes for which a study drug-related adverse event was reported for at least 10% of patients in the Phase 2 Investigational Arm overall.

[c] Includes only Preferred Terms for which a study-drug related event was reported for at least 10% of patients in the Phase 2 Investigational Arm overall.

Sex

The incidences of TEAEs of any grade were similar in both sexes and between the 2 treatment arms. Overall, females experienced higher rates of Grade ≥3 TEAEs (32 [84.2%] in the Investigational Arm vs. 24 [72.7%] in the Control Arm) in comparison to males (19 [73.1%] in the Investigational Arm vs. 21 [65.6%] in the Control Arm), but the magnitude of difference was similar between both treatment arms.

The most frequently reported TEAEs (regardless of causality, any grade) for patients in the Investigational Arm, in males versus females, respectively, were musculoskeletal pain (19 [73.1%] vs. 22 [57.9%]), nausea (15 [57.7%] vs. 32 [84.2%]), fatigue (18 [69.2%] vs. 26 [68.4%]), neutropenia (15 [57.7%] vs. 23 [60.5%]), and mucositis (14 [53.8%] vs. 20 [52.6%]).

Grade ≥3 TEAEs for male patients observed at higher (>5% point difference) incidence in the Investigational Arm than in the Control Arm, respectively, were neutropenia (14 [53.8%] vs. 11 [34.4%]), musculoskeletal pain (3 [11.5%] vs. 0), and lymphopenia (3 [11.5%] vs. 1 [3.1%]).

Grade ≥3 TEAEs for female patients observed at higher (>5% point difference) incidence in the Investigational Arm than in the Control Arm, respectively, were fatigue (4 [10.5%] vs. 0), neutropenia (21 [55.3%] vs. 11 [33.3%]), thrombocytopenia (6 [15.8%] vs. 0), anemia (8 [21.1%] vs. 4 [12.1%]), and abdominal pain, hyponatremia, and lymphopenia (each, 2 [5.3%] vs. 0).

Race

The safety population for the subgroup analysis of race consisted of 86.8% White patients and 13.2% Non-White. Overall, the incidence of TEAEs of any grade was similar in both race groups (White and Non-White) and in the 2 treatment arms. White patients experienced a higher incidence of Grade ≥3 TEAEs in comparison to Non-White patients, but the incidence of SAEs was similar between both groups.

Safety related to drug-drug interactions and other interactions

Apart from Study JGDI that was conducted to assess the potential for DDI between olaratumab and doxorubicin in STS, no additional studies were conducted (see clinical pharmacology).

Discontinuation due to adverse events

Summary tables of AE leading to dose modification are presented below:

Table 49: Olaratumab dose modifications (Safety population, JGDG phase 2)

	Investigational Arm N = 64 n (%)	Control Arm: Olaratumab Monotherapy after Doxorubicin Treatment[a] N = 30 n (%)
Patients with Dose Delay	37 (57.8)	8 (26.7)
Patients with Dose Reduced	16 (25.0)	1 (3.3)
Patients with Dose Held	20 (31.3)	2 (6.7)
Patients with Infusion Interrupted	8 (12.5)	4 (13.3)

Abbreviations: N = number of treated patients; n = number of patients in category.
Note: Dose delays and dose reductions could have occurred in the same patient.
a Patients initially randomized to the Control Arm who received olaratumab monotherapy after discontinuation of doxorubicin.

The majority of Olaratumab dose modifications (including dose delays, dose reduction, dose held and infusion rate modification) occurred as a result of AEs. The most common (in >5% of patients) AEs leading to modification of olaratumab (regardless of relationship to study therapy) were neutropenia (31 [48.4%]), thrombocytopenia (8 [12.5%]), febrile neutropenia and IRR (both 4 [6.3%]).

Table 50: Doxorubicin dose modifications (Safety population, JGDG phase 2)

	Investigational Arm N = 64 n (%)	Control Arm N = 65 n (%)
Patients with Dose Delay	16 (25.0)	12 (18.5)
Patients with Dose Reduced	16 (25.0)	10 (15.4)
Patients with Dose Held	8 (12.5)	3 (4.6)
Patients with Infusion Interrupted	0	1 (1.5)

Abbreviations: N = number of treated patients; n = number of patients in category.
Note: Dose delays and dose reductions could have occurred in the same patient.

The majority of modifications occurred as a result of AEs (patients with AE leading to modification of doxorubicin: 23 pts [35.9%] vs. 17 pts [26.2%] in the Investigational vs the Control group respectively). The most common (in >5% of patients in either arm) AEs leading to modification of doxorubicin were neutropenia (13 [20.3%] vs. 6 [9.2%] in the Investigational vs. the Control Arm) and febrile neutropenia (3 [4.7%] vs. 4 [6.2%]).

A summary table of AEs leading to treatment discontinuation are presented below:

Table 51: TEAE leading to discontinuation of study therapy, safety population, JGDG Study (Phase 2)

	Investigational Arm N = 64 n (%)	Control Arm N = 65 n (%)
Patients with any TEAE leading to discontinuation of:		
Any study drug	8 (12.5)	12 (18.5)
Olaratumab	5 (7.8)	NA
Doxorubicin	7 (10.9)	12 (18.5)
TEAEs leading to any study drug discontinuation		
Ejection fraction decreased	3 (4.7)	4 (6.2)
Infusion-related Reactions[a]	2 (3.1)	0
Respiratory failure	1 (1.6)	1 (1.5)
Cardiac failure congestive	1 (1.6)	0
Left ventricular dysfunction	1 (1.6)	0
Sinus bradycardia	1 (1.6)	0
Pneumonia	1 (1.6)	0
Mucositis[b]	1 (1.6)	0
Neutropenia[c]	0	1 (1.5)
Thrombocytopenia[d]	0	2 (3.1)
Intestinal obstruction[e]	0	1 (1.5)
Hypotension	0	1 (1.5)
Neutropenic sepsis	0	1 (1.5)
Sepsis	0	1 (1.5)
Procedural pain	0	1 (1.5)
Phantom pain	0	1 (1.5)
TEAEs leading to olaratumab discontinuation		
Infusion-related Reactions[a]	2 (3.1)	NA
Ejection fraction decreased	1 (1.6)	NA
Respiratory failure	1 (1.6)	NA
Sinus bradycardia	1 (1.6)	NA
Pneumonia	1 (1.6)	NA
TEAEs leading to doxorubicin discontinuation		
Ejection fraction decreased	3 (4.7)	4 (6.2)
Cardiac failure congestive	1 (1.6)	0
Infusion-related Reactions[a]	1 (1.6)	0
Left ventricular dysfunction	1 (1.6)	0
Mucositis[b]	1 (1.6)	0
Pneumonia	1 (1.6)	0
Respiratory failure	1 (1.6)	1 (1.5)
Sinus bradycardia	1 (1.6)	0
Thrombocytopenia[d]	0	2 (3.1)
Neutropenia[c]	0	1 (1.5)
Intestinal obstruction[e]	0	1 (1.5)
Hypotension	0	1 (1.5)
Neutropenic sepsis	0	1 (1.5)
Sepsis	0	1 (1.5)
Procedural pain	0	1 (1.5)
Phantom pain	0	1 (1.5)

Abbreviations: N = number of treated patients; n = number of patients in category; NA = not applicable
TEAE = treatment-emergent adverse event.
Note: Refer to Table APP.2.3.4.7.5.1 for the full list of PTs included in each consolidated TEAE term.

Note: Consolidated TEAE categories are italicized. For the list of preferred terms that were reported in Study JGDG, refer to Table JGDG.14.99, Table JGDG.14.101, and Table JGDG.14.102.

a Preferred term reported was hypersensitivity reaction.
b Preferred term reported was mucosal inflammation.
c Preferred term reported was neutropenia.
d Preferred term reported was thrombocytopenia.
e Preferred term reported was small intestinal obstruction.

Source: taedc, taecondc, taedcola, taecondcola, taedcchem, taecondcchem.

In the Investigational Arm, all events were considered related to any study drug, with the exception of "respiratory failure". In the Control Arm, the events considered unrelated to doxorubicin according to Investigator were Ejection fraction decreased (1 out of 4 events), respiratory failure, procedural pain, phantom pain, intestinal obstruction (leading to death). The other TEAEs leading to discontinuation listed in the table above were considered related to study drugs according to Investigator.

In the Crossover population (30 pts) of the Control Arm, there were 5 patients (16.7%) experiencing a total of 10 AEs leading to modification of olaratumab (vomiting, diarrhoea, fatigue, hyperbilirubinemia, gastroenteritis, influenza, weight decreased, tumour pain, acute renal failure, and flushing). Two patients (6.7%) discontinued olaratumab due to AE, one for IRR G4 related to olaratumab, and one for musculoskeletal pain Grade 3 (pain in extremity and back pain, unrelated to study drug according to investigator).

Post marketing experience

N/A

2.6.1. Discussion on clinical safety

A total of 485 patients have received olaratumab in 9 Phase 1 and 2 clinical studies. For the purpose of this application, the safety profile of olaratumab in combination with doxorubicin for the treatment of patients with advanced STS is mainly based on safety results from the Phase 2 portion of Study JGDG (main registration study). The safety data from this study included the analysis of treatment-emergent adverse events, adverse events of special interest and notable patients (those with at least one of the following: Discontinued study treatment due to any AE, experienced death while on any study treatment or within 30 days of last study dose, experienced suspected unexpected serious adverse reactions, discontinued any study treatment due to reasons other than AE or P, discontinued the study due to lost to follow-up or experienced AESIs).

Study JGDG was an early/phase exploratory trial and the overall exposure to the investigational treatment could be considered relatively low. The size of the safety dataset is considered small, and data on long-term use limited. During the procedure, the applicant provided a safety update report also provided to FDA, including 47 patients treated across 4 studies at the data cut-off of 20 January 2016 and the report together with the blinded safety data of the first interim safety analysis conducted by the independent Data Monitoring Committee (iDCM) for the ongoing phase 3 study JGDJ at the data cut-off of 19 February 2016, including 157 patients (of whom 100 treated with >2 cycles). The number of patients included in these two new safety reports was small and patients were heterogeneous (i.e. indication, dosage, country) and the interpretability of blinded data provided was quite limited. However, the supplementary data provided did not highlight any unknown safety finding.

A total of 64 patients were treated with the combination of doxorubicin and olaratumab and 30 patients in the control arm received olaratumab monotherapy after progression with doxorubicin. Those patients, although small in numbers, were exposed to a significant number of cycles (median 16.5 infusions in the doxorubicin + olaratumab arm and 4 as monotherapy in the control arm).

Known toxicities reported for doxorubicin, observed in the combination of olaratumab and doxorubicin include fatigue, anaemia, thrombocytopenia and alopecia. The added toxicity of olaratumab to doxorubicin is not trivial, given the remarkable increase in doxorubicin dose reductions. This finding suggests that the toxicity of the combination, although manageable, seems to be significant.

The frequency of certain AEs typically associated with doxorubicin was increased when using the combination with olaratumab indicating that olaratumab is not devoid from toxicity. This is noted especially for nausea (increased by a factor of 3), neutropenia (an absolute 20% higher), anaemia and thrombocytopenia (both of them raised above the 10% bar). This fact is probably reflecting the greater exposure to doxorubicin in the

experimental arm; however, the median duration for all of them (with the exception of diarrhoea) was no longer in the combination than in the monotherapy group.

The higher incidence of neutropenia in the investigational arm was not associated with a higher risk for infectious complications. However, the neutrophil count should be checked prior to olaratumab dosing on Day 1 and Day 8 of each cycle and neutrophil counts should be monitored during the treatment with olaratumab and doxorubicin and supportive care administered such as antibiotics or G-CSF as per local guidelines (see section 4.4 of the SmPC).

Administration of live or live-attenuated vaccines in patients immunocompromised by chemotherapeutic agents including doxorubicin, may result in serious or fatal infections. Vaccination with a live vaccine should be avoided in patients receiving olaratumab in combination with doxorubicin (see section 4.5 of the SmPC).

The higher incidence of painful events is also intriguing. They were diverse, in nature and anatomic location, and frequent (around 60% vs. 20% in control arm, 7.8% vs. 1.5% for Grade 3). Pain erodes quality of life more than many other side effects and it is a concern in the case of a palliative treatment where preserving the quality of life is paramount. A description of Musculoskeletal Pain, with severity and duration, has been reflected in section 4.8 of the SmPC. Although the higher frequency of painful events in the combination arm is not completely understood, it seems that they are limited to the first 4-5 cycles of treatment.

An analysis of all 16 patients with pain in extremity as an AE showed that most of them were disease-dependant. Moreover, by analysing the narratives of these patients, most of the cases of pain in extremities could have non-drug related explanation. However, no drug related events were reported in the Control arm. Pain in extremities is included in the “musculoskeletal pain” term and it is reflected in the SmPC.

The brief summary of safety data from the olaratumab monotherapy treatment did not show any additional safety concerns. However, the applicant was asked to discuss the relationship between haemorrhagic AEs and olaratumab observed across supportive studies, taking into account the clinical relevance of such events. The analysis of these haemorrhagic AEs revealed that the majority of them were considered unrelated to study drugs and they were mainly Grade 1-2. Nevertheless, plausibility of haemorrhagic events when targeting PDGFRα in patients cannot be ruled out, considering the current lack of biological data clarifying the mechanism of action of olaratumab. Based on the data provided, an increased risk of haemorrhagic events is observed across olaratumab studies. Platelet counts should be checked prior to olaratumab dosing on Day 1 and Day 8 of each cycle. Coagulation parameters should be monitored in patients with conditions predisposing to bleeding, such as anticoagulant use. In a study of olaratumab in combination with liposomal doxorubicin, there was one case of fatal intracranial haemorrhage in a patient who had experienced a fall while on treatment (see sections 4.4 and 4.8 of the SmPC).

The Applicant identified 3 AEs of special interest (AESIs) for olaratumab and/or doxorubicin: infusion-related reactions (IRR), cardiac arrhythmia and cardiac dysfunction.

IRRs, including anaphylactic reactions, were reported in clinical trials with olaratumab. The majority of these reactions occurred during or following the first olaratumab infusion. Symptoms of IRRs included flushing, shortness of breath, bronchospasm, or fever/chills, and in some cases manifested as severe hypotension, anaphylactic shock, or fatal cardiac arrest. Severe IRRs such as anaphylactic reactions can occur despite the use of premedication. Patients should be monitored during the infusion for signs and symptoms of IRRs in a setting with available resuscitation equipment. For management and dose adjustments in patients who experience Grade 1 or 2 IRR during the infusion, see section 4.2. In patients who have experienced a previous Grade 1 or 2 IRR, premedication with diphenhydramine hydrochloride (intravenously), paracetamol,

and dexamethasone is recommended. Olaratumab should be immediately and permanently discontinued in patients who experience Grade 3 or 4 IRR (see sections 4.2, 4.4 and 4.8 of the SmPC).

The addition of olaratumab did not seem to increase the frequency or severity of cardiac arrhythmia. However AEs of cardiac dysfunction were slightly more frequent in the investigational arm. This finding has to be put into the context of a higher doxorubicin exposure of these patients, compared to the control arm.

SAEs (any grade and Grade ≥3) were slightly more frequently reported in the investigational arm, than in the doxorubicin or olaratumab monotherapy arms. This was also the case for pain-related events, such as musculoskeletal and abdominal pain.

The rates of neutropenia and febrile neutropenia were comparable between both treatment arms, which provide reassurance.

It is noted that olaratumab doses were more prone to delays or reductions when combined with chemotherapy than when administered as monotherapy suggesting better tolerance to the monotherapy (the main reason for dose modifications being AEs).

A total of 10 deaths occurred during study therapy or within 30 days after the last dose, 5 due to AEs and 5 due to PD. One death occurred in a patient in the Control Arm who crossed over to olaratumab due to a cardiac arrest associated to olaratumab IRR in the context of an extensive cardiac history and prior doxorubicin cardiotoxicity. The risk of cardiac toxicity rises with increasing cumulative doses of anthracyclines, including doxorubicin and is higher in individuals with a history of cardiomyopathy, mediastinal irradiation or pre-existing cardiac disease. There are no data for the combination of olaratumab and doxorubicin in anthracycline pre-treated patients, including pre-treatment with doxorubicin. In order to minimise doxorubicin-related cardiotoxicity, the use of appropriate cardio-protective measures (LVEF measurement, such as ECHO or MUGA scan, ECG monitoring, and/or use of cardioprotective agents) should be considered and planned in all patients before the start and throughout the treatment. In the JGDG study, patients in both treatment groups that received 5 or more cycles of doxorubicin received dexrazoxane prior to each dose of doxorubicin from cycle 5 onwards to minimize the risk of doxorubicin-related cardiotoxicity (see section 4.4 of the SmPC)

Laboratory findings were consistent with the general AE data. Abnormal LVEF results were numerically more frequent in the investigational arm. However given the small numbers, no conclusion can be drawn. Overall, the incidence of patients with treatment-emergent ADA was low. In general, the presence of treatment-emergent ADA does not seem to have a large impact on the overall safety profile or the occurrence of IRRs. However, due to the small number of patients studied, definitive conclusions regarding the relationship between ADA and IRR cannot be established and must await the results of the phase III confirmatory study (See Annex II).

Overall, discontinuation due to AEs were similar in nature and frequency between both treatment arms, but all 3 reported deaths occurred in the control arm.

In study JGDG, the overall number of patients over the age of 65 was limited, and more particularly the very elderly patients (≥75). There was a higher incidence of Grade ≥3 adverse reactions, adverse reactions leading to discontinuation and a higher rate of haematological toxicity in the elderly population compared to the overall study population. The rates of discontinuation were comparable between treatment arms across all age groups (see sections 4.2 and 4.8 of the SmPC).

Patients with liver/renal impairment were not implicitly excluded from the registration study. However, a priori the impact of renal impairment on the safety of olaratumab is not expected to be significant. Only one patient with mild liver impairment was enrolled in the study, which does not allow reaching any conclusions on the safety in patients with hepatic impairment. However as doxorubicin is rapidly metabolised and predominantly eliminated by the biliary system, the toxicity of doxorubicin is enhanced in patients with hepatic impairment (see section 4.4 of the SmPC).

The safety profile in the LMS and non-LMS histological subtypes seems to be comparable. However, the small number of patients within the other STS subtype populations precludes any conclusion in this patient population. The applicant will conduct a post authorisation observational safety study to evaluate the safety and effectiveness of olaratumab in combination with doxorubicin in patients with advanced STS, including rare subtypes (see RMP).

In the investigational arm, females experienced Grade ≥3 TEAEs more frequently than males (32 [84.2%] vs. 19 [73.1%], respectively). This difference was also observed in the control arm (24 [72.7%] vs. 21 [65.6%] in the control arm, respectively). There were also differences in terms of the most frequently reported TEAEs, with the largest differences observed for musculoskeletal pain (19 [73.1%] males vs. 22 [57.9%] females) and nausea (15 [57.7%] males vs. 32 [84.2%] females). There was no clear explanation for these differences, partly due to the small sample size of the pivotal study.

Considering that the majority of patients included in the registration study were White (>80%), it is difficult to reach a conclusion on the safety profile of other race/ethnic groups with the evidence available at this time.

There is no experience with olaratumab overdose in human clinical trials. Olaratumab has been administered up to 20 mg/kg on days 1 and 8 of a 21 day cycle without reaching a maximum tolerated dose. In case of overdose, supportive therapy should be used. There is no known antidote to Olaratumab overdose (see section 4.9 of the SmPC).

Olaratumab may have minor influence on the ability to drive and use machines. Due to frequent occurrence of fatigue, patients should be advised to use caution when driving or operating machinery (see section 4.7 of the SmPC).

Olaratumab contains 146 mg sodium per each 50 mL vial which should be taken into consideration by patients on a controlled sodium diet.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Additional safety data needed in the context of a conditional MA

Study JGDG was an early/phase exploratory trial and the overall exposure to the investigational treatment could be considered relatively low. The size of the safety dataset is considered small only allowing identification of the most frequent adverse events, and data on long-term use limited. The Applicant will provide safety data from an ongoing confirmatory phase III trial which will address this issue.

Pain of different location and nature was the most remarkable finding in the safety evaluation of olaratumab. Pain is a relevant AE due to its potential impact on quality of life and the confirmatory phase 3 study is expected to refine data regarding the pain phenomena, its incidence, clinical course and optimal management.

2.6.2. Conclusions on the clinical safety

The safety of olaratumab plus doxorubicin as treatment of advanced STS patients and the added toxicity to the current standard treatment with doxorubicin seem to be manageable.

The CHMP considers the following measures necessary to address the missing safety data in the context of a conditional MA:

In order to further confirm the efficacy and safety of olaratumab in the treatment of patients with advanced soft tissue sarcoma, the MAH should submit the clinical study report of the phase III study JGDJ comparing doxorubicin plus olaratumab versus doxorubicin in patients with advanced or metastatic STS (including exploratory biomarker data) by 31 January 2020.

In addition, the MAH will submit the second interim safety analysis of the phase III study JGDJ by 31 December 2016.

The CHMP considers the following measures necessary to address issues related to safety:

The MAH should conduct and submit a post authorisation observational study to evaluate the safety and effectiveness of olaratumab in combination with doxorubicin in patients with advanced STS, including rare subtypes (see RMP)

2.7. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP):

The PRAC considered that the RMP version 1.0 (dated 14 January 2016) could be acceptable if the Applicant implements the changes to the RMP as described in the PRAC outcome section of the D94 PRAC Rapporteur RMP assessment report (AR) dated 09 June 2016.

The CHMP endorsed this advice without changes.

The Applicant implemented all changes to the RMP as requested by the PRAC and the CHMP, as also detailed in the RMP section of the Joint Updated PRAC / CHMP AR dated 09 September 2016.

The CHMP endorsed the RMP version 1.4, dated 14 September 2016, with the following content:

Safety concerns

Table 52 – Summary of the safety concerns

Important Identified Risks	• Infusion related reactions
Important Potential Risks	• Embryo-foetal toxicity, Teratogenicity • Off-label use

Missing Information	• Carcinogenicity, Genotoxicity • Long-term fertility impairment • Effect on breast feeding • Effectiveness in rare STS subtypes • Long term olaratumab use • Infrequently occurring adverse events • Use in very elderly patients (>75 years) • Use in patients with severe renal or hepatic impairment • Use in paediatric patients

Abbreviation: STS = soft tissue sarcoma.

Pharmacovigilance plan

Table 53 – *Ongoing and planned pharmacovigilance activities / studies in the PV plan*

Study / Activity Type, Title, and Category (1-3)	**Objectives**	**Safety Concerns Addressed**	**Status (Planned, Started)**	**Date for Submission of Interim or Final Reports (Planned or Actual)**
I5B-MC-JGDJ A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Doxorubicin plus Olaratumab versus Doxorubicin plus Placebo in Patients with Advanced or Metastatic Soft Tissue Sarcoma (Category 2)	To compare the safety and efficacy in patients with advanced or metastatic STS after treatment with doxorubicin plus olaratumab versus doxorubicin plus placebo	Key to understanding the benefit-risk profile of olaratumab: • Infusion-related reactions • Long-term use of olaratumab • Infrequently occurring AEs • Use in very elderly patients (>75 years) • Use in patients with severe renal or hepatic impairment	Started	31 Jan 2020
I5B-IE-JGDI Phase 1 study - Pharmacokinetics of doxorubicin following olaratumab in patients with advanced STS (Category 3)	To rule out that olaratumab had no effect on the PK of co-administered doxorubicin.	Infrequently occurring AEs	Started	Q4 2017
Post authorization observational study to evaluate the safety and effectiveness of olaratumab in combination with doxorubicin in patients with advanced STS, including rare subtypes (Category 3)	To understand the benefit-risk profile of olaratumab in combination with doxorubicine in routine clinical practice in patients with advanced STS, including rare subtypes	• Effectiveness in rare STS subtypes • Long-term use of olaratumab • Infrequently occurring AEs • Use in very elderly patients (>75 years) • Use in patients with severe renal or hepatic impairment	Planned	Protocol to be submitted 3 months after Commission Decision

Risk minimisation measures

Safety Concern	Routine Risk Minimisation Measures	Additional Risk Minimisation Measures
Important Identified Risks		
• Infusion related reactions	Proposed text in SmPC	None
Important Potential Risks		
• Embryo-foetal toxicity, Teratogenicity • Off-label use	Proposed text in SmPC Proposed text in SmPC	None
Missing Information		
• Carcinogenicity, Genotoxicity • Long-term fertility impairment • Effect on breast feeding • Effectiveness in rare STS subtype • Long term use of olaratumab • Infrequently occurring adverse events • Use in very elderly patients (>75 years) • Use in patients with severe renal or hepatic impairment • Use in paediatric patients	Proposed text in SmPC Proposed text in SmPC Proposed text in SmPC Not applicable Not applicable Proposed text in SmPC Proposed text in SmPC Proposed text in SmPC Proposed text in SmPC Proposed text in SmPC	None

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. New Active Substance

The applicant declared that olaratumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers olaratumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Labelling exemptions

A request to omit certain particulars from the labelling as per Art.63.3 of Directive 2001/83/EC has been submitted by the applicant and has been found unacceptable by the QRD Group for the following reasons:

The QRD Group is of the view that the current proposal is not considered sufficiently justified.

It is acknowledged that including full particulars on the vial label, particularly for the trilingual, may be challenging. However, there is certain information that is critical for the safe and effective use of this medicinal product and it should, therefore, be included.

Considering that the size of the container is 50ml, the QRD Group is of the view that more information than the currently proposed minimum particulars can be included.

The applicant is invited to first explore alternative labelling solutions such as labelling wrap ups or concertina, which is already used for other products.

The following information is considered essential to ensure the safe and correct use of the product and should also be included in the vial labelling:

- '*For single use only*'
- '*Do not shake*'
- Regarding the special storage conditions, at least, the statement "*Keep the vial in the outer carton*" is considered especially relevant for the immediate labelling. If space allows '*Store in a refrigerator*' or '*Do not freeze*' should also be considered for inclusion.

An exemption to the obligation to include the remaining particulars (excipients, out of sight and reach of children, special disposal, etc.) is, however, considered acceptable.

The particulars to be omitted as per the QRD Group decision described above will however be included in the Annexes published with the EPAR on EMA website, and translated in all languages but will appear in grey-shading to show that they will not be included on the printed materials.

2.10.3. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Lartruvo (olaratumab) is included in the additional monitoring list as:

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU

- It is approved under a conditional marketing authorisation [REG Art 14(7)]

Therefore the summary of product characteristics and the package leaflet includes a statement that this

medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

STS is a rare group of heterogeneous mesenchymal tumours. There are more than 50 histological subtypes of STS, associated with distinct clinical profiles, response to individual therapy and prognosis.

The olaratumab application is for the treatment in combination with doxorubicin, of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin.

3.1.2. Available therapies and unmet medical need

Surgery is the gold-standard, and often only, curative treatment. Radiotherapy is often used to control local-recurrence in aggressive histological subtypes and/or when appropriate margins cannot be obtained, but it has no effect on cure rates. Front-line advanced-disease treatment of the vast majority of STS subtypes patients still rely on doxorubicin, a 40-year old drug, based on historical non-controlled research. Although some progress has been made in the second-line setting, it has not translated into OS benefits in the first-line treatment.

3.1.3. Main clinical studies

The olaratumab application is based on study JGDG, an open-label, multicenter, randomized phase 1b/2 trial conducted in the United States, which enrolled patients (age ≥18 years) with histologically or cytologically confirmed, advanced STS not amenable to treatment with surgery or radiotherapy.

In the Phase 2 portion, patients were randomized to receive doxorubicin plus olaratumab or doxorubicin alone. The primary objective of the Phase 2 portion was to compare the PFS of patients treated with olaratumab in combination with doxorubicin versus patients treated with doxorubicin alone. OS was a secondary endpoint.

3.2. Favourable effects

In the primary analysis (using the ITT population based on investigator assessment), the study met the protocol-defined final significance level for PFS (2-sided alpha=0.1999). The combination of olaratumab and doxorubicin provided an improvement in median PFS of 2.5 months over doxorubicin alone (stratified HR = 0.672 [95% CI: 0.442, 1.021]; p=0.0615), corresponding to a 32.8% reduction in the risk of progression or death. The median PFS results were 6.6 and 4.1 months for the combination arm versus doxorubicin alone respectively.

Results from a blinded independent review of radiologic scans support the investigator assessment (HR 0.670 95% CI: 0.401, 1.117). The median PFS results were 8.2 and 4.4 months for the combination arm versus doxorubicin alone respectively.

Olaratumab in combination with doxorubicin reduced the risk of death in this population by 53.7% (HR = 0.463; 95% CI: 0.301, 0.710; p=0.0003), with a median overall survival in the Investigational arm of 26.5 months compared to 14.7 months in the Control arm. The 3- and 6-month survival rates were (Investigational Arm vs. Control Arm) 95.2% versus 87.6% and 90.5% versus 73.3%, respectively.

Objective response rate (ORR) was higher in the combination arm (18.2%) than in the doxorubicin arm (11.9%), although the difference was not statistically significant (p=0.3214).

3.3. Uncertainties and limitations about favourable effects

Despite the unexpected and outstanding results in OS, the longer life expectancy of those patients treated with the combination is not intuitively linked to an increase in the delay of tumour progression.

No difference was seen between PDGFRα positive and negative which do not provide support to the mechanism of action. Certainly, the different methods used and the expression of the receptor not only in tumour cells but also on stroma, could explain at least partially this lack of pharmacodynamic effect.

Maintenance of single-agent olaratumab was allowed in the experimental arm, while crossover to single-agent olaratumab was permitted in control arm upon progression. Although it leaves behind important unanswered questions, allowing maintenance treatment for experimental targeted agents maximizes patient's survival options.

In summary, two main uncertainties about the beneficial effects of the experimental trial: the early nature of clinical research supporting it and the lack of correlation between the biological basis of the disease and the clinical benefit derived from treatment. These uncertainties should be addressed by the ongoing phase 3 confirmatory trial JGDJ.

3.4. Unfavourable effects

The most common adverse reactions were nausea, musculoskeletal pain, neutropenia and mucositis.

The most common serious adverse reactions (Grade ≥3) observed in olaratumab-treated patients are neutropenia (54.7 %) and musculoskeletal pain (7.8 %).

The most frequent adverse reactions associated with permanent treatment discontinuation occurred in 3 (4.7 %) patients of which the most frequent (≥ 1 %) were infusion-related reactions (3.1 %) and mucositis (1.6 %).

The incidence of nausea, neutropenia, anaemia and thrombocytopenia were increased in the combination arm compared to doxorubicin. There was a high incidence of painful events affecting over half of the patients which were diverse in nature and anatomic location.

3.5. Uncertainties and limitations about unfavourable effects

The size of the available safety database is considered limited and only allows identification of the most frequent adverse events. The Applicant will provide safety data from an ongoing confirmatory phase III trial which will address this issue.

Pain of different location and nature was the most remarkable finding in the safety section. Pain is a relevant AE due to its potential impact on quality of life, the most relevant endpoint in the palliative treatment setting. The trial data gave no clear relationship between the duration-severity of pain and the treatment with the combination. The confirmatory phase 3 trial is expected to refine data regarding pain phenomena, its incidence, clinical course and optimal management.

3.6. Effects Table

Table 54: Effects Table for Olaratumab in STS (data cut-off: 23 September 2014 [PFS]; 19 June 2015 [OS])

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
PFS (Inv)	Time from randomization until progression or death.	Median (months)	6.6	4.1	Stratified Log-rank p-value for: - PFS: 0.0615 - OS: 0.0003	See Discussion on Clinical Efficacy
		HR	0.672			
OS	Time from the date of randomization to the date of death	Median (months)	26.5	14.7	Few patients treated. Data from phase 2 study /Consistency in several sensitivity analyses.	
		HR	0.463			
ORR	Proportion of patients achieving a best overall response of PR or CR	%	18.2	11.9	Few patients treated. Response rate does not correlate with OS in STS	
Unfavourable Effects						
Nausea	Proportion		AE 73.4% G 3/4 1.6% SAE <1%	AE 52.3% G 3/4 3.1% SAE <1%		
Fatigue			AE 68.8% G 3/4 9.4% SAE <1%	AE 69.2% G 3/4 3.1% SAE <1%		
Musculo-skeletal pain			AE 64.1% G 3/4 7.8% SAE 4.7%	AE 24.6% G 3/4 1.5% SAE 1.5%		
Neutropenia			AE 59.4% G 3/4 54.7% SAE 4.7%	AE 38.5% G 3/4 33.8% SAE 4.6%		
Mucositis			AE 53.1% G 3/4 3.1% SAE <1%	AE 35.4% G 3/4 4.6% SAE <1%		

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
AE leading to discontinuations	Proportion		12.5% G3/4 N/A %	18.5% G3/4 N/A %		

Abbreviations: AE: adverse event; G: grade; HR: hazard ratio; N/A: not applicable; ORR: objective response rate; OS: overall survival; PFS: progression free survival; SAE: serious adverse event; STS: soft tissue sarcoma

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The request for conditional marketing authorisation is based on a single open-label, randomised phase 1b/2 trial (study JGDG) enrolling anthracycline-naïve patients with advanced STS. The analysis of efficacy showed a remarkable improvement in OS, meaningful enough as to request conditional approval.

The survival was improved in patients treated with olaratumab and Kaplan-Meier curves showed an early separation and a persistence of the OS benefit over time. After adjusting for factors most likely to affect prognosis, olaratumab maintained its effect on all histological subgroups analysed. If confirmed, these results could represent a shift in the treatment paradigm of advanced STS, introducing targeted treatments in the broad STS arena. Furthermore, the main uncertainties related to the survival outcome should be contextualized bearing in mind the different analyses aimed to show the robustness of the result.

However, the use of olaratumab as add-on to doxorubicin increases the frequency of AEs, worsening the tolerability. Higher rates of neutropenia, nausea, anaemia, mucositis, thrombocytopenia and painful events, were observed. Nevertheless, these AEs seem manageable and outweighed by the significant increase in survival. This is further supported by the proportion of treatment discontinuations due to AEs (12.5% vs 18.5% combination vs monotherapy).

3.7.2. Balance of benefits and risks

The results from the pivotal study show a statistically significant and clinically meaningful improvement in OS with the olaratumab plus doxorubicin combination compared to doxorubicin single agent (HR 0.463, 95% CI: 0.301- 0.710, p=0.0003; median gain of 11.8 months).

In view of the benefits, the increased toxicity of the treatment combination seems tolerable and manageable.

3.7.3. Additional considerations on the benefit-risk balance

Conditional marketing authorisation

As comprehensive data on the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product falls within the scope of Regulation (EC) No 507/2006 concerning conditional marketing authorisations, as it aims at the treatment of a life-threatening disease, and is designated as an orphan medicinal product.

Furthermore, the CHMP considers that the product fulfils the requirements for a conditional marketing authorisation:

- The benefit-risk balance is positive, as discussed.
- It is likely that the applicant will be able to provide comprehensive data.

The applicant has initiated a confirmatory Phase 3 double blind study, Study I5B-IE-JGDJ (JGDJ), in patients with advanced STS; the first patient first visit occurred in September 2015. The primary objective of Study JGDJ is to compare doxorubicin plus olaratumab versus doxorubicin plus placebo with respect to OS in 2 populations: (1) Patients with advanced or metastatic STS that is not amenable to treatment with surgery or radiotherapy with curative intent; and (2) Patients with advanced or metastatic leiomyosarcoma (LMS) that is not amenable to treatment with surgery or radiotherapy with curative intent.

As of 20 July 2016, the number of patients randomised to the Phase 3 Study JGDJ is 505 (pre-planned enrolment: 460), with all sites closed to screening except in Japan and Taiwan to meet local regulatory requirements. A single interim efficacy analysis is planned after 194 events for OS have been observed in the ITT population. Results will only be provided to the Independent Data Monitoring Committee (iDMC), while the applicant remains blinded to the data. In addition, the iDMC will perform unblinded safety reviews every 6 months following the first iDMC safety review meeting, with additional reviews performed per iDMC request. Therefore, granting a conditional MA should not jeopardize the recruitment and it is likely that the applicant will be able to provide results from the phase 3 study.

- Unmet medical needs will be addressed, as the survival benefit observed in the pivotal study is considered relevant in the treatment of advanced STS.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required as the survival advantage observed with olaratumab in the context of the pivotal study is considered important enough not to further delay the availability of this medicine to patients.

3.8. Conclusions

The overall B/R of Lartruvo is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP, by consensus, is of the opinion that Lartruvo is not similar to Yondelis within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Lartruvo is favourable in the following indication:

Lartruvo is indicated in combination with doxorubicin for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not

been previously treated with doxorubicin (see section 5.1).

The CHMP therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Other conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Additional risk minimisation measures

Not applicable

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	**Due date**
In order to further confirm the efficacy and safety of olaratumab in the treatment	

Description	Due date
of patients with advanced soft tissue sarcoma, the MAH should submit the clinical study report of the phase III study JGDJ comparing doxorubicin plus olaratumab versus doxorubicin in patients with advanced or metastatic STS (including exploratory biomarker data). In addition, the MAH will submit the second interim safety analysis of the phase III study JGDJ.	31 January 2020 31 December 2016

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that olaratumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.