OP201

ASCENT TRIAL

SYNOPTIC CSR

An Open-Label, Phase 1/2 Study of Melflufen and Dexamethasone for Patients with AL Amyloidosis Following at Least One Prior Line of Therapy

Protocol Title:	An Open-Label, Phase 1/2 Study of Melflufen and Dexamethasone for Patients with AL Amyloidosis Following at Least One Prior Line of Therapy
Indications Studied:	AL Amyloidosis
Test Drug:	Melphalan flufenamide (melflufen)
Study Phase:	Phase 1/2
First patient enrolled:	Cohort 1: 06 August 2020; Cohort 2: 29 January 2021; Cohort 3: Not initiated
Last patient completed:	05 January 2022
Early termination date:	04 November 2021
EudraCT number:	2018-002761-19
ClinicalTrials.gov Identifier:	NCT04115956
Sponsor:	Oncopeptides AB
Sponsor Signatory:	Simon Rubinstein, MB BCh Global Clinical Study Physician
Global Lead Investigator:	Giovanni Palladini, MD, PhD
Date of the Report:	01 March 2022 (date of Sponsor approval)

This study was conducted in accordance with the ethical principles of Good Clinical Practice, according to the International Council for Harmonisation (ICH) Harmonised Tripartite Guideline, including the archiving of essential documents.

SYNOPSIS

Name of Sponsor/Company: Oncopeptides AB	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For National Authority Use Only)*
Name of Product: Melflufen		
Name of Active Ingredient: melphalan flufenamide		

Title of Study:
An Open-Label, Phase 1/2 Study of Melflufen and Dexamethasone for Patients with AL Amyloidosis Following at Least One Prior Line of Therapy

Global Lead Investigator:
Giovanni Palladini, MD, PhD

Investigators:
Teresa Maria Cibeira, MD; Moshe Gatt, MD; Roman Hájek, MD; Arnaud Jaccard, MD; Krzysztof Jamroziak, MD; Efstathios Kastritis, MD; Ann Kristin Kvam, MD; Giovanni Palladini, MD; Vaishali Sanchorawala, MD, Stefan Schönland, MD; Ashutosh Wechalekar, MD.

For a list of investigators and sites, see Appendix 16.1.4.

Study centers
The study was planned to be conducted at 11 sites in 11 countries. At time of database lock (DBL), patients had been enrolled at 4 sites in 4 countries: Germany, Greece, Israel, and Norway.

Purpose of synoptic Clinical Study Report (CSR)
The objective of this synoptic CSR is to provide information on the use of melflufen in patients with amyloid light-chain (AL) amyloidosis.

Melflufen in combination with dexamethasone was approved on 26 February 2021 by the United States Food Drug Administration (US FDA) for the treatment of adult patients with relapsed or refractory multiple myeloma who have received at least 4 prior lines of therapy and whose disease is refractory to at least 1 proteasome inhibitor, 1 immunomodulatory agent, and 1 CD38-directed monoclonal antibody. The overall survival (OS) results and subgroup analyses from the Phase 3 Study OP-103 led to an FDA-requested partial clinical hold on the melflufen clinical study program. On 04 November 2021, investigators in all ongoing studies were informed by Oncopeptides that the studies would be prematurely terminated.

This synoptic CSR summarizes data up to the DBL of 25 January 2022.

Publications (Reference): Not applicable

Studied Period (Years) Date first patient enrolled: Cohort 1: 6 August 2020; Cohort 2: 29 January 2021; Cohort 3: Not initiated Date last patient completed: 05 January 2022 Date for DBL: 25 January 2022 Early termination date: 04 November 2021	**Phase of Development:** 1/2

Objectives

Phase 1

Primary:

- To explore the safety and tolerability
- To identify recommended Phase 2 dose (RP2D)

Secondary:

- To assess pharmacokinetic (PK) profile of melflufen in this patient population
- To assess best hematologic response
- To assess duration of hematologic response
- To assess the proportion of organ system responses
- To assess duration of organ system responses
- To assess hematologic overall response rate (ORR)
- To assess time to next AL amyloidosis treatment
- To assess OS

Exploratory:

- To assess minimal residual disease (MRD)

Phase 2

Primary:

- To evaluate the hematologic ORR after 4 cycles at the RP2D determined in Phase 1

Secondary:

- To assess safety and tolerability
- To assess best hematologic response
- To assess duration of hematologic response
- To assess the proportion of organ system responses
- To assess duration of organ system responses
- To assess time to next AL amyloidosis treatment
- To assess OS

Exploratory:

- To assess MRD

Study Endpoints

Phase 1

Primary:

- Frequency and grade of adverse events (AEs) and laboratory values
- Dose-limiting toxicity (DLT) during Cycle 1 up to a maximum dose of melflufen of 40 mg

Secondary:

- Melphalan plasma concentration post-melflufen administration
- Best hematologic response (complete response [CR], very good partial response [VGPR], partial response [PR], no response [NR], or progressive disease [PD])
- Duration of hematologic response (CR, VGPR, PR)
- Proportion of patients with kidney, cardiac or liver response, respectively
- Duration of organ system specific responses (separately for kidney, cardiac and liver)
- The proportion of patients who achieve a hematologic CR, VGPR, or PR
- Time to next AL amyloidosis treatment
- OS

Exploratory:

- MRD status in patients who achieve a hematologic CR

Phase 2

Primary:

- The proportion of patients who achieve a hematologic CR, VGPR, or PR

Secondary:

- Frequency and grade of AEs and laboratory values
- Best hematologic response (CR, VGPR, PR, NR, or PD)
- Duration of hematologic response (CR, VGPR, PR)
- Proportion of patients with kidney, cardiac or liver response, respectively
- Duration of system organ specific responses (separately for kidney, cardiac, and liver)
- Time to next AL amyloidosis treatment
- OS

Exploratory:

- MRD status in patients who achieve a hematologic CR

Methodology

For protocol and protocol amendments, see Appendix 16.1.1.

This was an open-label, Phase 1/2 multi-center study enrolling patients with AL amyloidosis following at least 1 prior line of therapy.

Treatment consisted of intravenous infusion of melflufen on Day 1 of each 28-day cycle (Cohort 1, 20 mg; Cohort 2, 30 mg; Cohort 3, 40 mg [not initiated]), in combination with per oral dexamethasone (40 mg, or 20 mg at investigator's discretion) on Days 1 and 2 of each 28-day cycle.

Planned Study design

In Phase 1, patients were to be enrolled in one of 3 dose levels of melflufen. In Phase 2, patients were to be treated with the RP2D identified in Phase 1. In both phases, treatment of each individual patient was planned to continue for up to 8 cycles or until any of the stopping events, described in Section **Duration of Treatment**, occurred.

Phase 1

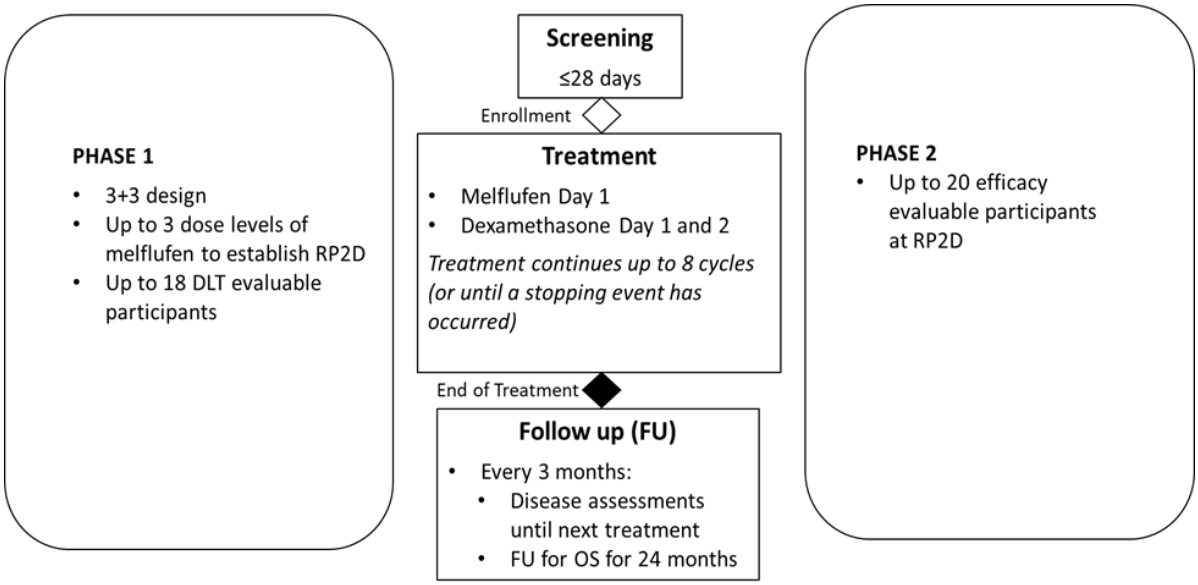
The Phase 1 design followed the standard 3+3 Phase 1 design with 3 to 6 DLT-evaluable patients at each dose level, depending on DLT observed in the first cycle of each patient. The definition of DLT is shown below (***Dose limiting toxicity***).

The first 3 patients were enrolled in Cohort 1 with a starting dose of 20 mg melflufen. Depending on the toxicity profile, subsequent additional patients were to receive the same, or the next higher dose (Cohort 2; 30 mg) of melflufen, according to the dose escalation rules. Depending on the toxicity profile of this dose, a third cohort (Cohort 3) of 3 to 6 patients were planned to receive the maximum dose of melflufen of 40 mg. Each individual cohort were planned to be evaluated after completion of Cycle 1 by a Data Monitoring Committee (DMC) to recommend dosing decisions and the RP2D. No patient was to be treated with a higher dose than 40 mg melflufen per 28-day cycle under this protocol.

Phase 2

Phase 2 was planned to include the 6 patients from Phase 1 that were treated at the RP2D, as well as an additional 20 efficacy-evaluable patients at the same dose, for a total of 26 efficacy-evaluable patients treated at the RP2D of melflufen.

Study design



Abbreviations: DLT dose limiting toxicity; FU follow up; OS overall survival; RP2D recommended Phase 2 dose.

Dose limiting toxicity

A DLT event was a melflufen-related event defined as any of the following:

- Thrombocytopenia*
  - Grade 3 or 4 with clinically significant bleeding
- Neutropenia*
  - Grade 4 with a duration of more than 5 days
  - Grade 3 or 4 with a duration of less than 5 days if resulting in neutropenic fever with elevated temperature (defined as absolute neutrophil count [ANC] <1000/mm^3 with a single temperature of >38.3°C or sustained temperature of ≥38°C for more than one hour)
- Non-hematologic toxicity**
  - Grade 3 or higher unless:
    - The toxicity could be managed with appropriate therapy (e.g. antiemetics and anti-diarrheals for nausea, vomiting and diarrhea)
      OR
    - Not clinically meaningful and/or transient according to the investigator in consultation with the medical monitor (headache, abnormal laboratory value, fatigue, alopecia)
- Inability to receive Cycle 2 Day 1 dose within 14 days from planned Cycle 2 Day 1, due to continued melflufen-related toxicity from Cycle 1.

* Prophylactic use of growth factors and platelet transfusions in Cycle 1 of the dose escalation cohorts in Phase 1 was not permitted.

** All assessments were to be reviewed by DMC.

Number of Patients (Planned and Analyzed)

Planned

Phase 1

Approximately 8 to 30 patients were planned to be screened to achieve 7 to 23 enrolled patients, and 6 to 18 DLT-evaluable patients. (Actual number of patients would depend on the number of dose levels needed to be tested, and rate of DLT-evaluable patients.)

Phase 2

Approximately 30 patients were planned to be screened to achieve 23 enrolled patients, and 20 efficacy-evaluable patients.

Analyzed

Phase 1

At DBL, 6 patients had been enrolled and analyzed.

A total of 3 patients were enrolled in Cohort 1 (20 mg melflufen for each treatment cycle), of which 2 patients discontinued, and one patient completed treatment.

Following a DMC meeting on 21 December 2020, the DMC agreed to proceed without modifications and open Cohort 2 (30 mg melflufen for each treatment cycle). A total of 3 patients were enrolled in Cohort 2, of which 2 patients discontinued, and one patient completed 8 cycles prior to study closure.

Following a DMC meeting on 30 July 2021, the DMC agreed to open Cohort 3 (40 mg melflufen for each treatment cycle) after the partial clinical hold was lifted.

The study was terminated prior to initiation of Cohort 3.

Phase 2

The study was terminated prior to initiation of Phase 2.

Diagnosis and Main Criteria for Inclusion

Diagnosis: Patients with AL amyloidosis.

Inclusion Criteria:

1. Male or female, age 18 years or older at the time of signing the informed consent
2. Proven histochemical diagnosis of AL amyloidosis based on tissue specimens with Congo red staining with exhibition of an apple-green birefringence confirmed with appropriate method of typing, e.g. mass spectrometry, immunofluorescence or immunohistochemistry (previous aspirate/biopsy tissue specimen result acceptable)
3. At least one prior line of therapy, defined as either one non-transplant regimen, one autologous stem cell transplant (ASCT), or one regimen of induction therapy followed by a single ASCT (without hematologic progression between induction and ASCT). No more than 4 cycles of melphalan containing chemotherapy were allowed
4. Measurable hematologic disease as defined by serum differential free light chain (dFLC) concentration ≥20 mg/L (dFLC is the difference between amyloid forming [involved] and non-amyloid forming [uninvolved] FLC)
5. Objectively measurable (cardiac, and/or renal and/or liver) organ amyloid involvement, as defined below (amyloid involvement of at least 1 required).
   a. *Cardiac involvement:* Mean wall thickness >12 mm on echocardiogram (ECHO), with no other cardiac cause or an elevated N-terminal pro-brain natriuretic peptide (NT-ProBNP; >332 ng/L) in the absence of renal failure or atrial fibrillation
   b. *Renal involvement*: Defined as proteinuria (predominantly albumin) >0.5 g/day in a 24-hour urine collection
   c. *Hepatic involvement:* Total liver span >15 cm in the absence of heart failure, or alkaline phosphatase >1.5 times institutional upper limit of normal (ULN)

   Amyloid involvement of other organ systems was allowed, but not required.
6. ECOG performance status ≤2.
7. Women of childbearing potential (WOCBP) must have had a negative serum or urine pregnancy test
8. Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information
9. Less than 30% plasma cells in bone marrow aspirate or biopsy
10. 12-lead screening safety electrocardiogram (ECG) with PR <220 millisecond (msec) and QTcF interval of ≤470 msec calculated by Fridericia Formula
11. ECHO with left ventricular ejection fraction (LVEF) ≥45% in patients with known cardiac

amyloidosis involvement

12. The following laboratory results had to be met:
    - ANC ≥1500 cells/mm^3 (1.5 x 10^9/L) (Growth factors could not be used within 10 days [14 days for pegfilgrastim] prior to initiation of therapy)
    - Platelet count ≥100 000 cells/mm^3 (100 x 10^9/L) without required transfusions during the 10 days prior to initiation of therapy
    - Hemoglobin ≥9.0 g/dl (red blood count [RBC] transfusions were permitted)
    - Total bilirubin ≤1.5 x ULN. Higher value was to be accepted in patients diagnosed with Gilbert syndrome, if approved by the medical monitor
    - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤1.5 x ULN

    Renal function: Estimated glomerular filtration rate (eGFR) by chronic kidney disease – epidemiology collaboration (CKD-EPI) formula ≥45 mL/min
13. Male patient agreed to use contraception during the treatment period and for at least 90 days after the last dose of melflufen and refrained from donating sperm during this period

OR

Female patient met one of the following conditions:

i. Not of childbearing potential

ii. Not currently pregnant or breastfeeding and agreed to follow contraceptive guidance during the treatment period and for at least 30 days after the last dose of melflufen

Exclusion Criteria:

1. Amyloidosis due to known mutations of the transthyretin gene or presence of another non-AL amyloidosis
2. Cardiac risk stage 3 with NT-proBNP >5000 pg/mL
3. Evidence of gastro-intestinal bleeding
    - Frank bleeding within 6 months prior to initiation of therapy
    - Positive feces-hemoglobin/fecal occult blood test within 6 months prior to initiation of therapy if clinically relevant. In case of a positive test within the last 6 months, a colonoscopy and upper endoscopy were required to exclude clinically relevant conditions. Should the first examination provide a satisfactory explanation to the GI-bleed, the second examination might have been cancelled at the discretion of the investigator
4. Evidence of mucosal or internal bleeding and/or platelet transfusion refractory (i.e. platelet count failed to increase by ≥10 000 cells/mm^3 [10 x 10^9/L] after transfusion of an appropriate dose of platelets)
5. Medically documented cardiac syncope, New York Heart Association Functional Classification (NYHA) Class 3 or 4 congestive heart failure, myocardial infarction within the previous 6 months, unstable angina pectoris, clinically significant ventricular arrhythmias, or atrioventricular (AV) block
6. Clinically significant finding on 24hr Holter recording performed at screening, including but not limited to high degree AV block (2nd degree type 2 or 3rd degree AV block), ventricular arrythmias and sign of sick sinus syndrome. (Bundle branch block was acceptable if clinically

stable for ≥6 months)

7. Supine systolic blood pressure <90 mm Hg, ***or*** orthostatic hypotension defined as a decrease in systolic blood pressure upon standing of >20 mmHg ***or*** symptomatic orthostatic hypotension regardless of the amount of the drop in mmHg, despite medical management (e.g., midodrine, fludrocortisones) in the absence of volume depletion
8. Clinically significant factor X deficiency (in Investigator's opinion)
9. Clinically important autonomic disease (in Investigator's opinion)
10. Any medical conditions that, in the Investigator's opinion, would impose excessive risk to the patient or would adversely affect his/her participating in this study
11. Known active infection that was uncontrolled (including symptomatic or asymptomatic Corona virus disease [COVID-19]) ***or*** had required intravenous systemic therapy ***or*** had required oral anti-infective treatment within 14 days of initiation of treatment; Other wash out period was to be considered after consultation and approval of the medical monitor
12. Other malignancy diagnosed or requiring treatment within the past 3 years with the exception of adequately treated basal cell carcinoma, squamous cell skin cancer, carcinoma in-situ of the cervix or breast, and very-low and low risk prostate cancer in active surveillance as defined in National comprehensive cancer network (NCCN) Guideline: Prostate Cancer (NCCN 2019)
13. Pregnant or breast-feeding females
14. Serious psychiatric illness, active alcoholism, or drug addiction that may hinder or confuse compliance or follow-up evaluation
15. Known Human immunodeficiency virus (HIV) or active hepatitis C viral infection
16. Known active hepatitis B viral infection (defined as HBsAg+)
    - Patients with prior hepatitis B vaccine were permitted (defined as HBsAg-, Anti-HBs+, Anti-HBc-)
    - Non-active hepatitis B (HBsAg-, Anti-HBs+, Anti-HBc+) could be enrolled at the discretion of the investigator after consideration of risk of reactivation
17. Concurrent symptomatic multiple myeloma (symptomatic defined as presence of bone lesion, extramedullary plasmacytoma or hypercalcemia (Rajkumar et al. 2014)
18. POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein [M-protein] and skin changes)
19. Any of the following treatments, within the specified timeframe:
    - Previous cytotoxic therapies, including cytotoxic investigational agents, within 3 weeks (6 weeks for nitrosoureas) prior to initiation of therapy
    - The use of live vaccines within 30 days before initiation of therapy
    - Monoclonal antibodies (mAbs) within 4 weeks of initiation of therapy
    - Prednisone up to but no more than 10 mg orally once daily (q.d.) or its equivalent for symptom management of comorbid conditions was permitted but dose should be stable for at least 7 days prior to initiation of therapy
    - Concomitant immunotherapy, investigational therapy and anticoagulation therapy were not permitted (low dose i.e. ≤150 mg OD acetylsalicylic acid [ASA] permitted)

20. Residual side effects to previous therapy >Grade 1 prior to initiation of therapy (Alopecia, or neuropathy Grade 2 were permitted)
21. Prior autologous or allogeneic stem cell transplant within 12 weeks of initiation of therapy
22. Prior allogeneic stem cell transplant with active graft-versus-host-disease (GVHD)
23. Prior major surgical procedure or radiation therapy within 4 weeks of the first dose of study treatment
24. Known intolerance to steroid therapy, known hypersensitivity to melphalan or melflufen, or known hypersensitivity to any of the excipients of melflufen or the dexamethasone product

Test Products, Doses, and Modes of Administration

Melflufen was administered as a 30-minute intravenous infusion on Day 1 of each 28-day cycle via a central catheter. The starting dose of melflufen in Cohort 1 was 20 mg, and the starting dose of melflufen in Cohort 2 was 30 mg. Cohort 3 with a starting dose of 40 mg melflufen was not initiated.

As per investigators discretion, dexamethasone 20 mg was administered orally on Day 1 and 2 of each 28-day cycle. No patient received dexamethasone 40 mg.

Both melflufen and dexamethasone were administered in an outpatient treatment setting.

Duration of Treatment

Patients were planned to receive treatment until any of the following stopping events was reached*:

- Completion of Cycle 8
- Hematologic CR after Cycle 4
- Stable hematologic VGPR after Cycle 4 (stable defined as not changing over at least 2 cycles, i.e. 3 Cycle X Day 1 (CXD1) evaluations with the same assessment of response)
- Stable hematologic PR after Cycle 4 (stable defined as above for VGPR)
- Less than hematologic PR after Cycle 2 (i.e. less than PR at C3D1)
- Documented non-hematologic disease progression making continued treatment not meaningful in the opinion of the investigator
- Documented hematologic disease progression verified by the medical monitor
- Unacceptable toxicity, **OR**
- The patient/treating physician determined it was not in the patient's best interest to continue

* Patients who experienced benefit from the interventional therapy could continue treatment if felt in the best interest of the patient by the investigator, and if approved by the medical monitor, up to a maximum of 4 additional cycles per approval. Medical monitor approval had to be sought prior to continuing therapy despite a stopping event having been reached.

The hematologic response was evaluated by blood samples taken on CXD1 ±3 days. If the lab response was not available at CXD1, treatment could be given according to the protocol without contacting the medical monitor if the investigator determined this was in the best interest of the patient. If the hematologic response met any of above stopping criteria upon receipt of the lab report, the investigator needed to seek approval from the medical monitor, prior continuing with next treatment cycle, if this felt to be in the best interest of the patient by the investigator.

If, after 4 additional cycles had been given, it still felt to be in the best interest of the patient to continue treatment, a renewed medical monitor approval could be sought for up to 4 new additional cycles of therapy. New approvals could be given until a total of 12 cycles had been reached. No patient should receive more than 12 cycles of therapy. Treatment dose should not be higher than the dose last tolerated.

It was anticipated that a substantial number of patients would have cardiac AL amyloidosis. These patients may experience decreasing cardiac function during the course of the study and therefore warrant increased attention by the investigator. Treatment with study medication should only continue for as long as the investigator assessed that the potential benefits from continued treatment with study medication outweighed any potential risk. This assessment should be done at least once in each treatment cycle and was to be documented.

Criteria for Evaluation

Safety assessments:

- AE assessment
- Physical examination with vital signs, neurologic assessment and assessment of Eastern cooperative oncology group (ECOG) performance status
- Cardiac evaluations with ECHO and 12-lead ECG
- Clinical safety laboratory assessments: Hematology (complete blood count [CBC] with differential), Coagulation, and Blood chemistry, Urinalysis, eGFR
- Chest X-ray (may be replaced by CT-scan or other relevant imaging technique at investigator's discretion)
- Fecal hemoglobin
- Pregnancy test
- Bone marrow aspiration (BMA)
- Screening imaging for patients with known or suspected hepatomegaly or organomegaly

Efficacy assessments:

<u>Hematologic Response Assessments:</u>

- FLC levels and FLC ratio (involved FLC/uninvolved FLC)
- dFLC (difference between involved FLC and uninvolved FLC)
- Electrophoresis
  - Serum protein electrophoresis (SPEP)
  - Urine protein electrophoresis (UPEP)
- Immunofixation
  - Serum immunofixation
  - Urine immunofixation

  NB: Negative immunofixation required for CR assessment
- BMA (MRD, EuroFlow-based standardized approach next generation flow (NGF) or other validated high-sensitive standardized method), in patients with suspected hematologic CR). For sites without local Flow-based MRD evaluation available, case-by-case adapted solutions were to be implemented.

Cardiac Response Assessments:

- ECHO
  - Local assessments of ECHOs would guide the care of study patients during the study. In addition, ECHO recordings were to be submitted from sites to a central location for possible central review following end of treatment (EoT) of the last patient
- Cardiac risk assessment staging
  - N-terminal natriuretic peptide type (NT-ProBNP)
  - Troponin (cTnI or cTnT)
- NYHA classification

Liver Response Assessments:

- Alkaline phosphatase
- Physical examination
- Imaging assessment

Renal Response Assessments:

- 24-hour urine total protein (albumin)
- eGFR by CKD-EPI

Follow Up (FU) Assessments:

- Patients who discontinued therapy for reasons other than death, withdrawal of consent to participate in the study, or was lost to FU, were to be followed up every 3 months, for 24 months or as applicable, for collection of the following data:
  - Subsequent therapy:
    - Date of initiation of the next line of therapy to treat amyloidosis
    - Regimen initiated
    - Reason for initiation of subsequent therapy
  - OS:
    - Date of death
  - Serious AE (SAE)/AE resolution:
    - SAEs ongoing at the EoT visit were to be followed until resolution or stabilization with no expected resolution
    - Ongoing neutropenia and thrombocytopenia Grade 3 to 4 at the EoT visit were to be followed until resolution (≤Grade 2), or initiation of subsequent therapy
- Until initiation of subsequent therapy, the patient was to be assessed for organ and hematologic response every 3 months.
- Any second primary malignancy appearing during FU period was to be recorded.
- Following initiation of subsequent therapy, FU could be completed by phone contact. Death information from public sources, e.g. death registry or obituary listing, could also be used when available and verifiable.

Pharmacokinetics:

Levels of melphalan (the active metabolite of melflufen [melflufen is rapidly degraded in blood]) were to be analyzed in plasma samples drawn in Cycle 1 and 2 from all patients of Phase 1, at the following time points:

- 5 to 10 minutes after the end of infusion
- 1 to 2 hour/s after the end of infusion
- 3 to 8 hours after the end of infusion (as late as possible within the time frame)

3 plasma samples were to be collected at each time point. All PK samples had to be drawn peripherally and not from the central catheter.

Statistical Methods

For statistical analysis plan (SAP), see Appendix 16.1.9.1.

There was no formal hypothesis testing in this Phase 1/2 study.

The Phase 1 part followed a standard 3+3 design for which no specific hypothesis was defined.

The Phase 2 part was planned to primarily be used to obtain an initial estimation of the efficacy of melflufen in the AL amyloidosis patient population with no formal statistical tests being performed.

For purposes of analysis, the planned populations for analyses are defined below.

Population	Description
DLT-evaluable (Phase 1)	All patients who either: - Experienced a DLT during Cycle 1 or - if unable to start Cycle 2 as planned due to melflufen-related toxicity within 14 days from the planned Cycle 2 Day 1 **OR** - Had not experienced a DLT and was able to receive Cycle 2, Day 1 dose within 14 days from the planned Cycle 2 Day 1. Patients that had been replaced in the original assigned cohort were not included in the DLT-evaluable set. *This was the population to define the RP2D.*
Full analysis set (FAS) (Phase 1 and 2)	All patients who received at least one dose (or partial dose) of dexamethasone or melflufen. The FAS for Phase 1 was therefore to include all patients in dose finding part (Phase 1) that had received at least one dose (or partial dose) of dexamethasone or melflufen. *This was the population for all efficacy and safety endpoints in Phase 1.* The FAS for Phase 2 was therefore planned to include all patients treated at the RP2D in both Phase 1 and 2 combined. *This was the population for all efficacy and safety endpoints in Phase 2.* A patient included in FAS was defined as an efficacy-evaluable patient.
Safety analysis set	For definition, see Full analysis set (FAS).

Pharmacokinetic analysis set (Phase 1)	All patients who had received at least one melflufen dose and had sufficient PK samples taken appropriate for the evaluation of interest. *This was the analysis population for all PK analysis.*
Enrolled analysis set (Phase 1 and 2)	All patients who had signed the informed consent form.

All safety analyses were performed on the Safety analysis set. No formal statistical analysis was performed for the safety endpoints.

The endpoints used for safety assessments:

- Frequency and grade of AEs and laboratory values
- DLT during Cycle 1 up to a maximum dose of melflufen of 40 mg

The endpoints used for efficacy assessments:

- The proportion of patients who achieved a hematologic CR, VGPR, or PR (ORR)
- Duration of hematologic response (CR, VGPR, or PR)
- Best hematologic response (CR, VGPR, PR, NR or PD)
- Proportion of patients with kidney, cardiac, or liver response, respectively
- Duration of organ system specific response (separately for kidney, cardiac, and liver)
- Time to next AL amyloidosis treatment
- OS
- MRD status in patients who achieved a hematologic CR

SUMMARY

This study was prematurely terminated on 04 November 2021. The safety analyses were conducted on the data available at the time of DBL of 25 January 2022. Due to large number of incomplete or uncleaned data, data are presented descriptively on patient level.

Data on Cohort 1 (20 mg melflufen for each treatment cycle) and Cohort 2 (30 mg melflufen for each treatment cycle) are presented below. The study was terminated prior to initiation of Cohort 3 (40 mg melflufen for each treatment cycle).

Patient disposition

At DBL, a total of 6 patients were enrolled and treated at 4 investigative sites (Greece, 3 patients; Israel, 1 patient; Germany, 1 patient; Norway, 1 patient).

For complete Listings of patient disposition, see Appendix 16.2.1.

Cohort 1

A total of 3 patients were enrolled; 2 patients discontinued (1 due to lack of efficacy [Subject 3001-05] and 1 due to physician decision [Subject 3001-04]), and one patient completed treatment (Subject 3001-03).

Cohort 2

A total of 3 patients were enrolled; 2 patients discontinued (1 due to lack of efficacy [Subject 9721-01] and 1 due to physician decision [Subject 4901-01]), and one patient completed 8 cycles prior to study closure (Subject 4701-02).

Patient Demographics and Baseline Characteristics

For complete Listings of patient demographics and baseline characteristics, see Appendix 16.2.2.

Cohort 1

All patients were male, with an age range of 62 to 73 years. Heights ranged between 167 to 179 cm, and weights ranged between 73 to 79 kg. The patients received their AL diagnosis in the last 3 years (range December 2018 to December 2019). Patients had 1 to 3 prior lines of therapy. No patients had a prior transplant. All patients had heart involvement at study entry; 1 patient also had renal involvement (Subject 3001-04). eGFR ranged from 45.5 to 70.8 ml/min/1.73m^2. The best hematologic response was partial response for any prior therapy for all patients.

Cohort 2

All patients were male, with an age range of 62 to 80 years. Heights ranged between 168 to 176 cm, and weights ranged between 62.5 to 97.5 kg. One patient was diagnosed with AL in 2008; the other 2 patients were diagnosed in the last 3 years (February 2019 and June 2020). Patients had 2 to 5 prior lines of therapy. No patients had a prior transplant. 2 patients (Subjects 4901-01 and 4701-02) had heart involvement and soft tissue involvement at study entry, with 1 patient (Subject 4901-01) also presenting with nerve involvement. 1 patient had renal involvement only (Subject 9721-01). eGFR ranged from 64.9 to 98-114 ml/min/1.73m^2. The best hematologic response, to any prior therapy, achieved for Subject 9721-01 was complete response; the other 2 patients did not respond to prior therapies.

Safety Results

Safety and tolerability was the primary objective in the Phase 1 part of this study. All safety analyses were performed using the Safety analysis set.

For complete Listings of patient safety data, see Appendix 16.2.3.

Extent of Exposure

Cohort 1

Melflufen: The number of cycles were 8 for Subject 3001-03, 5 for Subject 3001-04, and 3 for Subject 3001-05. Their cumulative doses were 160 mg, 100 mg, and 60 mg, respectively. No dose modifications were reported, except for 1 patient having a 6-day delay in one cycle due to patient noncompliance.

Dexamethasone: The number of doses were 16 for Subject 3001-03, 10 for Subject 3001-04, and 6 for Subject 3001-05. Their cumulative doses were 320 mg, 200 mg, and 120 mg, respectively. No dose modifications were reported, except for 1 patient having a 6-day delay in one cycle due to patient noncompliance.

Cohort 2

Melflufen: The number of cycles were 8 for Subject 4701-02, 2 for Subject 4901-01, and 5 for Subject 9721-01. Their cumulative doses were 240 mg, 60 mg, and 150 mg, respectively.

Dexamethasone: The number of doses were 11 for Subject 4701-02, 4 for Subject 4901-01, and 10 for Subject 9721-01. Their cumulative doses were 220 mg, 80 mg, and 200 mg, respectively.

Adverse Events

AEs were coded using MedDRA® version 24.0. All AEs reported are MedDRA PTs unless stated otherwise.

Cohort 1

Among the 3 patients included in Cohort 1, 13 AEs were reported, of which oedema peripheral was the most common (experienced by all 3 patients). All AEs were Grade 1 or Grade 2. AEs included anaemia, diarrhoea, dysphonia, fatigue, hypoalbuminaemia, oedema peripheral, and orthostatic hypotension.

A Grade 2 anaemia in Subject 3001-05 was considered possibly related to melflufen by the investigator; all other AEs in Cohort 1 were considered not related to melflufen or dexamethasone.

The only AE recorded for Subject 3001-03 was oedema peripheral, which was resolved.

Most AEs for Subject 3001-04 were unresolved at the time of EoT, including diarrhoea, dysphonia, fatigue, hypoalbuminaemia, oedema peripheral, and orthostatic hypotension. The patient also experienced diarrhoea and oedema peripheral that resolved with sequelae.

Oedema peripheral was recorded on 3 occasions for Subject 3001-05; 2 occasions were resolved with sequelae, and one was unresolved. Anaemia was also recorded for Subject 3001-05, which resolved.

There were no dose delays or dose reductions due to AEs. No DLTs (as per definition, see Section Methodology) were observed. No actions were taken on study drugs due to AEs.

Cohort 2

Among the 3 patients included in Cohort 2, 8 AEs were reported, of which fatigue was the most common (experienced by 2 patients). All AEs were Grade 1 or Grade 2. AEs included dizziness, fatigue, haematuria, lip dry, neuropathy peripheral, urinary tract infection, and wound infection.

A Grade 2 fatigue in Subject 9721-01 was considered probably related to melflufen by the investigator, and probably related to dexamethasone by the investigator; all other AEs in Cohort 2 were considered not related to melflufen or dexamethasone.

Most AEs recorded for Subject 4701-02 (haematuria, urinary tract infection, and wound infection) were resolved, except for lip dry.

All AEs recorded for Subjects 4901-01 (dizziness, fatigue, and neuropathy peripheral) were resolved.

The only AE recorded for Subject 9721-01 was fatigue, which was resolved.

There were no dose delays or dose reductions due to AEs. No DLTs (as per definition, see Section Methodology) were observed. No actions were taken on study drugs due to AEs.

Serious Adverse Events

No SAEs were observed in either cohort.

Deaths

At DBL, 1 patient had died during long-term FU. Subject 3001-04 was enrolled in Cohort 1 and received 5 cycles of treatment with melflufen. Treatment was initiated on 17 September 2020 (Cycle 1) and the last cycle (Cycle 5) was administered on 7 January 2021. The patient died on 13 March 2021.

Efficacy Results

For complete Listings of patient efficacy data, see Appendix 16.2.4.

Cohort 1

Subject 3001-03 received 8 cycles of treatment. At Baseline, the patient presented with heart involvement. The patient achieved a durable hematologic VGPR, and heart response was observed.

Subject 3001-04 received 5 cycles of treatment. At Baseline, the patient presented with heart and renal involvement. The patient achieved a hematologic PR, and heart progression and kidney response was observed.

Subject 3001-05 received 3 cycles of treatment. At Baseline, the patient presented heart involvement. No hematologic or heart responses were observed.

Cohort 2

Subject 4701-02 completed 8 cycles prior to study closure. At Baseline, the patient presented with heart and soft tissue involvement. The patient achieved heart response. No hematologic response was observed.

Subject 4901-01 received 2 cycles of treatment. At Baseline, the patient presented with heart, nerve, and soft tissue involvement. No hematologic or organ responses were observed.

Subject 9721-01 received 5 cycles of treatment. At Baseline, the patient presented with renal involvement. The patient achieved hematologic PR. No renal response was observed.

CONCLUSION

Study OP201 was a Phase 1/2 study with the objective of exploring the safety and tolerability of melflufen in patients with AL amyloidosis following at least one prior line of therapy. The study was prematurely terminated on 04 November 2021.

The Sponsor's review of the 6 enrolled patients treated with a combination of melflufen (20 mg or 30 mg) and dexamethasone did not reveal any DLTs or SAEs. All AEs observed were Grade 1 or 2. There were no treatment-related dose modifications or dose delays. One patient died during long-term FU.

Due to the premature termination and limited data yield as a result, no conclusions could be drawn from this study.

REFERENCES

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Date of the Synoptic Report: 01 March 2022

APPENDICES

16.1. Study Information

- 16.1.1. Protocol and Protocol Amendments
- 16.1.2. Sample Case Report Form
- 16.1.4 List and Description of Investigators and Other Important Participants in the Study
- 16.1.5 Signatures of Global Lead Investigator and Sponsor's Responsible Medical Officer and Statistician
- 16.1.8 Audit Certificates *(Not applicable)*
- 16.1.9 Documentation of Statistical Methods

16.2. Patient Data Listings

- 16.2.1 Patient Disposition
- 16.2.2. Demographic and Baseline Characteristics
- 16.2.3. Patient Safety Data
- 16.2.4 Patient Efficacy Data

16.3. Case Report Forms *(Not applicable)*

- 16.3.1. CRFs for Deaths, Other Serious Adverse Events, and Withdrawals for Adverse Events (*Not applicable*)

16.4. Individual Patient Data Listing (US Archival Listings)