22 August 2024
EMA/438147/2024
Human Medicines Division

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

IMCIVREE

Setmelanotide

Procedure no: EMEA/H/C/005089/P46/009

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

© European Medicines Agency, 2024. Reproduction is authorised provided the source is acknowledged.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	27 May 2024	27 May 2024	☐
☐	CHMP Rapporteur Assessment Report	01 Jul 2024	01 Jul 2024	☐
☐	CHMP members comments	15 Jul 2024	15 Jul 2024	☐
☐	Updated CHMP Rapporteur Assessment Report	18 Jul 2024	18 Jul 2024	☐
☐	CHMP adoption of conclusions:	24 Jul 2024	24 Jul 2024	☐
☐	Submission			☐
☐	Re-start	24 Jul 2024	24 Jul 2024	☐
☐	CHMP Rapporteur Assessment Report	07 Aug 2024	07 Aug 2024	☐
☐	CHMP members comments	12 Aug 2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	16 Aug 2024	n/a	☐
☒	CHMP adoption of conclusions:	22 Aug 2024	22 Aug 2024	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for CHMP plenary discussion: substantial disagreement between the Rapporteur and other CHMP members and/or at the request of the Rapporteur or the Chair

Table of contents

1. Introduction

On 25/04/2024, the MAH submitted a completed paediatric study for Imcivree, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The scope of this post approval measure is to submit the final clinical study report (CSR) for this study.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Whilst the study does not form part of the EU setmelanotide paediatric investigation plan, it was conducted in part in the paediatric population and was sponsored by the IMCIVREE (setmelanotide) marketing authorisation holder. As such, the CSR qualifies for stand-alone submission under Article 46 of Regulation (EC) 1901/2006. The study submitted is part of the ongoing development program for the setmelanotide QW formulation.

2.2. Information on the pharmaceutical formulation used in the study

The following treatments and dose regimens were used:

- Setmelanotide (RM-493): N-[carbonyl-methoxypolyethylene glycol 2000]-1,2-distearoyl-glycero-3-phosphoethanolamine sodium salt (mPEG-DSPE) formulation for **daily** administration and FluidCrystal® formulation for **weekly** administration.
- Setmelanotide 2 mg, 2.5 mg, or 3.0 mg QD and Setmelanotide 20 mg, 25 mg, or 30 mg QW administered subcutaneously (SC) (lot numbers 9949525Y, RYMAB21605, 21605, 21630, 9950658 21629).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for Study RM-493-037:

A Phase 3, Randomised, Double-Blind Trial of Two Formulations of Setmelanotide (Daily and Weekly) With a Crossover to Open-Label Once Weekly Setmelanotide in Patients With Specific Gene Defects in the Menalocortin-4 Receptor Pathway who are Currently on a Stable Dose of the Once Daily Formulation

2.3.2. Clinical study RM-493-037

Description

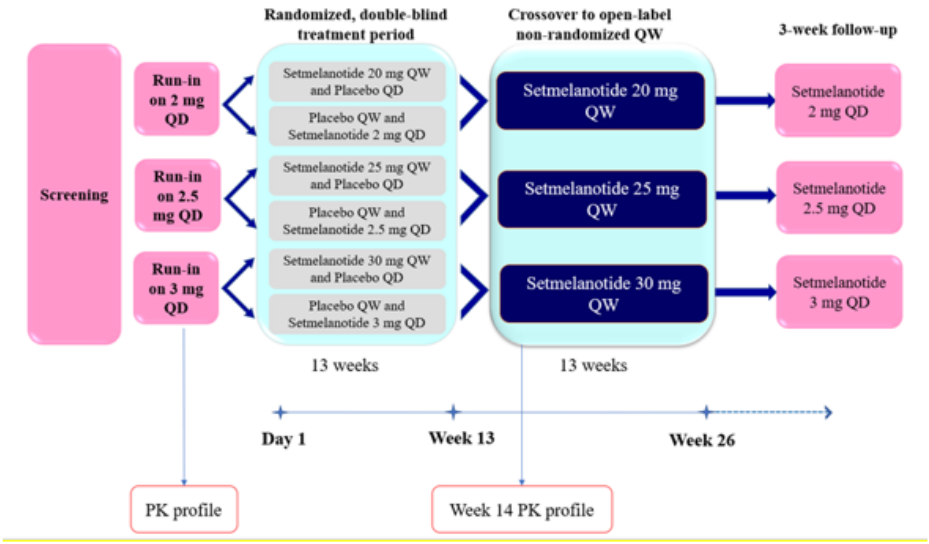
This was a Phase 3, double-blind, randomized, crossover to open-label, multicenter study designed to compare the pharmacokinetics (PK), safety, and efficacy of the once-weekly (QW) and once-daily (QD) formulations of setmelanotide, as well as evaluating the safety and efficacy up to 6 months of QW setmelanotide administration in patients with Bardet–Beidl syndrome (BBS), biallelic pro-

opiomelanocortin (POMC), proprotein convertase subtilisin/kexin type 1 (PCSK1), leptin receptor (LEPR) (PPL), or heterozygous PPL.

Study design

This study consisted of a screening period for transition from the long-term extension (LTE) trial RM-493-022; a run-in period of up to 1 week of continuation on the patient's current dose level of QD setmelanotide (2 mg, 2.5 mg, or 3 mg); a 13-week double-blind phase in which the patients were randomized to either QD or QW setmelanotide; a 13-week non-randomized, open-label phase where all patients received open-label QW setmelanotide; and a 3-week follow-up period in which all patients were returned to their run-in dose of QD setmelanotide for re-enrolment into Trial RM-493-022 or to resume the QD formulation in some other way.

Figure 1 Study design schematic



Abbreviations: PK: pharmacokinetic; QD: once daily; QW: once weekly.

Study participants

Eligible patients were those BBS, biallelic PPL, or heterozygous PPL patients who had been taking open-label QD setmelanotide in the LTE Trial RM-493-022 for at least 6 months - where the dose level must have been stable at 2 mg, 2.5 mg, or 3 mg of setmelanotide for at least the past 3 months - with accepted safety and tolerability and who wished to continue with setmelanotide treatment, and otherwise who met all inclusion and exclusion criteria.

Approximately 30 patients were targeted in three age groups: ≥18 years old, ≥12 to <18 years old, and ≥6 to <12 years old at the time of study entry.

Treatments

The treatment administered in this study was setmelanotide in both QD and QW frequency via SC injection.

Patients were administered doses of the QW setmelanotide that depended on the dose level (i.e. 2 mg, 2.5 mg, or 3 mg) on which they were in the open-label QD setmelanotide Trial RM-493-022. Given the PK, safety, and efficacy results for otherwise healthy patients with obesity in Trial RM-493-026, it was anticipated that 30 mg QW setmelanotide would provide PK, safety, and efficacy comparable to the 3

mg QD setmelanotide dose. Likewise, it was anticipated that 25 mg QW setmelanotide would provide PK, safety, and efficacy comparable to the 2.5 mg QD setmelanotide dose and that 20 mg QW setmelanotide dose would provide PK, safety, and efficacy comparable to the 2 mg QD setmelanotide dose.

Rapporteur's comment:

The dose selected for the once weekly (QW) formulation was based on the assumption that it would exhibit comparable PK, safety, and efficacy to the approved doses for the once daily (QD) formulation. However, the rationale behind this assumption was not provided.

Objective(s)

The **primary** objective was to compare the PK of the QD and QW formulations of setmelanotide.

The **secondary** objective was to assess the safety of the QW formulation of setmelanotide with up to 6 months (26 weeks) of drug administration.

Outcomes/endpoints

The **primary** endpoint was comparison of steady-state PK parameters (maximum plasma concentration [Cmax], time to maximum plasma concentration [Tmax], trough plasma concentration [Ctrough], area under the plasma concentration–time curve over the dosing interval [AUC0-tau]) of the QW and QD formulations of setmelanotide.

The **secondary** endpoint was safety outcomes, including AEs/SAEs, ISRs, and changes in laboratory parameters, vital signs, ECG recordings, and physical examination findings.

Sample size

The sample size was primarily driven by the availability of patients on stable doses of setmelanotide and by other clinical considerations as a formal non-inferiority study design for the QD vs QW formulation was not feasible because it requires a large sample size, which was unachievable in RGDO. The study was initially expected to enrol approximately 30 patients.

Randomisation and blinding (masking)

For the randomized, double-blind treatment period, patients were randomized in a 1:1 ratio to receive either QD or QW setmelanotide. Randomization was stratified by age group.

To maintain the blind during the 13-week randomized treatment period, all patients received placebo injections (mPEG-DSPE vehicle for the QD formulation or FluidCrystal® vehicle for the QW formulation) in addition to the setmelanotide injections in a double-dummy fashion.

No randomization or blinding was done for the 13-week open-label phase or for the 3-week QD follow-up phase.

PK analysis

Patients underwent serial blood sampling on the first day of the run-in period (visit 2) up to 24h postdose for the QD PK profile and at week 14 (visit 16) up to 168h postdose for measurement of steady-state setmelanotide concentrations (both QD and QW). In addition, serial blood samples were taken for the measurement of Ctrough setmelanotide concentrations (both QD and QW).

Plasma concentration–time data for setmelanotide were analyzed using noncompartmental methods.

The following PK parameters were determined: Cmax, tmax, Ctrough, AUC0-tau, AUClast, Clast, Tlast, T1/2

Rapporteur's comment:

It is unclear why PK profiling was scheduled at week 14, considering that both groups received a QW dose at that time. Ideally, the PK profiling should have occurred at week 13, when one group was on a QW dose and the other one on a QD dose. The MAH clarified that PK of setmelanotide QD and QW formulations could be compared at steady state using the visit 2 PK data and visit 16 (week 14) PK data of the QD-QW-QW group. Although this is agreed, the rationale for PK profiling of the QD-QD-QW group after switching to a QW dose (week 14), is still not understood.

Statistical Methods

The primary objective was to assess steady-state PK parameters (Cmax, Tmax, Ctrough, AUC0-tau) for QW setmelanotide compared with QD setmelanotide. The sample size was based on availability of the patients enrolled in the LTE trial and was not driven by formal statistical hypothesis testing on non-inferiority/similarity.

The PK profiles of the two formulations of setmelanotide were characterized, and steady-state PK parameters (Cmax, Tmax, Ctrough, AUC0-tau) were summarized for QD and QW setmelanotide for dose level and prior treatment regimen (QW or QD) during the double-blind phase of the study using descriptive statistics (e.g., n, mean, standard deviation, geometric mean, minimum, median, maximum, % coefficient of variation [CV], geometric mean CV, and confidence interval [CI]).

Adverse events (AEs)/Serious AEs (SAEs), including injection site reactions, as well as discontinuation due to AEs, were summarized descriptively. Injection site reactions for the QD and QW formulations were summarized separately.

Safety data, including laboratory evaluations, ECGs, physical examinations, and vital signs assessments, were summarized by time of collection. In addition, changes from baseline to any post-dose values were summarized for vital signs, ECGs, and clinical laboratory results.

Results

Participant flow/Recruitment

A total of 20 patients were screened of which 19 were randomized and treated (9 in the QD group and 10 in the QW group) in this study. The majority (78.9%) of patients completed the study. Four patients discontinued the study, of which 1 patient discontinued the study due to AEs (QD group), 1 due to lack of efficacy (QD group), and 2 were withdrawn by the parent/guardian (1 in QD group and 1 in QW group).

Note: During the study, based on feedback from the Food and Drug Administration (FDA), the primary endpoint was revised from one of efficacy to a primary endpoint assessing the PK profile of the QW formulation compared to the PK profile of the QD formulation. Further to the revision to the primary endpoint and objective, the FDA strongly recommended clarifying the mandatory and optional timepoints for PK collection after the blinded 14-week randomized period to ensure maximum characterization of 24-hour and 168-hour PK profiles of the setmelanotide daily and weekly formulations (QD and QW). The study was initially expected to enrol approximately 30 patients.

However, implementation of these revisions, notably the mandatory timepoints for PK collection for the 168-hour PK profile, required frequent visits to the investigational site. These visits were found to be inconvenient and undesirable to patients and resulted in slowed enrolment with a final patient enrolment of 20 patients. The PK profile was available for 9 patients on Week 14 starting at pre-dose up to and including 168 hours. In addition, the PK profile from pre-dose up to and including 120 hours was available for 2 patients.

Rapporteur's comment:

During the open-label period, the large majority of patients was treated with the 30 mg QW dose i.e. 14 out of 16 patients while only 1 patient was treated with the 20 mg and 1 patient with the 25 mg QW dose.

Baseline data

Patients were primarily White (84.2%) and female (57.9%) and were between the ages of 8 and 37 years with 9 patients below the age of 18 (of which 2 patients between 8 and 12 and 10 patients ≥18 years of age.

The most common medical history events (preferred terms [PTs]) at pre-enrolment (PTs occurring in ≥30% of patients) were Laurence–Moon–Bardet–Biedl syndrome (63.2%), skin hyperpigmentation (57.9%), obesity (52.6%), chronic kidney disease (36.8%), and cone-rod dystrophy and cognitive disorder (each in 31.6%).

In the QW setmelanotide group, 2 patients (20.0%) were on weight loss intervention (diet modification or exercise) while no patients in the QD setmelanotide group were on weight loss intervention.

Number analysed

Full Analysis Set (FAS) included all 19 patients who received at least 1 dose of setmelanotide after the randomization. Patients were analysed according to their randomly assigned treatment.

Per-Protocol Set included all patients in the FAS without any major protocol violations that would result in exclusion of the patients from the analysis. Patients were analysed according to their randomly assigned treatment.

Safety Analysis Set (SAS) included all patients who received at least 1 dose of protocol-specified study drug. Patients were analysed according to the treatment they actually received.

Pharmacokinetic Analysis Set included all 19 patients who received at least 1 dose of setmelanotide and who have had a sufficient number of measurable plasma concentrations to permit assessment of noncompartmental parameters.

Pharmacokinetic results

At visit 2 (run-in period), PK parameters are available for 19 patients. At visit 16 (week 14), PK parameters are available for 16 patients due to 3 drop-outs.

<u>QD dosing (visit 2)</u>

The mean Cmax was 29.4 ng/mL, 44.8 ng/mL, and 59.9 ng/mL after 2 mg (N=2), 2.5 mg (N=1), and 3 mg (N=16) QD, respectively, and occurred at a median Tmax of 5.88 hours to 6.91 hours. Due to limited data after observed Cmax, AUC0-tau could not be estimated for most patients at these dose

levels. Nevertheless, AUC0-tau could be calculated for 7 patients who received 3 mg QD; mean AUC0-tau was 975 h*ng/mL.

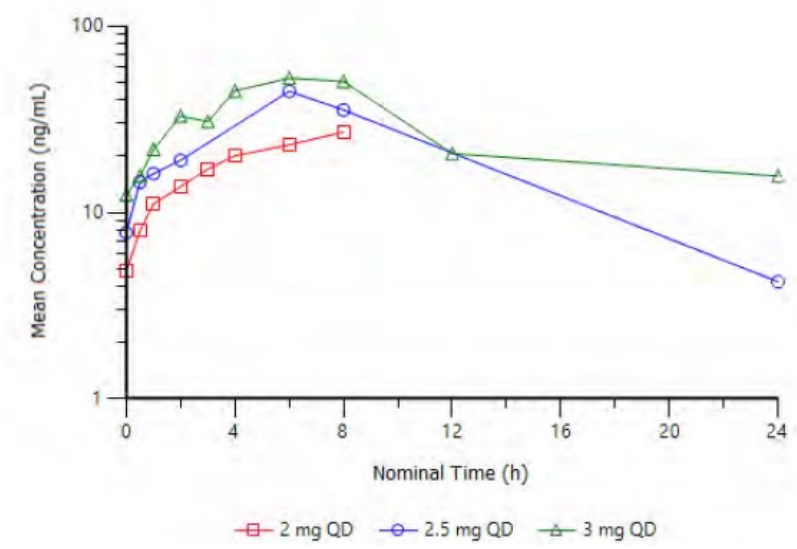


Figure 2. Mean setmelanotide concentration time profile on visit 2

QW dosing (visit 16)

Visit 16 consisted of 2 groups based on the dosing sequence, i.e., QD-QD-QW or QD-QW-QW, and dosing regimen during the double-blind period of 13 weeks. In general, the mean setmelanotide concentrations in the QD-QW-QW groups were higher than setmelanotide concentrations in the QD-QD-QW groups during Visit 16.

For patients previously on the QW regimen (QD-QW-QW), Cmax was 22.4 ng/mL (N=1), 32.7 ng/mL (N=1), and 57.3 ng/mL (N=7) for 20 mg, 25 mg, and 30 mg doses, respectively. Tmax ranged from 3.93 h after 20 mg to a median of 5.95 hours after 30 mg. AUC0-tau was 1590 h*ng/mL (N=1) after 20 mg, 2260 h*ng/mL (N=1) after 25 mg, and a mean of 5010 h*ng/mL (N=6) after 30 mg.

For patients previously on the QD regimen (QD-QD-QW), the mean Cmax was 31.8 ng/mL (N=7) and occurred at a median Tmax of 1.98 hours after a 30 mg QW dose. The mean AUC0-tau was 2470 h*ng/mL (N=6) for patients previously on the QD regimen.

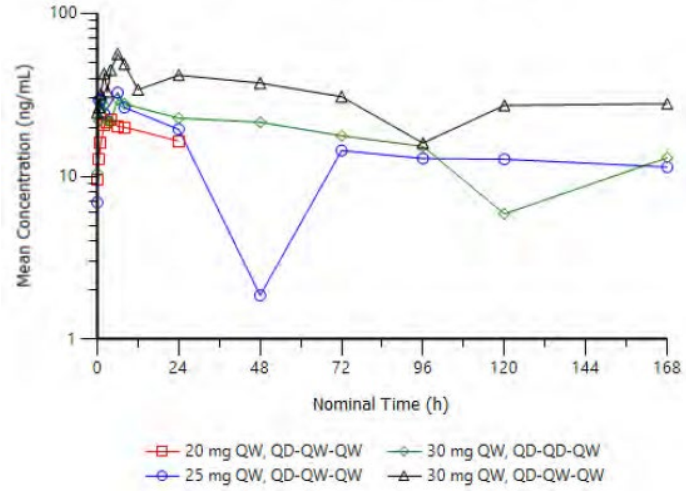


Figure 3. Mean setmelanotide concentration time profile on visit 16

Ctrough

At Visits 3, 7, and 11, Ctrough was higher for the patients on the QW regimen compared to those on the QD regimen. The mean Ctrough ranged from 11.7 ng/mL to 12.3 ng/mL for patients on the 3 mg QD regimen and from 15.6 ng/mL to 20.1 ng/mL for those on the 30 mg QW regimen.

Rapporteur's comment:

A comparison of setmelanotide concentrations between the two dosing sequences, QD-QD-QW or QD-QW-QW, is only possible for patients on a 30 mg QW dose in the open-label period (N=14) since half of these patients were on QD (ie. QD-QD-QW) and half on QW (i.e. QD-QW-QW) dosing during the double-blind period. For both groups, AUC0-tau was calculated at week 14 over a period interval of 168h.

*Setmelanotide PK parameters (Ctrough, Cmax and AUC0-tau) are higher in the QD-QW-QW group compared to subjects who remained on 3 mg QD during the double-blind period (QD-QD-QW). On the other hand, the mean exposure observed during a 24h interval after a 3 mg dose at visit 2 (975 h*ng/mL) suggests that exposure during a 1 week period for subjects receiving a daily 3 mg dose would be much higher than the 2470 h*ng/mL reported for the QD-QD-QW group at visit 16. By consequence results remain inconclusive whether a 3 mg QD dose would result in similar PK as a 30 mg QW dose*

Efficacy results

No specific efficacy results were provided.

Safety results

The incidence of **treatment-related** treatment-emergent adverse events (TEAEs) was comparable between the QD and QW setmelanotide groups, with the majority of events being mild or moderate in severity. Notably, no severe TEAEs were observed.

In the blinded period of the study, overall, 18 patients (94.7%) experienced at least 1 TEAE, with 78.9% of these TEAEs being considered treatment related. All patients (100%) in the QD setmelanotide group experienced at least 1 TEAE, with 77.8% (N=7) of these TEAEs being considered treatment related. In the QW setmelanotide group, 90.0% of patients (N=9) experienced at least 1 TEAE, with 80% (N=8) of these TEAEs being considered treatment related.

The **most common (i.e., occurring in ≥2 total patients) treatment related** TEAEs by MedDRA PT occurring in the Safety Analysis (SA) population from baseline to Week 14 were (QD vs QW setmelanotide groups) injection site pain (44.4% vs 60.0%), injection site erythema (44.4% vs 40.0%), injection site induration (22.2% vs 40.0%%), injection site haemorrhage (11.1% vs 30.0%%), injection site pruritus (0% vs 30.0%), nausea (22.2% vs 10.0%), injection site bruising (11.1% vs 10.0%), headache (11.1% vs 10.0%), menstruation irregular (11.1% vs 10.0%), and skin hyperpigmentation (11.1% vs 10.0%).

Table 1 Treatment-Related TEAEs by MedDRA SOC and PT from Baseline to Week 14 (SAS)

SOC / PT	Statistic	QD Setmelanotide (N=9)	QW Setmelanotide (N=10)	Total (N=19)
At Least 1 Treatment-Related TEAE	**n (%)**	**7 (77.8)**	**8 (80.0)**	**15 (78.9)**
General Disorders and Administration Site Conditions	**n (%)**	**6 (66.7)**	**8 (80.0)**	**14 (73.7)**
Injection site pain	n (%)	4 (44.4)	6 (60.0)	10 (52.6)
Injection site erythema	n (%)	4 (44.4)	4 (40.0)	8 (42.1)
Injection site induration	n (%)	2 (22.2)	4 (40.0)	6 (31.6)
Injection site haemorrhage	n (%)	1 (11.1)	3 (30.0)	4 (21.1)
Injection site pruritus	n (%)	0	3 (30.0)	3 (15.8)
Injection site bruising	n (%)	1 (11.1)	1 (10.0)	2 (10.5)
Fatigue	n (%)	1 (11.1)	0	1 (5.3)
Injection site inflammation	n (%)	0	1 (10.0)	1 (5.3)
Gastrointestinal Disorders	**n (%)**	**2 (22.2)**	**1 (10.0)**	**3 (15.8)**
Nausea	n (%)	2 (22.2)	1 (10.0)	3 (15.8)
Abdominal pain upper	n (%)	1 (11.1)	0	1 (5.3)
Diarrhoea	n (%)	1 (11.1)	0	1 (5.3)
Vomiting	n (%)	1 (11.1)	0	1 (5.3)
Nervous system Disorders	**n (%)**	**2 (22.2)**	**1 (10.0)**	**3 (15.8)**
Headache	n (%)	1 (11.1)	1 (10.0)	2 (10.5)
Seizure	n (%)	1 (11.1)	0	1 (5.3)
Reproductive System and Breast Disorders	**n (%)**	**1 (11.1)**	**1 (10.0)**	**2 (10.5)**
Menstruation irregular	n (%)	1 (11.1)	1 (10.0)	2 (10.5)
Dysmenorrhoea	n (%)	0	1 (10.0)	1 (5.3)
Skin and Subcutaneous Tissue Disorders	**n (%)**	**1 (11.1)**	**1 (10.0)**	**2 (10.5)**
Skin hyperpigmentation	n (%)	1 (11.1)	1 (10.0)	2 (10.5)
Cardiac Disorders	**n (%)**	**1 (11.1)**	**0**	**1 (5.3)**
Palpitations	n (%)	1 (11.1)	0	1 (5.3)
Metabolism and Nutrition Disorders	**n (%)**	**0**	**1 (10.0)**	**1 (5.3)**
Appetite disorder	n (%)	0	1 (10.0)	1 (5.3)
Neoplasms Benign, Malignant, and Unspecified (Including Cysts and Polyps)	**n (%)**	**0**	**1 (10.0)**	**1 (5.3)**
Melanocytic naevus	n (%)	0	1 (10.0)	1 (5.3)
Psychiatric Disorders	**n (%)**	**1 (11.1)**	**0**	**1 (5.3)**
Libido decreased	n (%)	1 (11.1)	0	1 (5.3)
Respiratory, Thoracic, and Mediastinal Disorders	**n (%)**	**0**	**1 (10.0)**	**1 (5.3)**
Dry throat	n (%)	0	1 (10.0)	1 (5.3)

Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; N / n: number; PT: Preferred Term; QD: once daily; QW: once weekly; SAS: safety analysis set; SOC: System Organ Class; TEAE: treatment-emergent adverse event.
If a patient had more than 1 event in a given SOC or PT, then they were only counted once for that SOC or PT.
Source: Table 14.3.1.5

In the QW open-label period of the study, 68.8% of patients experienced at least 1 TEAE, with 50.0% (N=8) of these AEs being considered treatment related. Overall, the most **commonly** reported treatment related TEAEs by MedDRA PT occurring in the SA population from Week 14 to Week 26 were injection site induration, injection site pain, and skin hyperpigmentation (each in 2 patients, 12.5%).

Table 2 Treatment-Related TEAEs by MedDRA SOC and PT from Week 14 to Week 26 (SAS)

SOC / PT	Statistic	20 mg QW Setmelanotide (N=1)	25 mg QW Setmelanotide (N=1)	30 mg QW Setmelanotide (N=14)	Total (N=16)
At Least 1 Treatment-Related TEAE	**n (%)**	**0**	**1 (100.0)**	**7 (50.0)**	**8 (50.0)**
General Disorders and Administration Site Conditions	**n (%)**	**0**	**1 (100.0)**	**3 (21.4)**	**4 (25.0)**
Injection site induration	n (%)	0	1 (100.0)	1 (7.1)	2 (12.5)
Injection site pain	n (%)	0	1 (100.0)	1 (7.1)	2 (12.5)
Injection site erythema	n (%)	0	1 (100.0)	0	1 (6.3)
Injection site haemorrhage	n (%)	0	0	1 (7.1)	1 (6.3)
Injection site mass	n (%)	0	0	1 (7.1)	1 (6.3)
Injection site pruritus	n (%)	0	0	1 (7.1)	1 (6.3)
Gastrointestinal Disorders	**n (%)**	**0**	**1 (100.0)**	**2 (14.3)**	**3 (18.8)**
Diarrhoea	n (%)	0	0	1 (7.1)	1 (6.3)
Nausea	n (%)	0	1 (100.0)	0	1 (6.3)
Vomiting	n (%)	0	0	1 (7.1)	1 (6.3)
Infections and Infestations	**n (%)**	**0**	**1 (100.0)**	**1 (7.1)**	**2 (12.5)**
Nasopharyngitis	n (%)	0	1 (100.0)	0	1 (6.3)
Tinea versicolour	n (%)	0	0	1 (7.1)	1 (6.3)
Skin and Subcutaneous Tissue Disorders	**n (%)**	**0**	**1 (100.0)**	**1 (7.1)**	**2 (12.5)**
Skin hyperpigmentation	n (%)	0	1 (100.0)	1 (7.1)	2 (12.5)
Alopecia	n (%)	0	1 (100.0)	0	1 (6.3)
Cardiac Disorders	**n (%)**	**0**	**1 (100.0)**	**0**	**1 (6.3)**
Palpitations	n (%)	0	1 (100.0)	0	1 (6.3)
Metabolism and Nutrition Disorders	**n (%)**	**0**	**0**	**1 (7.1)**	**1 (6.3)**
Decreased appetite	n (%)	0	0	1 (7.1)	1 (6.3)
Neoplasms Benign, Malignant, and Unspecified (Incl Cysts and Polyps)	**n (%)**	**0**	**0**	**1 (7.1)**	**1 (6.3)**
Melanocytic naevus	n (%)	0	0	1 (7.1)	1 (6.3)
Nervous System Disorders	**n (%)**	**0**	**1 (100.0)**	**0**	**1 (6.3)**
Headache	n (%)	0	1 (100.0)	0	1 (6.3)
Sleep paralysis	n (%)	0	1 (100.0)	0	1 (6.3)
Psychiatric Disorders	**n (%)**	**0**	**0**	**1 (7.1)**	**1 (6.3)**
Mood altered	n (%)	0	0	1 (7.1)	1 (6.3)
Vascular Disorders	**n (%)**	**0**	**1 (100.0)**	**0**	**1 (6.3)**
Haematoma	n (%)	0	1 (100.0)	0	1 (6.3)

Abbreviations: MedDRA: Medical Dictionary for Regulatory Activities; N / n: number; PT: Preferred Term; QD: once daily; QW: once weekly; SAS: safety analysis set; SOC: System Organ Class; TEAE: treatment-emergent adverse event.
If a patient had more than 1 event in a given SOC or PT, then they were only counted once for that SOC or PT.
Source: Table 14.3.1.6

The **clinical laboratory** evaluation did not reveal any relevant safety concerns related to setmelanotide treatment given as both QD and QW formulations. No patient reported abnormal hematology or chemistry values of CTCAE Grade ≥3. No clinically meaningful shifts in hematological or chemistry parameters from baseline were observed. During the blinded-part of the study, only 1 patient (QW setmelanotide group) with normal eosinophils at baseline had abnormal eosinophils at Week 1 and Week 9. During the open-label part of the study, abnormal eosinophils were reported in 1 patient in the 30-mg QW setmelanotide group at Week 14, whose baseline eosinophil values were normal.

Rapporteur's comment:

*During the study, 2 patients had **abnormal eosinophil values** (1 in the QW setmelanotide group in the blinded-part – dose not mentioned - and 1 in the QW 30 mg group during the open-label part) while their baseline values were normal. Eosinophilia will be discussed for the currently authorised QD formulation in a separate safety variation for Imcivree to be submitted by the MAH, as requested in the context of variation EMEA/H/C/005089/II/0018 by the CHMP and committed to by the MAH.*

During the blinded-part of the study, most patients reporting abnormal glucose, LDL cholesterol, HDL cholesterol, and triglycerides levels had abnormal values for these parameters at baseline. No clinically meaningful differences were observed between the QD and QW setmelanotide groups. During the open-label part of the study, abnormal glucose, HDL cholesterol, LDL cholesterol, and triglycerides levels were reported in the 30-mg QW setmelanotide group; none of these parameters with abnormal values were reported in the 20-mg QW and 25-mg QW setmelanotide groups.

Rapporteur's comment:

*During the open-label part of the study, some of the 14 patients in the 30-mg QW group reported abnormal glucose (N=1), HDL cholesterol (N=5), LDL cholesterol (N=1), and triglycerides levels (N=6) while no abnormal values were reported for these parameters in the 20-mg QW and 25-mg QW groups - which of course only consisted of 1 patient in each group. The MAH did not mention these abnormal values in the Clinical Expert Report and simply cited it in the CSR without any details nor discussion. Especially for the **abnormal HDL cholesterol (5/14) and triglyceride values (6/14),** there was a strikingly high number of patients in the 30 mg QW group.*

An other concern was formulated by the CHMP about these observations. The explanation provided by the MAH showed that all (5) patients with low HDL values during the study (2 treated with 3 mg QD and 3 treated with 30 mg QW during the DB period) also had low HDL values at baseline and that all (6) patients with increased triglyceride values during the study (4 treated with 3 mg QD and 2 treated with 30 mg QW during the DB period) also had increased triglyceride values at baseline. Moreover, there was no sign that daily setmelanotide treatment had an impact on these values in the index studies (before entering the 037 study). Consequently, the currently available data do not show a decrease of HDL values nor an increase of triglyceride values due to setmelanotide so there is no need for reviewing the PI of the daily formulation nor of the future weekly formulation in relation to these values.

The findings of the study suggest no major safety concerns related to **vital signs, physical examination, ECG, or suicidality/depression**.

There were **no events of special interest** defined in the protocol; however, based on experience with setmelanotide in other indications, a more in-depth evaluation of **injection site reactions** was performed. Injection site reactions were generally mild and well-tolerated during the study, with most occurring in the first 14 weeks of the study. Moderate injection site reactions were infrequent and primarily observed in the QW setmelanotide group, with only 1 instance in the QD group (erythema). Notably, only the 30 mg QW group experienced moderate induration at later timepoints.

No deaths or treatment-emergent SAEs were reported during the study.

There was 1 TEAE that led to **study drug withdrawal**. A 15-year old male BBS patient in the 3 mg QD group – with a history of seizures since 15 years and concomitant use of anti-epileptic medication - experienced multiple episodes of increased seizure activity of mild severity at different timepoints after the second setmelanotide dose during the blinded study period. This was followed by an ultimate

episode of moderate intensity a few days later which led to study drug withdrawal and was considered to be related to study drug; it resolved on the same day.

In the QD setmelanotide and QW setmelanotide groups, 4 and 7 patients, respectively, tested positive for antibodies to α-MSH. **No** patients tested positive for **anti-setmelanotide antibodies**.

2.3.3. Discussion on clinical aspects

The scope of this PAM P-46 procedure is the submission of the CSR for the Phase 3 study RM-493-037 comparing the PK, safety, and efficacy of the QW and QD formulations of setmelanotide, as well as evaluating the safety and efficacy up to 6 months of QW setmelanotide administration in patients with BBS, POMC, PCSK1, LEPR PPL or heterozygous PPL coming from the LTE trial RM-493-022.

PK

Given the primary objective of this study to compare the PK of the QD and QW formulation of setmelanotide, the choice for PK profiling at week 14, when both groups received a QW dose, was questioned during the first round While the response of the MAH that QD and QW steady state PK could be compared using visit 2 and week 14 PK data (of the QD-QW-QW group) is agreed, the added value of PK profiling at week 14 for the QD-QD-QW group is still unclear in view of the study objective.

At the start of this study, it was anticipated that a 30 mg QW setmelanotide would provide PK, safety, and efficacy comparable to the 3 mg QD setmelanotide dose. However, the limited PK data collected from subjects initially on a 3 mg QD dose revealed higher setmelanotide PK concentrations in the QD-QW-QW group compared to subjects who remained on 3 mg QD during the double-blind period (QD-QD-QW). These findings contradict the relative high exposure observed during a 24h interval after a 3 mg QD dose at visit 2. By consequence, based on the data currently presented, it remains **inconclusive** whether the assumption of **comparable PK** between the selected doses of QD and QW setmelanotide formulations is valid. The MAH clarified that no additional PK analyses are currently planned as setmelanotide QD and QW are titrated to effect. It will be a matter of assessment at time of the MAA if the totality of data could support a setmelanotide QW formulation.

Safety

The safety data collected in this Phase 3 study are **very limited** as only 19 patients were included (9 in the QD group and 10 in the QW group) of which merely 15 completed the study: only 6 patients were treated with the QW formulation for 13 weeks (after 13 weeks QD formulation) and only 9 patients were treated with the QW formulation for 26 weeks.

Based on the limited data, setmelanotide QD and QW were **well tolerated** and the TEAEs were **manageable** during the study as there were **no** setmelanotide-related deaths or other SAEs or severe TEAEs reported.

There were 2 cases of **abnormal eosinophil values** during the study with the QW formulation; eosinophilia will be discussed for the QD formulation in a separate safety variation to which the MAH has committed.

There was a strikingly high number of patients in the 30 mg QW group who reported **abnormal HDL cholesterol** (5/14) **and triglyceride values** (6/14) during the open-label part of the study. The explanation provided upon CHMP request by the MAH showed that all patients with low HDL values during the study also had low HDL values at baseline and that all patients with increased triglyceride values during the study also had increased triglyceride values at baseline, and that there was no sign that daily setmelanotide treatment had an impact on these values in the index studies (before entering the 037 study). Consequently, the currently available data do not show a decrease of HDL values nor

an increase of triglyceride values due to setmelanotide so there is no need for reviewing the PI of the daily formulation nor of the future weekly formulation in relation to these values.

There were **no clinically significant effects** on other clinical laboratory values, ECG, blood pressure, heart rate or other vital signs and physical examination, or on suicidality or depression, and there was only 1 TEAE that led to **withdrawal of study drug** (increased seizure activity in a patient with a history of seizures).

The safety profile of setmelanotide QD and QW during the study was generally **consistent** with that observed in previous clinical trials with the QD formulation as the **most common** treatment-related TEAEs in the blinded period were injection site pain, injection site erythema, injection site induration, injection site haemorrhage, injection site pruritus, nausea, injection site bruising, headache, menstruation irregular, and skin hyperpigmentation and in the QW open-label period injection site induration, injection site pain, and skin hyperpigmentation.

3. Rapporteur's overall conclusion and recommendation

x Fulfilled:

No regulatory action required. The MAH has provided a response to the list of RFIs which are considered to be resolved or are not pursued in the context of this PAM. If the totality of data are sufficient to support a setmelanotide QW formulation, will be a matter of assessment at time of MAA.

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

Other concerns

Pharmacokinetics

1. The PK measurement at the end of the double blind period is considered essential with regard to the primary objective to compare PK of setmelanotide after QD and QW administration. In this context, the applicant is asked toclarify the choice for PK profiling at week 14, given that both groups received a QW dose at that time and to provide more detailed information of PK profiling at week 14: time of QW administration and time of collection of the blood samples.

2. At visit 16 (week 14), all patients received a QW dose. By consequence, the corresponding period interval is 168h. For both the 30 mg QD-QD-QW and QD-QW-QW group, AUC0-tau was determined for 6 subjects at visit 16, whereas PK data up to and including 168h are only available for 3 and 4 subjects, respectively. Therefore, the MAH is asked to clarify how period interval was defined for the PK parameter AUC0-tau at visit 16.

3. While it was anticipated that a 30 mg QW setmelanotide would provide PK comparable to the 3 mg QD setmelanotide dose, limited PK data observed at visit 16 and visit 2 show conflicting results and cannot confirm the assumptions made. The MAH should clarify if further data will be collected to establish a PK bridge between the QD and QW formulation.

Clinical safety

4. During the open-label part of the study, there was a strikingly high number of patients in the 30 mg QW group who reported **abnormal HDL cholesterol** (5/14) **and triglycerides** (6/14), which was not mentioned in the Clinical Expert Report and was simply cited in the CSR without any details nor discussion. The MAH should discuss these cases of abnormal HDL cholesterol and triglycerides levels further, including but not limited to baseline levels and demographic data, attributed group during the blinded-phase (QD and at what dosage, or QW 30 mg), increase/decrease and degree of deviation to normal levels, outcome, treatment-relatedness assessment, dose-dependence etc. The necessity of reviewing this in the to be submitted safety variation (as committed to in variation EMEA/H/C/005089/II/0018) for the QD formulation should be discussed, as well as the potential impact on the future PI of the QW formulation.

The timetable is a 30 day response timetable with clock stop.

5. Assessment of the MAH responses to Request for supplementary information

Pharmacokinetics

Question 1

The PK measurement at the end of the double blind period is considered essential with regard to the primary objective to compare PK of setmelanotide after QD and QW administration. In this context, the applicant is asked to clarify the choice for PK profiling at week 14, given that both groups received a QW dose at that time and to provide more detailed information of PK profiling at week 14: time of QW administration and time of collection of the blood samples.

Summary of MAH answer

The study protocol states that the primary objective of the study is the comparison of steady-state PK parameters (maximum plasma concentration [Cmax,], time to maximum plasma concentration [tmax], trough plasma concentration [Ctrough], area under the plasma concentration-time curve over the dosing interval [AUCt]) for QW compared with QD setmelanotide. However, the sample size was based on availability of the patients enrolled in the long term extension study and is not driven by formal statistical hypothesis testing on non-inferiority/similarity. Thus, only descriptive PK statistics were to be provided.

With the aforementioned study limitations in mind, the 24-hour QD PK was assessed utilizing the first dose in Study RM-493-037, which was QD steady state setmelanotide, as participants were rolled over from other setmelanotide clinical studies on a stable dose of QD setmelanotide. Week 14 was chosen for the 168-hour PK sampling so as to compare QW at steady state versus QW de novo (that is, switched from QD). In addition, the 24-hour PK exposure (AUC) of QD setmelanotide was used to qualitatively compare to QW by multiplying the QD AUC0-24 by 7 to get the weekly exposure parameter. All PK assessments were qualitative in nature to allow the MAH to assess the viability of the QW formulation.

Rapporteur Assessment

The MAH clarified that the PK comparison between setmelanotide QD and QW dosing could be made using the PK data obtained at visit 2 (=QD steady state) and at week 14 (visit 16) for the QD-QW-QW groups (= QW steady state). Week 14 was chosen for the 168h PK sampling to additionally allow comparison of setmelanotide QW at steady state to QW de novo. No detailed information was provided regarding the timing of PK profiling at week 14.

Although it is agreed that QD and QW steady state PK could be compared using visit 2 and visit 16 PK data (of the QD-QW-QW group), limited subjects have PK profiling up to 24h at visit 2. Since subjects switched to a QW formulation at week 14, PK samples collected after the QW switch (of the QD-QD-QW group) cannot be used to determine QD steady state PK parameters.

Overall, the rationale and added value of comparing PK parameters at week 14 between the "steady state QW group" and the "de novo QW group" is still unclear considering the primary PK objective of the study.

Conclusion

Issue not pursued.

If the totality of data are sufficient to support dosing for a QW setmelanotide formulation, will be a matter of assessment at the time of MAA for the QW formulation.

Question 2

At visit 16 (week 14), all patients received a QW dose. By consequence, the corresponding period interval is 168h. For both the 30 mg QD-QD-QW and QD-QW-QW group, AUC0-tau was determined for 6 subjects at visit 16, whereas PK data up to and including 168h are only available for 3 and 4 subjects, respectively. Therefore, the MAH is asked to clarify how period interval was defined for the PK parameter AUC0-tau at visit 16.

Summary of MAH answer

AUC0-t values were extrapolated where data to 168 h was not available. The interval was defined as 0 h to 168 h and allowed Winnonlin to extrapolate AUC values if subjects had at least 3 points after tmax that met the R2 criteria (>0.8).

• For the 30mg QD-QD-QW group, 4 of the 7 subjects had tlast < ~168, and 3 of those had data sufficient for extrapolation. Therefore, we reported values for 6 subjects.

• For the QD-QW-QW group, 3 of the 7 subjects had tlast < ~168, and we were able to extrapolate values for 2 of those.

Rapporteur Assessment

The MAH clarified that for both the QD-QD-QW and QD-QW-QW group, the period interval for AUCtau at visit 16 was correctly defined as a 1 week interval (168h). If possible, AUC0-t values were extrapolated where data to 168 h was not available.

Conclusion

Issue resolved

Question 3

While it was anticipated that a 30 mg QW setmelanotide would provide PK comparable to the 3 mg QD setmelanotide dose, limited PK data observed at visit 16 and visit 2 show conflicting results and cannot confirm the assumptions made. The MAH should clarify if further data will be collected to establish a PK bridge between the QD and QW formulation.

Summary of MAH answer

The MAH is not currently planning on performing any additional PK analysis as setmelanotide QD and QW are titrated to effect. The MAH believes, based on the safety, tolerability, limited efficacy data and PK results of Study RM-493-037 and the safety, tolerability and PK results in healthy obese volunteers (in Study RM-493-026), that the doses chosen give exposure (Cmax and AUC) sufficient to safely and effectively treat patients.

Rapporteur Assessment

The MAH clarified that no additional PK analysis are planned. If the totality of data will be sufficient to support a setmelanotide QW formulation, will be a matter of assessment at time of the MAA.

Conclusion

Issue not pursued

Clinical safety

Question 4

During the open-label part of the study, there was a strikingly high number of patients in the 30 mg QW group who reported **abnormal HDL cholesterol** (5/14) **and triglycerides** (6/14), which was not mentioned in the Clinical Expert Report and was simply cited in the CSR without any details nor discussion. The MAH should discuss these cases of abnormal HDL cholesterol and triglycerides levels further, including but not limited to baseline levels and demographic data, attributed group during the blinded-phase (QD and at what dosage, or QW 30 mg), increase/decrease and degree of deviation to normal levels, outcome, treatment-relatedness assessment, dose-dependence etc. The necessity of reviewing this in the to be submitted safety variation (as committed to in variation EMEA/H/C/005089/II/0018) for the QD formulation should be discussed, as well as the potential impact on the future PI of the QW formulation.

Summary of MAH answer

As noted in the Study RM-493-037 CSR Preliminary Assessment Report from CHMP, 5 of the 14 patients in the open label 30 mg QW group had abnormal (low) HDL values and 6 of the 14 patients had abnormal (high) triglyceride values at some point during the study. Of the 5 patients with abnormal (low) HDL values at baseline and mid-study (Week 14), 4 (80.0%) also had abnormal (low) HDL at study end. One patient had a borderline value at the end of the study that was classified as normal in the study database (1.04 mmol/L [reference range: >1.04 mmol/L] Table 1). Of the 6 patients with abnormal (high) triglyceride values at some point during the study, 5 (83.3%) had abnormal values at baseline and every timepoint in the study. One patient had a high level at baseline and normal values at the other timepoints (Table 2). Furthermore, HDL and triglyceride values for these patients in the index studies, before entry into the 037 program, did not show an adverse impact of daily setmelanotide treatment on these parameters. Therefore, the MAH concludes that treatment with setmelanotide does not adversely or otherwise affect HDL or triglyceride levels.

Table 1: Patients in Study RM-493-037 With Abnormal HDL Values

Patient	Demographics (Age/Sex/Race)	Baseline HDL (mmol/L)	Dose: Doub Blinded Period	HDL (mmol/L) at end of Stage 1 (Week 14)	Dose: Open-Label QW Period	HDL (mmol/L) at end of Stage 2	Reference Limit
[redacted]	20 years Female White	0.98 L	3 mg QD	0.96 L	30 mg QW	1.04 N	>1.04
[redacted]	17 years Female White	0.83 L	3 mg QD	0.88 L	30 mg QW	0.78 L	>1.04
[redacted]	14 years Male White	1.04 L	30 mg QW	0.85 L	30 mg QW	0.91 L	>1.17
[redacted]	37 years Male White	0.96 L	30 mg QW	0.85 L	30 mg QW	0.91 L	>1.04
[redacted]	16 years Male White	0.80 L	30 mg QW	0.83 L	30 mg QW	0.83 L	>1.04
HDL-C reference range: 0-15Y >1.17 mmol/L; ≥16Y ≥1.04 mmol/L L=Low; N=Normal							

Table 2: Patients in Study RM-493-037 With Abnormal Triglyceride Values

Patient	Demographics (Age/Sex/Race)	Baseline TG (mmol/L)	Dose: Double Blind Period	TG (mmol/L) at end of Stage 1 (Week 14)	Dose: Open-Label QW Period	TG (mmol/L) at end of Stage 2	Reference Limit
[redacted]	17 years Female Other	1.45 H	3 mg QD	1.25 H	30 mg QW	1.34 H	<1.02
[redacted]	37 years Female White	2.46 H	3 mg QD	2.47 H	30 mg QW	2.28 H	<1.70
[redacted]	17 years Female White	2.05 H	3 mg QD	2.27 H	30 mg QW	2.36 H	<1.70
[redacted]	14 years Male White	1.46 H	30 mg QW	1.60 H	30 mgQW	1.70 H	<1.02
[redacted]	24 years Female White	1.79 H	3 mg QD	1.66 N	30 mg QW	1.08 N	<1.70
[redacted]	16 years Female White	1.24 H	30 mg QW	1.41 H	30 mg QW	1.18 H	<1.02
Triglyceride reference range: 0-9Y <0.85 mmol/L; 10-17Y <1.02 mmol/L; 18-110Y <1.70 mmol/L N=Normal; H=High							

Rapporteur Assessment

The explanation provided by the MAH showed that all (5) patients with low HDL values during the study (2 treated with 3 mg QD and 3 treated with 30 mg QW during the DB period) also had low HDL values at baseline and that all (6) patients with increased triglyceride values during the study (4 treated with 3 mg QD and 2 treated with 30 mg QW during the DB period) also had increased triglyceride values at baseline. Moreover, there was no sign that daily setmelanotide treatment had an impact on these values in the index studies (before entering the 037 study). Consequently, the currently available data do not show a decrease of HDL values nor an increase of triglyceride values due to setmelanotide, so there is no need for reviewing the PI of the daily formulation nor of the future weekly formulation in relation to these values.

Conclusion

Issue resolved