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Human Medicines Division

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

Optison

perflutren

Procedure no: EMA/PAM/0000291275

Note

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

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Table of contents

1. Introduction

On 1 August 2025, the MAH submitted a completed paediatric study for Optison, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study GE-191-008, A Phase 4, Open-Label, Non-randomized, Multicenter Study to Evaluate Safety and Efficacy of Intravenous Administration of Optison for Contrast-Enhanced Echocardiography in Pediatric Patients is a stand-alone study that was conducted to fulfil a post-marketing commitment to US FDA.

2.2. Information on the pharmaceutical formulation used in the study

Optison (Perflutren Protein-Type A Microspheres Injectable Suspension, USP) is a sterile non-pyrogenic suspension for intravenous injection.

No changes have been made to the formulation of the product for pediatric use.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

GE-191-008
A Phase 4, Open-Label, Non-randomized, Multicenter Study to Evaluate Safety and Efficacy of Intravenous Administration of Optison for Contrast-Enhanced Echocardiography in Pediatric Patients

2.3.2. Clinical study

Clinical study number and title

GE-191-008, A Phase 4, Open-Label, Non-randomized, Multicenter Study to Evaluate Safety and Efficacy of Intravenous Administration of Optison for Contrast-Enhanced Echocardiography in Pediatric Patients.

Description

Methods

Study design

This was a Phase 4, open-label, non-randomized, multi-centre, multi-dose study conducted between 03 March 2021 – 27 March 2023 at 8 centres in the United States. The study was designed to evaluate overall efficacy and safety of intravenous administration of Optison at various doses in paediatric patients undergoing transthoracic echocardiography. The study procedure involved one visit for each subject. For echocardiographic imaging, standard apical 4-chamber (A4C) and 2-chamber (A2C) views were obtained at baseline using tissue harmonic imaging, thereafter with contrast using a contrast-

imaging mode. Additional views were obtained at the clinician's discretion. All image views were obtained prior to and after contrast administration until 10 minutes post injection. All images were recorded on disk and sent to the image core lab for preparation of independent blinded image evaluation (BIE) which was carried out by 3 qualified and trained readers. The BIE was coordinated by the Sponsor Imaging Technology Group. Efficacy assessment was based on the results of the BIE. Clinical safety data were collected throughout the study, beginning at baseline throughout 72 hours post Optison administration.

Study participants

A subject was enrolled into the study only if all inclusion criteria and none of the exclusion criteria were fulfilled.

Inclusion Criteria

Subjects were included in the study if they met all of the following criteria:

(1) The subject was between ≥9 and <18 years of age and weighed ≥20 kg.

(2) The subject was clinically indicated to undergo a transthoracic echocardiogram.

(3) The subject had a suboptimal non-contrast echocardiogram defined as ≥2 contiguous segments in any given view that could not be visualized.

(4) The subject was able to comply with study procedures.

(5) A parent or legal guardian of the subject had signed and dated an informed consent form, and age-appropriate paediatric assent had been obtained where appropriate.

(6) Post-menarchal female subjects must have had a negative urine pregnancy test at screening and at pre-dose on the day of Optison administration.

(7) Post-menarchal female subjects must have been practicing abstinence or using an effective form of birth control (e.g., intrauterine device, oral contraceptives, contraceptive implants or injections, diaphragm with spermicide, cervical cap, or consort use of condom) for at least 30 days before being enrolled in the study.

Exclusion Criteria

Subjects were excluded from participating in this study if they met any of the following criteria:

(1) The subject had previously been enrolled in this study.

(2) The subject had received an IMP within 30 days before or was scheduled to receive one from time of entry into this study until completion of the follow-up period proposed for this study.

(3) The subject had a known or suspected hypersensitivity to any of the components of Optison, blood, blood products, or albumin.

(4) The subject had pulmonary hypertension or unstable cardiopulmonary conditions.

(5) The subject had severe liver disease based on medical history.

(6) The subject had a recent (<6 months) neurological event.

(7) The subject presented any clinically active, serious, life-threatening disease, with a life expectancy of less than 1 month or where study participation may have compromised the management of the subject or other reason that in the judgment of the investigator made the subject unsuitable for participation in the study.

(8) The subject was a pregnant or lactating female or was a female of childbearing potential who was not using an acceptable form of birth control (negative urine pregnancy test was also required).

Treatments

Each subject underwent an echocardiographic procedure first without contrast administration, then with intravenous bolus injection of Optison administered according to body weight (≥20 to ≤28 kg, >28 to ≤40 kg, and >40 kg). Each subject received administrations of 2 different dose levels. Injections were administered at least 10 minutes apart between the 2 dose levels to allow for clearance of the previous dose. The table below shows the exposure to Optison.

Table 1 Summary of Exposure to Optison (Safety Population)

Dose Level Category	Statistics	Weight group: ≤40 kg N=8	Weight group: >40 kg N=29	Overall N=37
Dose Level 1 Number of Administrations, n (%)	1	8 (100.0)	26 (89.7)	34 (91.9)
	2	0	3 (10.3)	3 (8.1)
	3	0	0	0
OPTISON Injection (mL) [1]	n	8	29	37
	Mean (SD)	0.18 (0.046)	0.22 (0.062)	0.21 (0.061)
	Median	0.20	0.20	0.20
	Q1, Q3	0.15, 0.20	0.20, 0.20	0.20, 0.20
	Min, Max	0.1, 0.2	0.2, 0.4	0.1, 0.4
Dose Level 2 Number of Administrations, n (%)	1	6 (75.0)	28 (96.6)	34 (91.9)
	2	2 (25.0)	1 (3.4)	3 (8.1)
	3	0	0	0
OPTISON Injection (mL) [1]	n	8	29	37
	Mean (SD)	0.33 (0.046)	0.41 (0.074)	0.39 (0.078)
	Median	0.30	0.40	0.40
	Q1, Q3	0.30, 0.35	0.40, 0.40	0.40, 0.40
	Min, Max	0.3, 0.4	0.4, 0.8	0.3, 0.8

Max=Maximum; Min=Minimum; SD=Standard Deviation; Q1, Q3=1st and 3rd quartiles.
[1] Total dose at this dose level.

Objective(s)

To study the efficacy and safety of Optison in paediatric patients in order to determine suitable dosage and administration instructions and any technical differences in instrumentation or settings that may affect Optison performance and safety in paediatric patients compared to adult patients.

Outcomes/endpoints

Primary Endpoint:

• Visualization of the 12 segments of the LV wall in standard A4C and A2C views measured by the qualitative EBD visualization scale.

Secondary Endpoints:

• Overall safety profile in terms of occurrence of adverse events (AEs) and changes in vital signs, arterial oxygen saturation, physical examinations and 12-lead electrocardiograms (ECGs) following administration of different Optison doses in pediatric patients.

• LV opacification (LVO) assessed by visual peak contrast intensity and peak LV contrast filling, and duration of contrast enhancement following intravenous administration of Optison at various doses.

• Comparison of diagnostic confidence of LV EBD and wall motion between non-contrast and Optison-enhanced echocardiography at various doses.

• Comparison of diagnostic confidence in the evaluation of LVEF between non-contrast and Optison-enhanced echocardiography.

Sample size

Approximately 50 patients were originally planned to be enrolled, with a minimum of 10 subjects in each of the originally specified weight groups (≥20 kg to ≤28 kg, >28 kg to ≤40 kg, and >40 kg). Per a United States Food and Drug Administration (FDA) advice/information request dated 16 February 2023, a reduction of the originally planned sample size was agreed, from 50 evaluable subjects to approximately 30. It was also agreed that the original requirement for a minimum of 10 subjects to be enrolled into each body weight group be removed. The specification for a minimum number of subjects with a body weight below 40 kg was removed, while patients weighing less than 40 kg would continue to be enrolled.

Randomisation and blinding (masking)

This was a non-randomized study.

Statistical Methods

All statistical analyses were performed with SAS® software (version 9.4). Relevant variables were presented using the appropriate descriptive statistics. Summary statistics for continuous variables consisted of the sample size (n), mean, standard deviation (SD), median (1st and 3rd quartile), and minimum and maximum values. For categorical variables, the number and percentage of responses in each level were presented. The suitable dosage of Optison for CE-echo in paediatric patients was primarily determined by the improvement in the number of segments adequately visualized over non-contrast images, supplemented by LVO peak contrast intensity assessed as medium or better, peak LV contrast filling to around 67% or better, and duration of contrast enhancement ≥1.5 minutes. Image quality and diagnostic confidence, as well as overall safety of Optison in the paediatric population, were also taken into consideration for the dose selection. No hypotheses were tested in this dose-finding study. Efficacy analyses were performed on the FAS and PP populations.

Results

Participant flow

In total 39 subjects provided informed consent/assent and were included in the enrolled population. Two subjects withdrew prior to dosing. A total of 37 subjects received ≥1 dose of Optison and were included in the safety population. The full analysis set (FAS) population included 37 subjects who had completed the study and had non-contrast harmonic and Optison -enhanced echocardiographic imaging, irrespective of the quality of CE- echo. Of this, 30 subjects did not have an important protocol deviation that impacted the primary endpoint and were included in the per protocol (PP) population. The PP population, defined as subjects who did not have an important protocol deviation that impacted the primary endpoint, included 30 subjects. Among these 30 subjects, 2 subjects had important protocol deviations that affected Optison Dose Level 1 only; as such, these 2 subjects were kept in the PP population, but their Dose Level 1 data were excluded from PP analyses.

Recruitment

This open-label study consisted of 37 paediatric subjects of ≥9 and <18 years of age (mean age: 13.4 years), who weighed between 27 kg and 150 kg (mean body mass index [BMI], 28.69 kg/m2; median

BMI, 28.04 kg/m2), and who were clinically indicated for a transthoracic echocardiogram because they were likely to have a limited transthoracic echocardiographic window based on body habitus and/or previous cardiac operation or because they had a previous suboptimal non-contrast echocardiogram (defined as 2 contiguous segments not properly visualized).

Baseline data

The baseline data and summary of medical history are presented in the tables below.

Table 2 Summary of Baseline Demographics Characteristics (Safety Population)

Parameter		Weight Group: ≤40 kg N=8	Weight Group: >40 kg N=29	Overall N=37
Age (years)	n	8	29	37
	Mean (SD)	10.4 (1.60)	14.3 (2.09)	13.4 (2.56)
	Median	10.0	15.0	14.0
	Q1, Q3	9.5, 10.5	13.0, 16.0	11.0, 16.0
	Min, max	9, 14	9, 17	9, 17
Gender, n (%)	Female	3 (37.5)	11 (37.9)	14 (37.8)
	Male	5 (62.5)	18 (62.1)	23 (62.2)
Race, n (%)	White	6 (75.0)	20 (69.0)	26 (70.3)
	Black or African American	0	3 (10.3)	3 (8.1)
	Asian	1 (12.5)	0	1 (2.7)
	American Indian or Alaska Native	0	1 (3.4)	1 (2.7)
	Native Hawaiian or Other Pacific Islander	0	0	0
	Multiple	1 (12.5)	1 (3.4)	2 (5.4)
	Other	0	0	0
	Unknown	0	3 (10.3)	3 (8.1)
	Not reported	0	1 (3.4)	1 (2.7)
Ethnicity, n (%)	Hispanic or Latino	3 (37.5)	15 (51.7)	18 (48.6)
	Not Hispanic or Latino	5 (62.5)	13 (44.8)	18 (48.6)
	Not Reported	0	1 (3.4)	1 (2.7)
Weight (kg)	n	8	29	37
	Mean (SD)	32.24 (5.779)	85.35 (33.189)	73.87 (36.805)
	Median	28.90	73.90	67.20
	Q1, Q3	27.90, 38.75	57.50, 114.80	42.01, 102.00
	Min, max	26.9, 39.9	41.5, 149.7	26.9, 149.7
Weight Category 1[1], n (%)	≥20 to ≤28 kg	2 (25.0)	0	2 (5.4)
	>28 to ≤40 kg	6 (75.0)	0	6 (16.2)
	>40 kg	0	29 (100.0)	29 (78.4)
Weight Category 2[1], n (%)	≤40 kg	8 (100.0)	0	8 (21.6)
	>40 kg	0	29 (100.0)	29 (78.4)
Height (cm)	n	8	29	37
	Mean (SD)	139.70 (11.439)	160.97 (14.634)	156.37 (16.457)
	Median	141.75	162.20	157.70
	Q1, Q3	134.15, 143.15	153.60, 172.00	142.90, 170.60
	Min, max	119.5, 160.0	127.0, 184.8	119.5, 184.8
BMI (kg/m^2)	n	8	29	37
	Mean (SD)	16.60 (2.826)	32.03 (9.353)	28.69 (10.539)
	Median	15.70	30.91	28.04
	Q1, Q3	14.27, 19.30	24.22, 37.74	20.87, 35.81
	Min, max	13.4, 20.9	17.3, 56.6	13.4, 56.6

Max=Maximum; Min=Minimum; SD=Standard deviation; Q1, Q3=1st and 3rd quartiles
Body mass index (BMI) = weight (kg) / (height (m))^2
Note: Percentages were calculated based on the number of subjects with non-missing values.
[1] Based on the collections from CRF at subject enrollment.

Table 3 Summary of Medical History (Safety Population)

System Organ Class	Weight group: ≤40 kg N=8 n (%)	Weight group: >40 kg N=29 n (%)	Overall N=37 n (%)
Any medical history	7 (87.5)	26 (89.7)	33 (89.2)
Blood and lymphatic system disorders	1 (12.5)	0	1 (2.7)
Cardiac disorders	1 (12.5)	5 (17.2)	6 (16.2)
Congenital, familial and genetic disorders	5 (62.5)	16 (55.2)	21 (56.8)
Endocrine disorders	1 (12.5)	1 (3.4)	2 (5.4)
Eye disorders	1 (12.5)	0	1 (2.7)
Gastrointestinal disorders	3 (37.5)	2 (6.9)	5 (13.5)
General disorders and administration site conditions	0	1 (3.4)	1 (2.7)
Immune system disorders	2 (25.0)	3 (10.3)	5 (13.5)
Infections and infestations	2 (25.0)	1 (3.4)	3 (8.1)
Injury, poisoning and procedural complications	1 (12.5)	0	1 (2.7)
Investigations	0	2 (6.9)	2 (5.4)
Metabolism and nutrition disorders	0	6 (20.7)	6 (16.2)
Musculoskeletal and connective tissue disorders	3 (37.5)	1 (3.4)	4 (10.8)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (12.5)	1 (3.4)	2 (5.4)
Nervous system disorders	0	3 (10.3)	3 (8.1)
Pregnancy, puerperium and perinatal conditions	0	1 (3.4)	1 (2.7)
Psychiatric disorders	0	6 (20.7)	6 (16.2)
Renal and urinary disorders	0	1 (3.4)	1 (2.7)
Reproductive system and breast disorders	0	3 (10.3)	3 (8.1)
Respiratory, thoracic and mediastinal disorders	2 (25.0)	8 (27.6)	10 (27.0)
Skin and subcutaneous tissue disorders	0	2 (6.9)	2 (5.4)
Surgical and medical procedures	1 (12.5)	9 (31.0)	10 (27.0)
Vascular disorders	1 (12.5)	7 (24.1)	8 (21.6)

N = Total number of subjects in that weight group; n = Number of subjects (out of N) that had an abnormal history for that body system.
Note: Subjects reporting more than one condition in a category are counted only once for that category.
MedDRA coding dictionary version 24.0

Number analysed

Subject disposition is summarized in the table below.

Table 4 Subject Disposition by Weight Group (All Subjects)

Disposition of Subjects	Weight Group: ≤40 kg N=8 n (%)	Weight Group: >40 kg N=31 n (%)	Overall N=39 n (%)
Number of Subjects Enrolled [1]	8	31	39
Number of Subjects in Safety Population [2]	8 (100.0)	29 (93.5)	37 (94.9)
Number of Subjects in FAS Population [3]	8 (100.0)	29 (93.5)	37 (94.9)
Number of Subjects in PP Population [4]	7 (87.5)	23 (74.2)	30 (76.9)
Number of Subjects Who Completed the Study	8 (100.0)	29 (93.5)	37 (94.9)
Number of Subjects Discontinued from the Study	0	2 (6.5)	2 (5.1)
Reason for Discontinuation			
Adverse Event	0	0	0
Screen Failure	0	0	0
Patient Voluntarily Withdrew Consent	0	1 (3.2)	1 (2.6)
Lost to Follow-Up	0	0	0
Investigator Decision	0	0	0
Other	0	1 (3.2)	1 (2.6)

FAS=Full analysis set; PP=Per protocol
Notes: All percentages were calculated based on the number of subjects enrolled.
[1] The Enrolled subjects consisted of all subjects who signed informed consent.
[2] The Safety population consisted of all enrolled subjects who received ≥1 dose of OPTISON in the study.
[3] The FAS population consisted of all enrolled subjects who had available non-contrast harmonic images and OPTISON-enhanced echocardiographic images, irrespective of the quality of CE-echo.
[4] The PP population consisted of all subjects in the FAS population who did not have an important protocol deviation impacting the study primary endpoint.

Efficacy results

Primary efficacy endpoint:

Results relating to the visualization of individual LV wall segments demonstrated systematic EBD visualization score improvements across all segments with the use of CE-echo relative to non-contrast echocardiography. Analysis of LV EBD scores between non-contrast and each Optison dose level by paired t-test demonstrated statistically significant increases in both the mean number of visualized LV wall segments and mean total LV EBD score in the overall PP population (n=30; all readers, all comparisons, p<0.0001). These statistically significant differences were preserved in analyses of the >40 kg weight group (n=23; all readers, all comparisons, p<0.0001). In the ≤40 kg weight group (n=7), statistically significant differences were largely preserved, however differences in mean number of visualized LV wall segments for Reader 3 did not reach statistical significance (non-contrast vs. Optison Dose Level 1, p=0.1496; non-contrast vs. Optison Dose Level 2, p=0.1483). Results relating to suboptimal echocardiograms showed that fewer echocardiograms were classified as suboptimal from non-contrast to Optison Dose Level 1 and again to Optison Dose Level 2 for the majority of readers in the overall PP population (Reader 1, 30/30 [100.0%] vs. 7/28 [25.0%] vs. 9/30 [30.0%]; Reader 2, 29/30 [96.7%] vs. 5/28 [17.9%] vs. 4/30 [13.3%]; Reader 3, 24/30 [80.0%] vs. 10/28 [35.7%] vs. 8/30 [26.7%]). This trend was broadly preserved within the ≤40 kg and >40 kg weight groups. A general trend of improved visualization with Optison Dose Level 2 relative to Dose Level 1 was evident in primary endpoint measures.

Secondary Efficacy Endpoints:

Left Ventricular Opacification – Peak LV contrast intensity of medium or higher was reported for a greater proportion of subjects at Optison Dose Level 2 compared to Dose Level 1 in the >40 kg weight group for the majority of readers (Reader 1, 22/23 [95.7%] vs. 20/22 [90.9%]; Reader 2, 22/23 [95.7%] 19/22 [86.4%]; Reader 3, 21/23 [91.3%] vs. 20/22 [90.9%]). In the ≤40 kg weight group peak LV contrast intensity was reported as medium or higher by all readers for all subjects. Peak LV contrast filling of ≥67% was reported in a slightly higher proportion of subjects with Optison Dose Level 2 relative to Dose Level 1 in the >40 kg weight group for the majority of readers (Reader 1, 22/23 [95.7%] vs. 19/22 [86.4%]; Reader 2, 22/23 [95.7%] vs. 20/22 [90.9%]; Reader 3, 21/23

[91.3%] vs. 20/22 [90.9%]). In the ≤40 kg weight group, peak LV contrast filling of 100% was reported by all readers and for all subjects, with the exception of a single reading in 1 subject. LV contrast enhancement durations were generally longer at Optison Dose Level 2 as compared with Dose Level 1, in the overall PP population and within the ≤40 kg and >40 kg weight groups.

Image Quality and Diagnostic Usefulness – Results relating to image quality showed that fewer images were classed as uninterpretable from non-contrast to Optison-enhanced imaging. Improvements in image quality were evident from Optison Dose Level 1 to Dose Level 2 for the overall PP set, as well as within the >40 kg weight group, as shown by a decrease in the proportion of poor quality images (Reader 1, 5/22 [22.7%] vs. 3/23 [13.0%]; Reader 2, 3/22 [13.6%] vs. 2/23 [8.7%]; Reader 3, 5/22 [22.7%] vs. 4/23 [17.4%]). Regarding diagnostic usefulness, in the overall PP set there was a general increase in the proportion of images that were classified as diagnostic from non-contrast to Optison-enhanced imaging, for the majority of readers. In the ≤40 kg weight group all images at both Optison dose levels were classified as diagnostic. In the >40 kg weight group, some advantage was conferred by the higher Optison dose according to the majority of readers (non- contrast vs. Optison Dose Level 1 vs. Dose Level 2: Reader 1, 5/23 [21.7%] vs. 17/22 [77.3%] vs. 20/23 [87.0%]; Reader 2, 21/23 [91.3%] vs. 20/22 [90.9%] vs. 21/23 [91.3%]; Reader 3, 6/23 [26.1%] vs. 17/22 [77.3%] vs. 19/23 [82.6%]).

Diagnostic Confidence of LV EBD and Wall Motion – In the overall PP population, there was a general improvement in diagnostic confidence for LV EBD and wall motion from non-contrast to Optison Dose Level 1 and again to Dose Level 2, with an increasing number of subjects' image assessments falling within the moderate/high confidence categories (Reader 1, 5/30 [16.7%] vs. 22/28 [78.6%] vs. 27/30 [90.0%]; Reader 2, 3/30 [10.0%] vs. 23/28 [82.1%] vs. 27/30 [90.0%]; Reader 3, 10/30 [33.3%] vs. 24/28 [85.7%] vs. 29/30 [96.7%]). This trend was preserved within >40 kg weight group, while there was little difference evident between Optison dose levels in the ≤40 kg group.

Diagnostic Confidence in the Evaluation of LVEF – An increase in the proportion of subjects' images with moderate or high diagnostic confidence in the evaluation of LVEF was observed in the overall PP population, from non-contrast to Optison Dose Level 1 and again to Dose Level 2, for all readers (Reader 1, 1/30 [3.3%] vs. 21/28 [75.0%] vs. 27/30 [90.0%]; Reader 2, 4/30 [13.3%] vs. 24/28 [85.7%] vs. 27/30 [90.0%]). This trend was generally preserved in both the ≤40 kg and >40 kg weight groups.

Dose Suitability – A greater proportion of subjects were considered suitable to Optison Dose Level 2 than to Dose Level 1 in the overall PP population and for all readers (Reader 1, 20/28 [71.4%] vs. 28/30 [93.3%]; Reader 2, 21/28 [75.0%] vs. 28/30 [93.3%]; Reader 3, 14/28 [50.0%] vs. 16/30 [53.3%]). This trend was preserved within both the ≤40 kg and >40 kg weight groups.

Safety results

A total of 13 out of 37 subjects (35.1%) in the safety population experienced a total of 25 TEAEs. All TEAEs were mild to moderate in intensity and none were serious. No deaths or other serious or significant events occurred. No TEAEs led to study discontinuation.

Overall, 6 subjects (16.2%) in the study population experienced a total of 12 TEAEs that were considered related to Optison by the investigator. Most of these TEAEs (9/12 [75.0%]) were mild, and most (10/12 [83.3%]) were reported as recovered/resolved on the day of onset. The most common MedDRA SOC for the TEAEs related to Optison was Nervous system disorders. TEAEs reported under this SOC included MedDRA PTs of headache (2 subjects), migraine (1 subject), taste disorder (2 subjects), dysgeusia (1 subject) and dizziness (1 subject). The second most common SOC considered related to Optison by the investigator was Gastrointestinal disorders. TEAEs within this SOC included

nausea (2 subjects), abdominal discomfort (1 subject), and abdominal pain (1 subject). One subject experienced mild and transient injection site pain (SOC, General disorders and administration site conditions), which was considered by the investigator to be related to Optison. Nine out of the 12 TEAEs that were considered related to Optison by the investigator were mild in severity: nausea, taste disorder, dysgeusia, injection site pain, headache (in 1 out of 2 subjects), abdominal pain, and abdominal discomfort. The remaining 3 TEAEs were of moderate severity and included dizziness, headache (1 out of 2 subjects), and migraine. All TEAEs that were considered related to Optison by the study investigator were clinically anticipated (expected as per current reference safety information), except one case of mild abdominal pain.

Vital sign, ECG and physical examination results revealed no notable trends. All changes were considered small, and none were clinically significant.

The MAH assessed the TEAEs of abdominal pain, abdominal discomfort, dizziness, headache, migraine, nausea, and injection site pain to be caused by either underlying congenital, vascular and/or gastrointestinal disorder, use of concomitant medications, or a combination of these factors, or associated with administration technique. According to the MAH, these AEs are not considered to be adverse reactions for which a causal relationship with Optison is a reasonable possibility. Dysgeusia was reported in 3 TEAE reports as non-serious, mild in severity and with a duration of up to approximately 15 minutes. Out of the 3 subjects, 1 male subject belonged to the ≤40 kg weight group and the remaining two female subjects belonged to the >40 kg weight group. According to the MAH, the short time to onset and transient nature of dysgeusia supports a causal relationship with Optison. The estimated frequency of dysgeusia is 3 out of 37 (8.1%), and MedDRA frequency category is 'common'. As per the MAH, dysgeusia is the only adverse reaction and the sole TEAE that was reported with a frequency of 5% or more. All three reports of Dysgeusia were also assessed as related to Optison by the investigator.

The TEAEs of clavicle fracture, supraventricular extrasystoles, diarrhoea, vomiting, mood swings, and cough were assessed as unlikely related to Optison by both the investigator and MAH. As per the MAH, clavicle fracture, cough, diarrhoea, vomiting and mood swings were likely related to pre-existing medical conditions in the study subject. Vital signs, electrocardiogram, and physical examination results revealed no notable trends. All changes were considered small, and none were clinically significant. There were no observable differences in adverse event frequency between the 2 weight groups. Due to the relatively small number of subjects in this study, no other subgroup comparisons were made.

The MAH concludes that overall, Optison was very well tolerated in the paediatric subjects, with a favourable safety profile regardless of body weight and dose used.

3. Discussion on clinical aspects

GE-191-008 is a Phase 4, open-label, non- randomized, multicentre study to evaluate safety and efficacy of intravenous administration of Optison for contrast-enhanced echocardiography in paediatric patients, to determine suitable paediatric dosage and administration instructions and to detect any technical differences in instrumentation or settings that may affect Optison performance and safety in paediatric compared to adult patients.

Optison is not currently approved for marketing in the paediatric population. The clinical study GE-191-008 was designed to satisfy a post-marketing commitment (PMC) to US FDA at the time of the original new drug application for Optison.

Regarding efficacy, Study GE-191-008 demonstrated consistent improvements across all measures of LV opacification and EBD with the use of Optison-enhanced echocardiography in paediatric patients 9-

17 years of age, relative to non-contrast harmonic imaging. A higher dose of Optison led to greater improvements compared to a lower dose. These findings are in line with those reported for adults.

Regarding safety, Optison seemed to be well tolerated in paediatric patients, with a favourable safety profile, regardless of body weight and dose used. All reported TEAEs were mild to moderate in severity, transient, and none were serious. No TEAEs led to study discontinuation or death.

In total, 6 participants (16.2%) experienced a total of 12 TEAEs. Of these, 9/12 (75.0%) were mild, and 10/12 (83.3%) recovered/resolved on the day of onset. The SOC "Nervous system disorders" was the most common, including the PTs headache (2 participants), migraine (1 participant), taste disorder (2 participants), dysgeusia (1 participant), and dizziness (1 participant). The SOC "Gastrointestinal disorders" was the second most common, including the PTs nausea (2 participants), abdominal discomfort (1 participant), and abdominal pain (1 participant). Injection site pain (mild and transient) was reported in one participant.

The MAH proposes the TEAEs headache, migraine, dizziness, nausea, abdominal discomfort, abdominal pain, and injection site pain to be caused by either underlying disorders, concomitant medications, a combination of these, or associated with administration technique. The assessment of the MAH is acknowledged; however, nausea is a known AE of Optison in adults, and it seems reasonable that this AE could also affect children and adolescents.

A causal relation between dysgeusia (occurring in 3/37, 8.1% of participants) and administration of Optison was identified by the MAH. Based on the timing of the event in relation to administration of Optison in combination with short duration a causal relation seems reasonable. Dysgeusia is already listed as a common AE in the Optison EU SmPC.

4. CHMP's overall conclusion and recommendation

The results of study GE-191-008 show a similar safety profile of Optison in children and adolescents as in adults. No new safety concerns have been identified. The overall benefit-risk ratio of Optison remains positive. It is agreed with the MAH that no updates of the EU SmPC are needed.

☒ **Fulfilled:**

No regulatory action required.