25 April 2024
EMA/224087/2024
Human Medicines Division

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

Kapruvia

Difelikefalin

Procedure no: EMEA/H/C/005612/P46/005

Note

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

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Submission	28.11.2023	28.11.2023	☐
☐	CHMP Rapporteur Assessment Report	10.04.2024	20.03.2024	☐
☐	CHMP members comments	15.04.2024	n/a	☐
☐	Updated CHMP Rapporteur Assessment Report	18.04.2024	n/a	☐
☒	CHMP adoption of conclusions:	25.04.2024	25.04.2024	☐

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1. Introduction

On 20th November 2023, the MAH submitted a completed paediatric study for Kapruvia (difelikefalin), 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 KOR-PED-201, "An Open-label, Single Arm Study to Evaluate the Pharmacokinetics of a Single Dose of Intravenous Difelikefalin in Adolescents Aged 12 to 17 Years on Haemodialysis" is part of a clinical development program required by EMEA-002565-PIP02-19.

An overview of the clinical studies required by EMEA-002565-PIP02-19 is provided in Table 1.

Table 1 Clinical Studies Required by EMEA-002565-PIP02-19 for Kapruvia (difelikefalin, solution for injection)

Study Title	Study Number	Date of Completion	Date of Submission o final CSR
An Open-label, Single Arm Study to Evaluate the Pharmacokinetics of a Single Dose of Intravenous Difelikefalin in Adolescents Aged 12 to 17 Years on Haemodialysis	KOR-PED-201	30 May 2023	30 Nov 2023[a]
An Open-label, Single Arm Study to Evaluate the Safety and Tolerability of Intravenous Difelikefalin in Adolescents Aged 12 to 17 Years on Haemodialysis with Moderate-to-Severe Pruritus	KOR-PED-202	March 2026[b]	TBD[c]

CSR=Clinical Study Report; TBD= To be Determined
a) Deadline for submission of paediatric study results as per Article 46 of REGULATION (EC) No 1901/2006
b) Timeline as agreed in EMEA-002565-PIP02-19
c) The timeline for the submission of the CSR for KOR-PED-202 is going beyond the timeline of this submission, so no information on future submission(s) can be provided within this submission

2.2. Information on the pharmaceutical formulation used in the study

Difelikefalin is used in the same formulation (solution for injection) in this study as centrally authorised for adults (EU/1/21/1605/001-2).

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

KOR-PED-201, "An Open-label, Single Arm Study to Evaluate the Pharmacokinetics of a Single Dose of Intravenous Difelikefalin in Adolescents Aged 12 to 17 Years on Haemodialysis".

2.3.2. Clinical study

KOR-PED-201, "An Open-label, Single Arm Study to Evaluate the Pharmacokinetics of a Single Dose of Intravenous Difelikefalin in Adolescents Aged 12 to 17 Years on Haemodialysis".

Description

The primary objective of KOR-PED-201 study was to evaluate the pharmacokinetic (PK) profile of a single dose of difelikefalin in adolescents aged 12 to 17 years on HD, and the secondary objective was to evaluate the safety and tolerability of a single dose of difelikefalin in this population.

Methods

KOR-PED-201 was a multicentre, open-label, single-arm, single-dose study. A single dose of difelikefalin was administered as an intravenous (IV) bolus based on 0.5 µg/kg of dry body weight on Day 1 within 15 minutes after completion of HD treatment on the first HD treatment of the calendar week (HD #1). The expected duration of subject participation was up to 32 days, including a:

1. Screening period (up to 21 days), during which informed consent was obtained; demographics, medical history, and prior and concomitant medications were recorded; a physical examination was performed; height, prescription dry body weight, vital signs, and 12-lead ECG were measured; serum pregnancy test was performed, haematology, and serum chemistry were assessed; and eligibility was determined.

2. PK period (3 days), with 3 visits (on Day 1, Day 2, and Day 3). Study drug was administered on Day 1. The Day 1 visit also included confirmation of eligibility, safety assessments, PK blood sampling, recording concomitant medications, and vital signs. The Day 2 visit included safety assessments, PK blood sampling, recording concomitant medications, and vital signs. Day 3 was also the day of the second HD treatment and included safety assessments, PK blood sampling, recording concomitant medications, vital signs, and 12-lead ECG.

3. Follow-up period 7 (up to 10) days after study drug administration. The follow-up visit included recording concomitant medications and any AEs.

All post-dose PK samples were to be obtained from a venous access different than the one used to administer the study drug, see table below. On Day 1, samples were to be obtained pre-dose, and at 5 minutes, 15 minutes, 30 minutes, 2 hours, and 6 hours post-dose (6 samples in total). On Day 2, a sample was to be obtained at 24 hours post-dose given on Day 1, and on Day 3 a sample was to be obtained 44 or 48 hours after study drug administration on Day 1 but before the second HD treatment and a second sample was to be obtained within 5 minutes after the second HD treatment.

PK sampling time points are presented in the table:

Study Day	Nominal Hour	Nominal Minutes	Time	Allowed Window
1	0		Pre-dose	Not applicable
1		5		±1 minute
1		15		±2 minutes
1		30		±2 minutes
1	2			±30 minutes
1	6			±2 hours
2	24			±2 hours
3	48 (44)[1]		Pre-HD #2	±2 hours
3		5	Post-HD #2	±5 minutes

1 Time point could be scheduled at the usual dialysis time of the day (corresponding to 44 hours post-dose) or at 48 hours post-dose; in either case a ±2-hour window was allowed.

Notes: HD=Haemodialysis

Pharmacokinetic analysis

Concentration-time data for difelikefalin were analysed using noncompartmental methods in Phoenix™ WinNonlin® (Version 8.3.4, Certara, L.P.) in conjunction with Certara IntegralTM (Version 23.4.1, Certara USA, Inc.). Integral provides protected and structured storage, audit trails, and version control for study data, analyses, and related files, supporting 21 CFR Part 11 compliance. During the PK analysis, concentrations BLQ up to the time of the first quantifiable concentration were treated as zero. Embedded (values between 2 quantifiable concentrations) and terminal BLQ concentrations were treated as "missing".

Main PK-parameters calculated: T_{max}, C_{max}, C_{44}, AUC_{inf}, AUC_{0-48}, AUC_{last}, $T_{½}$, CL, V_z, and ER_d.

Bioanalytical method: Plasma samples were analysed using a validated LC-MS/MS method difelikefalin with a validated lower limit of quantitation of 0.0500 ng/ml for difelikefalin

Study participants and Participant flow

Planned: at least 6 subjects evaluable for the PK endpoint

Screened: 10 subjects

Received study treatment: 8

Completed: 8 subjects

Analysed: 8 subjects in the Safety Set and 7 subjects in the PK Set

Results

Pharmacokinetic results

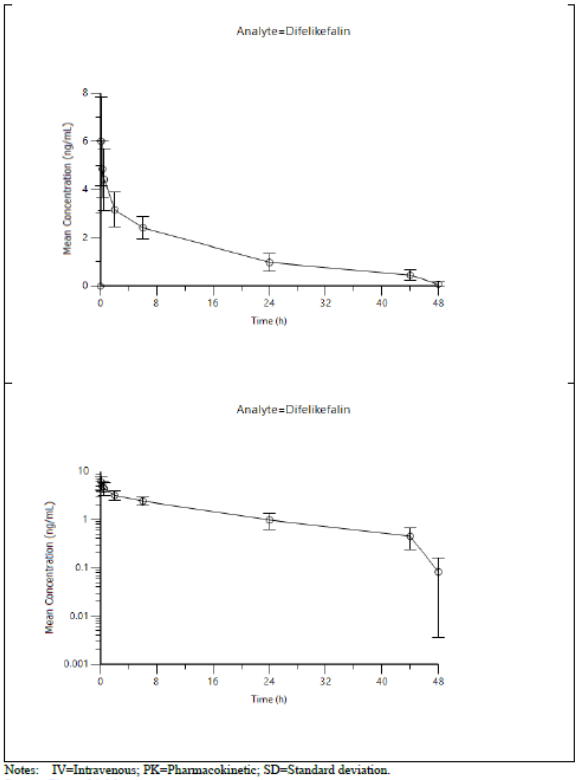
The PK of a single difelikefalin dose of 0.5 µg/kg of dry body weight was assessed in 7 adolescents on HD (cohort details under safety results). Descriptive statistics for concentration-time data are provided in Table 12 and mean data for concentration-time profile are presented in Figure 3.

Table 12 Difelikefalin Concentration-Time Data, Summary Statistics (PK Set; N=7)

Day	Time Text	Time (h)	n	Mean (ng/ml)	SD (ng/ml)	CV (%)	Min (ng/ml)	Median (ng/ml)	Max (ng/ml)	Geo Mean (ng/ml)	Geo CV (%)
1	Pre-dose	0.00	7	0.00	0.00	NC	0.00	0.00	0.00	NC	NC
1		0.0833	7	6.00	1.83	30.6	3.56	6.57	8.07	5.74	33.6
1		0.250	7	4.85	1.16	23.9	3.15	4.73	6.61	4.73	25.0
1		0.500	7	4.41	1.29	29.2	2.75	4.24	6.47	4.25	29.7
1		2.00	7	3.16	0.722	22.8	2.06	3.15	4.40	3.09	23.7
1		6.00	7	2.42	0.475	19.7	1.67	2.27	3.15	2.38	20.5
2		24.0	7	0.980	0.354	36.1	0.532	1.05	1.39	0.921	40.4
3	Pre-HD #2	44.0	6	0.451	0.216	47.9	0.145	0.459	0.731	0.398	64.9
3	Post-HD #2	48.0	6	0.0829	0.0793	95.7	0.00	0.0746	0.196	NC	NC

Notes: Plasma samples were analysed using a bioanalytical method with a validated lower limit of quantitation of 0.0500 ng/ml for difelikefalin. Concentrations are reported in ng/ml to 3 significant figures. Concentrations BLQ are set to zero (0.00 ng/ml) in this data summarisation.
BLQ= below limit of quantification; CV=Coefficient of variation; Geo=Geometric; HD=Haemodialysis; Max=Maximum; Min=Minimum; NC=Not calculated; PK=Pharmacokinetic; SD=Standard deviation.
Source: Table 14.4.1

Figure 3 Mean (SD) Difelikefalin Concentration-Time Profile after IV Administration of 0.5 µg/kg of Dry Body Weight Difelikefalin to Adolescents Aged 12 to 17 Years on HD on Linear and Semi-Logarithmic Scales (PK Set, N=7)



Notes: IV=Intravenous; PK=Pharmacokinetic; SD=Standard deviation.
Source: Figure 14.4.1

Individual PK parameters with descriptive statistics are summarised in Table 13.

Table 13 Difelikefalin PK Parameters after IV Administration of 0.5 µg/kg of Dry Body Weight Difelikefalin to Adolescents Aged 12 to 17 Years on HD (PK Set, N=7)

Parameter	n	Mean	SD	CV%	Geo Mean	Geo CV%	Min	Median	Max
T_{max} (h)	7						0.0667	0.0833	0.250
C_{max} (ng/ml)	7	6.03	1.81	30.0	5.78	33.1	3.56	6.57	8.07
C_{44} (ng/ml)(1)	6	0.451	0.216	47.9	0.398	64.9	0.145	0.459	0.731
AUC_{0-48} (h*ng/ml)(2)	7	63.4	17.4	27.4	61.2	29.7	38.1	62.8	87.2
AUC_{last} (h*ng/ml)	7	61.6	17.7	28.8	59.2	31.6	37.5	60.9	84.9
AUC_{inf} (h*ng/ml)	7	72.5	23.7	32.6	68.9	36.5	39.8	73.0	100
AUC_{Extrap} (%)	7	13.9	5.40	38.8	12.9	47.9	5.80	14.6	22.2
$T_{1/2}$ (h)	7	15.4	4.44	28.8	14.8	31.8	9.15	17.0	20.9
T_{last} (h)	7	42.2	8.03	19.0	41.4	23.4	24.8	44.0	50.2
C_{last} (ng/ml)	7	0.462	0.199	43.1	0.415	59.7	0.145	0.478	0.731
CL (ml/min)(3)	7	5.71	1.76	30.9	5.50	29.8	3.74	5.31	8.85
V_z (l)(3)	7	7.30	1.92	26.3	7.06	29.8	4.20	7.79	9.95
CL (ml/min/kg)(4)	7	0.128	0.0474	37.1	0.121	36.5	0.0831	0.114	0.209
V_z (l/kg)(4)	7	0.157	0.0258	16.4	0.155	16.5	0.122	0.152	0.200
ER_d (%)(5)	5	81.2	12.0	14.8	80.5	14.4	68.8	79.2	100

1 Concentration at 44 hours post-dose, prior to haemodialysis #2 (Note: the concentration at 44 hours post-dose was not available for [redacted]
2 Concentrations occurring post haemodialysis #2 were not used for AUC_{0-48} calculations
3 Based on actual dose administered
4 Based on nominal dose (0.5 µg/kg of dry body weight)
5 Extraction ratio during haemodialysis (Note: Concentrations at 44 hours post-dose and at 5 minutes post haemodialysis #2 were not available for [redacted]
Notes: CV=Coefficient of variation; Geo=Geometric; IV=Intravenous; Max=Maximum; Min=Minimum; PK=Pharmacokinetics; SD=Standard deviation.
Source: Table 14.4.3

As planned in the SAP, a descriptive comparison of most relevant PK parameters in adolescents (this study) and adults (from the previous CR845-CLIN2005 study) is shown in Table 14, see below. Cmax, AUC0-48, and AUCinf values in KOR-PED-201 and in the previous study in an adult HD population (CR845-CLIN2005) after administration of 1 dose of difelikefalin 0.5 µg/kg of dry body weight were as follows:

- Mean (95% confidence intervals) Cmax was 6.03 (4.36 to 7.71) ng/ml for adolescents (KOR-PED-201) and 5.43 (4.19 to 6.68) ng/ml for adults (CR845-CLIN2005).
- Median (range) Cmax was 6.57 (3.56 to 8.07) ng/ml for adolescents (KOR-PED-201) and 5.35 (3.36 to 7.04) ng/ml for adults (CR845-CLIN2005).
- Mean (95% confidence intervals) AUC0-48 was 63.4 (47.4 to 79.5) h*ng/ml for adolescents (KOR-PED-201) and 56.5 (42.0 to 71.0) h*ng/ml for adults (CR845-CLIN2005).
- Median (range) AUC0-48 was 62.8 (38.1 to 87.2) h*ng/ml for adolescents (KOR-PED-201) and 56.1 (36.6 to 78.3) h*ng/ml for adults (CR845-CLIN2005).

- Mean (95% confidence intervals) AUCinf was 72.5 (50.6 to 94.4) h*ng/ml for adolescents (KOR-PED-201) and 81.0 (50.1 to 111.9) h*ng/ml for adults (CR845-CLIN2005).
- Median (range) AUCinf was 73.0 (39.8 to 100) h*ng/ml for adolescents (KOR-PED-201) and 81.0 (39.2 to 119.3) h*ng/ml for adults (CR845-CLIN2005).

Intersubject variability (measured using CV%) was generally comparable for adolescent and adult HD populations for Cmax, AUC0-48, and AUCinf, ranging from 27.4% to 32.6% in adolescents (KOR-PED-201) and from 24.9% to 41.3% in adults (CR845-CLIN2005) (Table 14).

In this study in adolescents (KOR-PED-201), mean (SD) total clearance was 5.71 (1.76) ml/min. Mean T1/2 in adolescents was 15.4 (4.44) hours, lower than in CR845-CLIN2005 study in adults: 24.4 (12.6) hours; however, large SDs should be noted for this parameter especially for the study in adults (Table 13 and [11]).

Table 14 Comparison of PK Parameters after IV Administration of 0.5 µg/kg of Dry Body Weight Difelikefalin: Adolescents (KOR-PED-201) versus Adults (CR845-CLIN2005)

							95% CI for the Mean		Range	
Population	Parameter	n	Mean	Median	SD	CV%	Lower	Upper	Minimum	Maximum
Adolescents	C_{max} (ng/ml)	7	6.03	6.57	1.81	30.0	4.36	7.71	3.56	8.07
	AUC_{0-48} (h*ng/ml)	7	63.4	62.8	17.4	27.4	47.4	79.5	38.1	87.2
	AUC_{inf} (h*ng/ml)	7	72.5	73.0	23.7	32.6	50.6	94.4	39.8	100
Adults	C_{max} (ng/ml)	7	5.43	5.35	1.35	24.9	4.19	6.68	3.36	7.04
	AUC_{0-48} (h*ng/ml)	7	56.5	56.1	15.7	27.8	42.0	71.0	36.6	78.3
	AUC_{inf} (h*ng/ml)	7	81.0	81.0	33.4	41.3	50.1	111.9	39.2	119.3

Source: Table 14.4.3; Table in Statistical Analysis Plan Version 1.0 (13 July 2023) "Mean (SD) PK Parameters in Adults after Difelikefalin 0.5 µg/ml on Day 1" (Appendix 16.1.9); Clinical Study Report CR845-CLIN2005 "A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Safety and Pharmacokinetics of Intravenous CR845 in Hemodialysis Patients, and Its Safety and Efficacy in Hemodialysis Patients with Uremic Pruritus", Cara Therapeutics Inc., 17 May 2020.
Note: Parameter values for adults were converted from pg/ml to ng/ml for comparison purposes
CI=Confidence intervals; CV=Coefficient of variation; PK=Pharmacokinetics; SD=Standard deviation.

Conclusion: The PK profile following administration of 1 difelikefalin dose of 0.5 µg/kg, based on dry body weight, in adolescents on HD (KOR-PED-201) was comparable to that in adults on HD (CR845-CLIN2005). In particular, this was shown in a pre-specified numerical comparison of the median and 95%. confidence intervals for the mean for Cmax, AUC0-48, and AUCinf values. Theoverall drug exposure following administration of 1 dose of difelikefalin of 0.5 µg/kg, based on dry body weight, was found to be comparable between adolescents and adults on HD.

Safety results

The Safety Set included 3 (37.5%) males and 5 (62.5%) females. Mean age at informed consent was 15.0 years; minimum age was 12 years and maximum age 17 years. The majority of subjects in the Safety Set were White (75.0%) and all were not Hispanic or Latino (100%). Mean dry body weight and body-mass index (BMI) were 44.6 kg and 21.0 kg/m2, respectively. The mean (SD) time since onset of (chronic kidney disease) CKD was 4.8 (4.14) years and the mean (SD) time since first HD was 3.3 (3.09) years. The most commonly reported primary reason for CKD was classified as "other" (5 [62.5%] subjects). Demographic and baseline characteristics were similar for the PK set.

In the Safety Set, medical and surgical history was reported in 7 (87.5%) subjects. The most common medical and surgical history terms by SOC were blood and lymphatic system disorders (75.0% of subjects) and surgical and medical procedures (50.0% of subjects). The most common medical and surgical history terms by PT were nephrogenic anaemia (62.5% of subjects) and hypertension (37.5% of subjects). Medical history was similar for the PK Set.

Eight subjects received a single difelikefalin dose of 0.5 µg/kg of dry body weight and were part of the Safety Set.

There were no deaths and no serious TEAEs reported during the study.

2 TEAEs were reported in 1 (12.5%) subject. Both TEAEs were nervous system disorders (1 event each of headache and dizziness) and started 2 minutes after study drug administration. These TEAEs were considered mild and possibly related to study drug by the Investigator. Both events resolved and no action was taken with the study drug. The event of dizziness was also considered a TEAESI. No TEAEs led to study withdrawal.

Table 15 Overall Summary of TEAEs (Safety Set, N=8)

	Difelikefalin (N=8)
Any TEAE, n (%), E	1 (12.5%), 2
Any TEAESI, n (%), E	1 (12.5%), 1
Any SAE, n (%), E	0, 0
Any death, n (%), E	0, 0
Any TEAE related to difelikefalin, n (%), E	1 (12.5%), 2
Any SAE related to difelikefalin, n (%), E	0, 0
Any TEAE with any alternative causality or confounding factors, n (%), E	0, 0
Any TEAEs leading to difelikefalin withdrawal, n (%), E	0, 0
Any TEAEs leading to difelikefalin interruption, n (%), E	0, 0
Any TEAEs leading to study discontinuation, n (%), E	0, 0
TEAEs by severity[1]	
Mild, n (%), E	1 (100%), 2
Moderate, n (%), E	0, 0
Severe, n (%), E	0, 0

1 Percent calculated out of number of subjects experiencing a TEAE

Notes: Treatment-emergent is defined as any AE which occurs on or up to 7 days after administration of difelikefalin. Treatment emergent includes any pre-existing adverse event that worsens in severity on or after administration of difelikefalin.
E=Number of events; SAE=Serious adverse event; TEAE=Treatment-emergent adverse event; TEAESI=Treatment-emergent adverse event of special interest

Table 16 TEAEs by SOC and PT (Safety Set, N=8)

SOC PT	Difelikefalin N (%)	Number of Events
Any TEAE	1 (12.5%)	2
Nervous system disorders	1 (12.5%)	2
Dizziness	1 (12.5%)	1
Headache	1 (12.5%)	1

Note: Subjects are counted at most once per SOC and at most once per PT.
Treatment emergent is defined as any AE which occurs on or up to 7 days after administration of difelikefalin.
Treatment emergent includes any pre-existing adverse event that worsens in severity on or after administration of difelikefalin.
MedDRA Version 24.1
PT=Preferred term; SOC=System organ class; TEAE(s)=Treatment-emergent adverse event(s).

Laboratory parameters were consistent with the underlying condition of this population (CKD on HD) and abnormal values were generally considered as NCS. Clinically significant abnormalities in laboratory parameters (creatinine and urea nitrogen) were reported in 1 subject overall.

Vital signs showed no trends or clinically relevant changes over time. Physical examination findings at Screening were normal except for clinically significant abnormal findings in 1 (12.5%) subject in the body systems of general appearance, skin, and abdomen.

ECG parameters were generally stable from Baseline to Day 3. There was a decrease in mean (SD) PR interval from 206.8 (218.74) milliseconds at Baseline to 133.4 (28.56) milliseconds at Day 3. Of note, 1 subject had a change in PR interval from 744 milliseconds at Baseline to 112 milliseconds at Day 3; the ECG at Baseline was not considered CS by the Investigator. A shift in 12-lead ECG overall interpretation from normal at Baseline to abnormal NCS at Day 3 was reported in 1 (12.5%) subject (Table 14.3.7.6). This was not the subject who had a PR interval of 744 milliseconds at Baseline described above.

2.3.3. Discussion on clinical aspects

The study KOR-PED-201 is part of the approved clinical paediatric development plan for Kapruvia. The strategy is to first confirm that the same dose as in adults with chronic-kidney disease-associated pruritus on haemodialysis (HD) of 0.5 µg/kg difelikefalin, results in a similar exposure in adolescents on HD.

The pharmacokinetics of a single dose of 0.5 µg/kg difelikefalin was evaluated in 8 adolescents. The plasma PK-profile over 48 hr was determined from 9 plasma samples and plasma PK-parameters were determined by NCA. The PK-methodology applied in the study was adequate. The final PK-set included 7 adolescents, as one subject was excluded, as all the samples were below LLOQ. An explanation of the lack of plasma data for this subject is not available. This is acceptable, though not optimal. The key adolescent exposure PK-parameters, mean Cmax, mean AUC0-48 and mean AUCinf, were compared with previous determined adult parameters. The mean Cmax, mean AUC0-48 and mean AUCinf were very comparable with the adult parameters, 1.21 fold, 1.12 fold, 0.89 fold of adult values, respectively. Also their respective 95% confidence interval were very comparable. In conclusion, it has been demonstrated that the administration of a single dose of difelikefalin of 0.5 µg/kg, based on dry body weight provides comparable exposure in adolescents as in adults on HD.

Eight adolescents received a single dose of which one subject reported 2 TEAEs. The events were headache and dizziness, in line with the already known safety profile in adults. No deaths and no serious TEAEs occurred and no TEAEs led to study withdrawal.

One subject who had elevated creatinine, urea nitrogen and urea nitrogen/creatinine ratio at Screening, Baseline, and Day 3 which showed no increase over the time of dosing and thus not can be accounted to the drug.

CKD patients undergoing HD have a markedly increased CV risk, which is likely to be further impacted by CKD-aP why electrocardiograms are of special interest in this setting. A numerical decrease in mean PR interval from Baseline to Day 3, mainly driven by one subject. One change in overall classification of ECG from normal to abnormal but not clinically significant was made by the investigator for one subject. This does not point in the direction of any negative cardiac influence.

As no new safety signals were identified it is endorsed to further investigate difelikefalin 0.5 µg/kg of dry body weight in adolescents on HD with moderate-to-severe pruritus after multiple administrations, as planned as the next part of the clinical paediatric development program.

The information on PK and safety from this study should be incorporated in the SmPC.

3. Overall conclusion and recommendation

It has been demonstrated that the administration of a single dose of difelikefalin of 0.5 µg/kg, based on dry body weight provides comparable exposure in adolescents as in adults on HD.

The safety profile of difelikefalin 0.5 µg/kg of dry body weight, administered in adolescents as a single IV dose, was consistent with the known safety profile of difelikefalin in adults.

This information should be reflected in the SmPC.

☐ **Fulfilled:**
In view of the available data regarding [….] the MAH should either submit a variation in accordance with Articles 16 and 17 of Regulation (EC) No 726/2004 or provide a justification for not doing so. This should be provided without any delay and ***no later than 60 days after the receipt*** of these conclusions.

☒ **Not fulfilled:**
Based on the data submitted, the MAH should provide additional data part of this procedure. (see section "Request for supplementary information")

4. Request for supplementary information

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

1) It has been demonstrated that the administration of a single dose of difelikefalin of 0.5 µg/kg, based on dry body weight provides comparable exposure in adolescents as in adults on HD.

   The safety profile of difelikefalin 0.5 µg/kg of dry body weight, administered in adolescents as a single IV dose, was consistent with the known safety profile of difelikefalin in adults.

   This information should be reflected in the SmPC.

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

MAH responses to Request for supplementary information

Question 1

It has been demonstrated that the administration of a single dose of difelikefalin of 0.5 µg/kg, based on dry body weight provides comparable exposure in adolescents as in adults on HD.

The safety profile of difelikefalin 0.5 µg/kg of dry body weight, administered in adolescents as a single IV dose, was consistent with the known safety profile of difelikefalin in adults.

This information should be reflected in the SmPC.

Response to Question 1

The Applicant acknowledges the reviewer's recommendation to reflect the currently available information from KOR-PED-201 in the Summary of Product Characteristics (SmPC).

In order to inform healthcare professionals about the available data in adolescents receiving a single intravenous dose of difelikefalin of 0.5 µg/kg, the Applicant proposes the addition of the below wording to section 4.2 and Section 5.1 of the SmPC.

Section 4.2 Posology and method of administration – Posology, Current wording

Paediatric population

"The safety and efficacy of difelikefalin in children aged 0-17 years has not yet been established. No data are available."

Proposed wording

Paediatric population

"The safety and efficacy of difelikefalin in adolescents aged 12 to17 years has not yet been established. Currently available data are described in section 5.1.

The safety and efficacy of difelikefalin in children below 12 years has not yet been established. No data are available in patients below 12 years."

Section 5.1 Pharmacodynamic properties – Clinical efficacy and safety

Current wording

Paediatric population

"The European Medicines Agency has deferred the obligation to submit the results of studies with difelikefalin in one or more subsets of the paediatric population in the treatment of chronic kidney disease associated pruritus (see section 4.2 for information on paediatric use)."

Proposed wording

Paediatric population

"A total of 8 adolescents (12 to 17 years) on haemodialysis were enrolled in an openlabel, single arm study to evaluate the pharmacokinetics of a single dose of intravenous difelikefalin. It has been demonstrated that the administration of a single dose of difelikefalin of 0.5 µg/kg, based on dry body weight provides comparable exposure between adolescents and adults on HD. The safety profile of difelikefalin 0.5 µg/kg of dry body weight, administered in adolescents as a single intravenous dose, was consistent with the known safety profile of difelikefalin in adults.

The European Medicines Agency has deferred the obligation to submit the results of studies with difelikefalin in one or more subsets of the paediatric population in the treatment of chronic kidney disease associated pruritus (see section 4.2 for information on paediatric use)."

Assessors comment:

The MAH provided as requested a wording including the new knowledge acquired from the KOR-PED-201 study. This is endorsed.

Issue resolved.

5. CHMP overall conclusion and recommendation – after the assessment of the response

It has been demonstrated that the administration of a single dose of difelikefalin of 0.5 µg/kg, based on dry body weight provides comparable exposure in adolescents as in adults on HD.

The safety profile of difelikefalin 0.5 µg/kg of dry body weight, administered in adolescents as a single IV dose, was consistent with the known safety profile of difelikefalin in adults.

☒ **Fulfilled**

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

"An Open-label, Single Arm Study to Evaluate the Pharmacokinetics of a Single Dose of Intravenous Difelikefalin in Adolescents Aged 12 to 17 Years on Haemodialysis".

Clinical studies

Product Name: Kapruvia Active substance: difelikefalin

Study title	Study number	Date of completion	Date of submission of final study report
KOR-PED-201, "An Open-label, Single Arm Study to Evaluate the Pharmacokinetics of a Single Dose of Intravenous Difelikefalin in Adolescents Aged 12 to 17 Years on Haemodialysis"	2021-000894-94	30 May 2023	20 November 2023