IQWiG Reports – Commission No. A20-120

# Sucroferric oxyhydroxide (control of serum phosphorus levels in paediatric patients with CKD) –

## Benefit assessment according to §35a Social Code Book V[1]

## Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Sucroferric Oxyhydroxide (Serumphosphatkontrolle bei Kindern und Jugendlichen mit CKD) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 10 March 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

**List of abbreviations**

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| AE | adverse event |
| CKD | chronic kidney disease |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| RCT | randomized controlled trial |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SPC | Summary of Product Characteristics |

# 2 Benefit assessment

## 2.1 Executive summary of the benefit assessment

### Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug sucroferric oxyhydroxide. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 14 December 2020.

### Research question

The aim of this report is to assess the added benefit of sucroferric oxyhydroxide in comparison with therapy upon the physician's discretion as the appropriate comparator therapy (ACT) for the control of serum phosphorous level in children and adolescents 2 years and older with chronic kidney disease (CKD) stage 4 to 5 (as defined by a glomerular filtration rate < 30 mL/min/1.73 m²) or with CKD requiring dialysis. Table 2 shows the research question of the present benefit assessment.

Table 2: Research question of the benefit assessment of sucroferric oxyhydroxide

| **Indication** | **ACT**[a] |
|---|---|
| Control of serum phosphorous levels in children and adolescents 2 years and older in CKD stage 4 to 5 (as defined by a glomerular filtration rate < 30 mL/min/1.73 m²) or with CKD requiring dialysis | Therapy upon the physician's discretion[b] |
| a. Presented is the ACT specified by the G-BA.<br>b. Guidelines recommend calcium-containing phosphate binders (individually or in combination) and sevelamer carbonate for reducing phosphorous levels in children and adolescents with CKD. In the present indication, calcium-containing phosphate binders are not approved for children and adolescents. Sevelamer carbonate is approved for the treatment of hyperphosphataemia in children with CKD who are > 6 years old and have a body surface area > 0.75 m². There is a discrepancy between the drugs approved for the indication versus those used in practice and recommended by the guidelines. In clinical studies, the following drugs and drug classes may be taken into consideration as comparators: calcium-containing phosphate binders and sevelamer carbonate.<br>ACT: appropriate comparator therapy; CKD: chronic kidney disease; G-BA: Federal Joint Committee | |

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier in comparison with the ACT specified by the G-BA. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

**Results**

***Study pool and study characteristics***

The study pool consists of the study PA-CL-PED-01, an open-label, multicentre RCT comparing sucroferric oxyhydroxide with calcium acetate for controlling serum phosphorous levels in children and adolescents with CKD.

The PA-CL-PED-01 study included children and adolescents ≥ 2 to < 18 years of age with hyperphosphataemia due to CKD stage 4 or 5. CKD had to be in stage 4 or 5 (estimated glomerular filtration rate < 30 mL/min/1.73m²) or stage 5D (≥ 2 months of adequate maintenance haemodialysis or peritoneal dialysis prior to study inclusion). A total of 85 children and adolescents, stratified by age group, were randomly allocated to treatment, 66 of whom were allocated to the sucroferric oxyhydroxide arm and 19 to the calcium acetate arm.

The PA-CL-PED-01 study consisted of a titration phase taking up to 10 weeks (Stage 1) and a 24-week maintenance phase (Stage 2). After completing at least 4 weeks of treatment and reaching a serum phosphorous level within the age-specific target range, the children and adolescents were allowed to switch from the titration phase to the maintenance phase. This design results in a minimum treatment duration of 28 weeks and a maximum treatment duration of 34 weeks.

The treatment in the intervention arm was in accordance with the Summary of Product Characteristics (SPC) of sucroferric oxyhydroxide. Although control arm treatment – calcium acetate – is not approved for children and adolescents, calcium acetate is recommended by guidelines and specified by the G-BA as a possible control in clinical trials. The dosage used in the PA-CL-PED-01 study is in line with guidelines. The PA-CL-PED-01 study provided for appropriate therapy of the underlying disease.

The primary outcome of the study was change in serum phosphorous level in the intervention arm to the end of the titration phase. Secondary outcomes were the comparison of serum phosphorous levels in the intervention and control arms as well as adverse events (including fatalities). Neither health-related quality of life nor patient-relevant outcomes on morbidity were surveyed.

***Implementation of the ACT***

The G-BA specified therapy upon the physician's discretion as the ACT and listed calcium-containing phosphate binders and sevelamer carbonate as potential comparators in clinical trials. The PA-CL-PED-01 study used calcium acetate as the only drug in the control arm. Therefore, any conclusions, e.g. on any added benefit of sucroferric oxyhydroxide, can be drawn only in comparison with calcium acetate. The company's dossier does not supply any data on any other phosphate binders.

***Data from the PA-CL-PED-01 study not usable***

The data from the PA-CL-PED-01 study are unsuitable for answering the present research question. This is due to systematically shortened follow-up durations.

For patients who had discontinued the study drug, the follow-up observation was discontinued as per study protocol. As a result, the follow-up durations for all outcomes are systematically shortened. Drawing reliable conclusions for the entire study duration of at least 24 weeks would have required surveying the outcomes for the entire period (potentially under further treatment with subsequent therapies).

In a very high percentage of patients, the study drug was discontinued, with the discontinuations occurring very early and differing in frequency between study arms. Slightly more than a third of patients in the intervention arm and slightly more than half of those in the control arm discontinued the study drug already during the titration phase. Markedly fewer than half of patients continued the study drug to the end of the maintenance phase. The most common reasons for leaving the study were discontinuation due to adverse events (AE) (12 patients in the intervention arm and 6 in the control arm) and kidney transplantation (11 versus 4 patients). The data on treatment duration show that fewer than half of patients in the intervention arm and presumably even fewer than a quarter of patients in the control arm continued treatment for 24 weeks. Certainly, in half of patients of the control arm, treatment lasted a maximum of 7 weeks.

Due to the low percentage of patients who completed 24 weeks of the study, no conclusion can be drawn on the added benefit of sucroferric oxyhydroxide after a minimum study duration of 24 weeks.

***Central patient-relevant outcomes for the present therapeutic indication not surveyed***

The PA-CL-PED-01 study surveyed only outcomes on laboratory values and AEs, with the outcome of all-cause mortality being operationalized through fatal AEs. Hence, no data are available on health-related quality of life, symptoms, or late complications. Surveying patient-relevant outcomes on morbidity, such as renal osteopathies, developmental disorders, or cardiovascular events, requires long-term investigations with a duration of at least 12 months.

***Summary***

Based on its design, the PA-CL-PED-01 study is relevant for deriving an added benefit of sucroferric oxyhydroxide in comparison with calcium acetate. However, the data are unusable because the majority of patients in the PA-CL-PED-01 study did not complete the follow-up duration of 24 weeks required in the presence of chronic disorders. This loss to follow-up is explained by the fact that a very large percentage of patients discontinued the study drug at a very early time and, as per study protocol, follow-up ended 2 weeks after discontinuation of the study drug. Further, the percentages of patients who discontinued study participation differed greatly between the two treatment arms. In addition, the study failed to survey central patient-relevant outcomes for the present therapeutic indication.

***Results on added benefit***

The data from the PA-CL-PED-01 study are unsuitable for assessing the added benefit of sucroferric oxyhydroxide in comparison with calcium acetate. Consequently, there is no hint of an added benefit of sucroferric oxyhydroxide in comparison with calcium acetate; an added benefit is therefore not proven.

Since the company's dossier provides no data on the other treatment options of the ACT (therapy upon the physician's discretion, choosing from calcium-containing phosphate binders and sevelamer carbonate), there is no hint of added benefit of sucroferric oxyhydroxide in comparison with these treatment options. An added benefit is therefore not proven.

## Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of added benefit of sucroferric oxyhydroxide.

Table 3: Sucroferric oxyhydroxide – probability and extent of added benefit

| Indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|
| Control of serum phosphorous levels in children and adolescents 2 years and older in CKD stage 4 to 5 (as defined by a glomerular filtration rate < 30 mL/min/1.73 m²) or with CKD requiring dialysis | Therapy upon the physician's discretion[b] | Added benefit not proven |

a. Presented is the ACT specified by the G-BA.
b. Guidelines recommend calcium-containing phosphate binders (individually or in combination) and sevelamer carbonate for reducing phosphorous levels in children and adolescents with CKD. In the present indication, calcium-containing phosphate binders are not approved for children and adolescents. Sevelamer carbonate is approved for the treatment of hyperphosphataemia in children with CKD who are > 6 years old and have a body surface area > 0.75 m². There is a discrepancy between the drugs approved for the indication versus those used in practice and recommended by the guidelines. In clinical studies, the following drugs and drug classes may be taken into consideration as comparators: calcium-containing phosphate binders and sevelamer carbonate.

ACT: appropriate comparator therapy; CKD: chronic kidney disease; G-BA: Federal Joint Committee

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

## 2.2 Research question

The aim of this report is to assess the added benefit of sucroferric oxyhydroxide in comparison with therapy upon the physician's discretion as the ACT for the control of serum phosphorous level in children and adolescents 2 years and older with CKD stage 4 to 5 (as defined by a glomerular filtration rate < 30 mL/min/1.73 m²) or with CKD requiring dialysis. Table 4 shows the research question of the present benefit assessment.

Table 4: Research question of the benefit assessment of sucroferric oxyhydroxide

| **Indication** | **ACT[a]** |
|---|---|
| Control of serum phosphorous levels in children and adolescents 2 years and older in CKD stage 4 to 5 (as defined by a glomerular filtration rate < 30 mL/min/1.73 m²) or with CKD requiring dialysis | Therapy upon the physician's discretion[b] |
| a. Presented is the ACT specified by the G-BA.<br>b. Guidelines recommend calcium-containing phosphate binders (individually or in combination) and sevelamer carbonate for reducing phosphorous levels in children and adolescents with CKD. In the present indication, calcium-containing phosphate binders are not approved for children and adolescents. Sevelamer carbonate is approved for the treatment of hyperphosphataemia in children with CKD who are > 6 years old and have a body surface area > 0.75 m². There is a discrepancy between the drugs approved for the indication versus those used in practice and recommended by the guidelines. In clinical studies, the following drugs and drug classes may be used as comparators: calcium-containing phosphate binders and sevelamer carbonate.<br>ACT: appropriate comparator therapy; CKD: chronic kidney disease; G-BA: Federal Joint Committee | |

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided in the company's dossier compared with the ACT specified by the G-BA. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This departs from the inclusion criteria used by the company, which provided no information on the minimum study durations.

## 2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources cited by the company in the dossier:

- Study lists on sucroferric oxyhydroxide (status: 2 December 2020)
- Bibliographic literature search on sucroferric oxyhydroxide (most recent search on 10 November 2020)
- Search in trial registries / study results databases on sucroferric oxyhydroxide (most recent search on 6 December 2020)
- Search on the G-BA website for sucroferric oxyhydroxide (most recent search on 6 December 2020)

To check the completeness of the study pool:

- Search in trial registries on sucroferric oxyhydroxide (most recent search on 17 December 2020)

The check did not identify any additional relevant studies.

### 2.3.1 Included studies

The study listed in the table below was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: sucroferric oxyhydroxide versus therapy upon the physician's discretion

| Study | Study category | | | Available sources | | |
|---|---|---|---|---|---|---|
| | Approval study for the drug to be assessed (yes/no) | Sponsored study[a] (yes/no) | Third-party study (yes/no) | Clinical study report (yes/no [reference]) | Registry entries[b] (yes/no [reference]) | Publication (yes/no [reference]) |
| PA-CL-PED-01 | Yes | Yes | No | No[c] | Yes [3,4] | Yes [5] |

a. Study sponsored by the company.
b. References of trial registry entries and reports on the study design and/or results listed in the trial registries.
c. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the study report in Module 5 of the dossier.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool is consistent with that of the company.

### 2.3.2 Study characteristics

#### 2.3.2.1 Description of the PA-CL-PED-01 study

Table 6 and Table 7 present the study used in the benefit assessment.

Table 6: Characterization of the included study – RCT, direct comparison: sucroferric oxyhydroxide vs. calcium acetate

| Study | Study design | Population | Interventions (number of randomized patients) | Study duration | Location and time period conducted | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|
| PA-CL-PED-01 | RCT, open-label, parallel-group | Children and adolescents (< 18 years) with hyperphosphataemia due to CKD in stage 4 or 5, defined by:<br>▪ Estimated GFR[b] < 30 mL/min/1.73m² or<br>▪ with ≥ 2 months of adequate maintenance haemodialysis or peritoneal dialysis;<br>▪ with or without prior treatment with phosphate binders | Sucroferric oxyhydroxide (N = 66)<br>Calcium acetate (N = 19) | Screening: ≤ 7 weeks[c]<br>Treatment: 28 to 34 weeks<br>▪ Titration phase (Stage 1) 4 to 10 weeks<br>▪ Maintenance phase (Stage 2) 24 to 10 weeks<br>Follow-up observation: 2 weeks | France, Germany, Lithuania, Poland, Romania, Russia, United States<br>05/2016 – 02/2019 | Primary: Change in serum phosphorus level in the intervention arm to the end of the titration phase (Stage 1)<br>Secondary: AEs, fatal AEs |

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Estimated GFR as per Schwartz 2009 [6] based on data from Greenbaum 2020 [5].
c. Including a washout period of ≤ 3 weeks for children and adolescents who had already received phosphate binder treatment prior to the study start.

AE: adverse event; GFR: glomerular filtration rate; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characterization of the interventions – RCT, direct comparison: Sucroferric oxyhydroxide vs. calcium acetate

| Study | Intervention | Comparison |
|---|---|---|
| PA-CL-PED-01 | Sucroferric oxyhydroxide powder[a] or chewable tablet, oral | Calcium acetate oral solution, 667 mg per 5 mL |
| | Starting dose:<br>▪ 0 to < 1 year: 125 mg iron/day<br>▪ 1 to < 6 years: 500 mg iron/day<br>▪ 6 to < 9 years: 750 mg iron/day<br>▪ 9 to < 18 years: 1250 mg iron/day | Starting dose:<br>0.45 mL calcium acetate solution per kg body weight daily or a dose equivalent to that of the phosphate binder taken prior to study inclusion |
| | Dose changes:<br>▪ Efficacy: Dose increase or decrease to achieve age-specific target serum phosphorous level, provided the dose has been given for a minimum of 2 weeks<br>▪ Safety: any time<br>▪ 0 to < 6 years: increments of 125 mg or 250 mg iron/day<br>▪ 6 to < 9 years: increments of 125 mg, 250 mg, or 375 mg iron/day<br>▪ 9 to < 18 years: increments of 250 mg or 500 mg iron/day | Increments of 0.1 mL to 0.2 mL calcium acetate solution / kg body weight / day |
| | Maximum dose:<br>▪ 0 to < 1 year: 1000 mg iron/day<br>▪ 1 to < 6 years: 1250 mg iron/day<br>▪ 6 to < 9 years: 2500 mg iron/day<br>▪ 9 to < 18 years: 3000 mg iron/day | Maximum dose:<br>▪ ≤ 35 kg body weight: 1.25 mL calcium acetate solution / kg body weight / day<br>▪ > 35 kg body weight: 44 mL calcium acetate solution / day |
| | Discontinuation of study participation if serum phosphorous level or corrected total calcium level was outside the age-dependent safety range even after medication adjustment, or immediate discontinuation at corrected total serum calcium level < 1.63 mmol/L or > 3.0 mmol/L. | |
| | **Prior treatment**<br>▪ Maximum of 2 phosphate binders (e.g. sevelamer or other calcium-based phosphate binder)<br><br>**Concomitant treatment**<br><u>Disallowed</u><br>▪ Oral calcium supplements<br>▪ Antacids with aluminium, calcium, or magnesium<br>▪ Additional phosphate binders<br>▪ Antiarrhythmics or anticonvulsants<br>▪ Start of dialysis after randomization | |

a. For preparing a suspension.

RCT: randomized controlled trial

The PA-CL-PED-01 study is an open-label, multicentre RCT comparing sucroferric oxyhydroxide with calcium acetate for controlling the serum phosphorous level in children and adolescents with CKD.

The PA-CL-PED-01 study was to include children and adolescents 0 to < 18 years of age with hyperphosphataemia due to CKD stage 4 or 5 (see Table 8 for the hyperphosphataemia inclusion criterion). Children and adolescents > 1 to < 18 years of age had to be in CKD stage 4 or 5, while children < 1 year of age would have been eligible for inclusion regardless of CKD stage. CKD had to be in stage 4 or 5 (defined by an estimated glomerular filtration rate < 30 mL/min/1.73 m²) or in stage 5D (defined as ≥ 2 months adequate maintenance haemodialysis or peritoneal dialysis prior to study inclusion). Children treated with phosphate binders prior to study inclusion had to have received a maximum of 2 phosphate binders simultaneously and have been at a stable dose for ≥ 1 month prior to screening. Treatment with existing phosphate binders had to be discontinued prior to randomization, possibly followed by a wash-out phase of up to 3 weeks. Patients were to be randomly allocated to treatment as soon as the serum phosphorous level met the age-specific inclusion criterion (see Table 8). According to the study protocol, a total of 130 children were to be randomly allocated, stratified by age group, to the study treatment (sucroferric oxyhydroxide: 100 children and adolescents; calcium acetate: 30 children and adolescents). However, the study was terminated early due to recruitment problems. The early termination was coordinated with the European Medicines Agency. The last visit took place on 21 February 2019 [7]. Due to early termination of the study, a total of only 85 children and adolescents, ≥ 2 and < 18 years of age, were randomly allocated to their treatment; 66 of these children and adolescents were in the sucroferric oxyhydroxide arm versus 19 in the calcium acetate arm.

The PA-CL-PED-01 study consisted of a titration phase taking up to 10 weeks (Stage 1) and a 24-week maintenance phase (Stage 2). After completing at least 4 weeks of treatment and reaching a serum phosphorous level within the age-specific target range presented in Table 8, the children and adolescents were allowed to switch from the titration phase to the maintenance phase. This design results in a minimal treatment duration of 28 weeks and a maximum treatment duration of 34 weeks.

Table 8: Age-specific inclusion criteria, target ranges, and upper safety limits of serum phosphorous levels in the PA-CL-PED-01 study

| **Study** | **Age-specific serum phosphorous level** | | | | | |
|---|---|---|---|---|---|---|
| **PA-CL-PED-01** | **Inclusion criterion[a]** | | **Target range[a, b]** | | **Upper safety limit[a]** | |
| **Age** | mmol/L | mg/dL | mmol/L | mg/dL | mmol/L | mg/dL |
| ≥ 2 to < 6 years | ≥ 2.02 | ≥ 6.3 | 1.45–2.10 | 4.5–6.5 | 2.42 | 7.5 |
| ≥ 6 to < 13 years | ≥ 1.77 | ≥ 5.5 | 1.16–1.87 | 3.6–5.8 | 2.26 | 7.0 |
| ≥ 13 to < 18 years | ≥ 1.36 | ≥ 4.2 | 0.74–1.45 | 2.3–4.5 | 2.26 | 7.0 |

a. As indicated in study protocol.
b. Corresponds to the normal range as per [8].

The age-specific target ranges of the serum phosphorous levels are in line with the guidelines (e.g. [8]).

Treatment in the intervention arm was in accordance with the SPC of sucroferric oxyhydroxide (see [9,10]).

Treatment in the control arm – calcium acetate – is not approved for children and adolescents; however, calcium acetate is recommended in the guidelines and designated by the G-BA as a possible comparator in a clinical trial (see Table 4). Dosage in the PA-CL-PED-01 study is in accordance with the specifications in the guidelines (e.g. KDOQI Work Group [8] and Klaus 2006 [11]).

The study disallowed the use of several treatments as concomitant treatments (see Table 7). The start of some of the disallowed concomitant treatments (e.g. start of dialysis after randomization) required the affected patients to discontinue treatment with the study drug, which in turn resulted in the termination of follow-up. Since only a few patients discontinued the study drug for these reasons, adequate therapy of the underlying illness was ensured despite the prohibition of certain concomitant treatments.

The primary outcome of the study was change in serum phosphorous levels in the intervention arm to the end of the study's titration phase (Stage 1). Secondary outcomes were the comparison of serum phosphorous levels in the intervention and control arms as well as side effects (fatalities were surveyed through this outcome as well). Health-related quality of life or patient-reported outcomes on morbidity were not surveyed.

#### 2.3.2.2 Implementation of the ACT

The G-BA specified therapy upon the physician's discretion as the ACT. In this context, possible comparators are calcium-containing phosphate binders and sevelamer carbonate. In a direct comparative study, the implementation of "therapy upon the physician's discretion" requires that the investigator have a choice among several treatment options. The available selection and potential limitation of treatment options must be justified.

The PA-CL-PED-01 study used calcium acetate as the comparator. In Module 4 A (Section 4.3.1), the company argues that the investigator was free to choose a comparator other than calcium acetate (e.g., sevelamer carbonate) at the start of the study, provided that doing so was necessary in the investigator's medical opinion. The company has concluded that the selection of possible comparators provided in the PA-CL-PED-01 study fulfils the requirements regarding the ACT. IQWiG does not share this opinion. The information provided in the study protocol refers to the calcium acetate starting dose in the control arm and not to the choice of drug. According to the study protocol, patients were to receive calcium acetate either at the starting dose indicated by the dosing regimen in the study protocol or, if deemed more appropriate by the investigator, at a starting dose equivalent to that of the phosphate binder (calcium based or sevelamer) administered prior to study inclusion.

Therefore, any conclusions, e.g. on any added benefit of sucroferric oxyhydroxide, can be drawn only in comparison with calcium acetate. The company's dossier does not supply any data on any other phosphate binders.

#### 2.3.2.3 Patient characteristics

Table 9 shows the patient characteristics of the included study.

Table 9: Characterization of the study population – RCT, direct comparison: Sucroferric oxyhydroxide vs. calcium acetate (multipage table)

| **Study**<br>**Characteristic**<br>**Category** | **Sucroferric oxyhydroxide**<br>**n[a] = 65** | **Calcium acetate**<br>**n[a] = 15** |
|---|---|---|
| **PA-CL-PED-01** | | |
| Age [years], mean (SD) | 12.1 (4.1) | 12.3 (4.0) |
| Age groups, n (%) | | |
| 2 to < 6 years | 6 (9.2) | 1 (6.7) |
| 6 to < 12 years | 17 (26.2) | 4 (26.7) |
| 12 to < 18 years | 42 (64.6) | 10 (66.7) |
| Sex [f/m], % | 52/48 | 67/33 |
| Family origin, n (%) | | |
| Caucasian | 43 (66.2[b]) | 11 (73.3) |
| African American | 9 (13.8[b]) | 2 (13.3) |
| Other or missing | 13 (20.0)[b, c] | 2 (13.3)[b, c] |
| Region, n (%) | | |
| USA | 38 (58.5) | 11 (73.3 %) |
| Other than USA | 27 (41.5) | 4 (26.7) |
| Aetiology of CKD, n (%) | | |
| Congenital anomalies of the kidneys and urinary tract | 19 (29.2) | 3 (20.0) |
| Glomerulonephritis | 10 (15.4) | 4 (26.7) |
| Hypodysplasia and reflux | 2 (3.1) | 2 (13.3) |
| Obstructive uropathy | 8 (12.3) | 1 (6.7) |
| Polycystic kidney disease | 3 (4.6) | 0 (0.0) |
| Other | 23 (35.4) | 5 (33.3) |
| Disease duration at baseline, in years | | |
| Median ($Q_1$; $Q_3$) | 5.4 (1.5; 11.6) | 3.5 (1.7; 6.7) |
| Min, max | 0.1; 17.5 | 0.8; 12.0 |
| CKD stage, n (%) | | |
| 4 | 13 (20.0) | 1 (6.7) |
| 5 | 52 (80.0) | 14 (93.3) |

Table 9: Characterization of the study population – RCT, direct comparison: Sucroferric oxyhydroxide vs. calcium acetate (multipage table)

| **Study** **Characteristic** **Category** | **Sucroferric oxyhydroxide** **n[a] = 65** | | **Calcium acetate** **n[a] = 15** | |
|---|---|---|---|---|
| Dialysis at baseline, n (%) | | | | |
| Dialysis | 50 (76.9)[b] | | 14 (93.3)[b] | |
| Haemodialysis | 45 (69.2) | | 9 (60.0) | |
| Peritoneal dialysis | 5 (7.7) | | 5 (33.3) | |
| No dialysis | 15 (23.1) | | 1 (6.7) | |
| Prior treatment with phosphate binders, n (%) | | | | |
| Yes | 47 (72.3) | | 12 (80.0) | |
| No | 18 (27.7) | | 3 (20.0) | |
| Serum phosphorous level per age group at randomization | mmol/L | mg/dL | mmol/L | mg/dL |
| 2 to < 6 years | | | | |
| Mean (SD) | 2.4 (0.6) | 7.3 (2.0) | 1.9 (NC) | 6.0 (NC) |
| Median ($Q_1$; $Q_3$) | 2.4 (2.0; 3.0) | 7.5 (6.2; 9.2) | – | – |
| 6 to < 12 years | | | | |
| Mean (SD) | 2.2 (0.6) | 6.9 (1.9) | 2.3 (1.3) | 7.2 (3.9) |
| Median ($Q_1$; $Q_3$) | 2.2 (2.0; 2.5) | 6.8 (6.1; 7.6) | 2.3 (1.4; 3.3) | 7.2 (4.4; 10.1) |
| 12 to < 18 years | | | | |
| Mean (SD) | 2.0 (0.5) | 6.1 (1.5) | 2.1 (0.4) | 6.5 (1.2) |
| Median ($Q_1$; $Q_3$) | 1.9 (1.6; 2.3) | 5.9 (5.0; 7.0) | 2.1 (1.9; 2.3) | 6.5 (5.8; 7.1) |
| Serum phosphorous level at randomization, n (%) | | | | |
| Below lower limit of target range[d] | 2 (3.0) | | 1 (6.7) | |
| Within target range[d] | 11 (16.9) | | 1 (6.7) | |
| Above upper limit of target range[d] | 52 (80.0) | | 13 (86.7) | |
| Treatment discontinuation in titration phase (Stage 1), n (%)[e] | 23 (34.8[b]) | | 11 (57.9[b]) | |
| Treatment discontinuation in maintenance phase (Stage 2), n (%)[e] | 17 (25.8[b]) | | 6 (31.6[b]) | |
| Treatment discontinuation, total, n (%)[e] | 40 (60.6) | | 17 (89.5) | |
| Study discontinuation, n (%) | ND | | ND | |

a. Number of patients for whom the patient characteristics provided by the company are presented: patients with at least 1 dose of the study drug and at least 1 serum phosphorous value after randomization. Number of randomized patients N = 66 vs. N = 19.
b. IQWiG calculations.
c. Four categories: other origin, not further specified; Hawaiian or other Pacific Islander; Native American; missing.
d. See target range column in Table 8.
e. Data based on all 66 versus 19 randomized patients.

CKD: chronic kidney disease; f: female; m: male; n: Number of patients in the category; values which are based on different patient numbers are marked in the corresponding column if the deviation is relevant; N: number of randomized patients; NC: not calculable; ND: no data; $Q_1$: 1st quartile or 25% quantile; $Q_3$: 3rd quartile or 75% quantile; RCT: randomized controlled trial; SD: standard deviation

Patient characteristics are largely comparable between treatment arms. At 66%, adolescents 12 to 18 years of age made up the largest percentage of the study population. Slightly more than half of patients were female. In total, about 70% of patients were of Caucasian origin, and nearly two-thirds of patients were from the United States.

The vast majority of patients were in CKD stage 5, and almost all of these patients were on dialysis. About 75% of patients had received prior treatment with phosphate binders at baseline. In about 80% of patients, the serum phosphorous level at the start of study treatment was above the upper limit of the target range.

## 2.4 Results on added benefit: Data from the PA-CL-PED-01 study not usable

The data from the PA-CL-PED-01 study are unsuitable for answering the present research question. This is due to systematically shortened follow-up durations. For patients who discontinued taking the study drug, the follow-up observation was discontinued as per study protocol. As a result, the follow-up durations for all outcomes are systematically shortened. Hence, it is impossible to draw any conclusions on the added benefit of sucroferric oxyhydroxide after a minimum study duration of 24 weeks. In addition, central patient-relevant outcomes were not surveyed in the study presented by the company.

### 2.4.1 Discontinuation of the study drug and differences in treatment duration

Table 10 shows the number of patients who discontinued the study drug as well as the mean and median treatment durations.

Table 10: Discontinuation of the study drug, reasons for discontinuation, and treatment duration – RCT, direct comparison: sucroferric oxyhydroxide vs. calcium acetate

| **Study**<br>**Category** | **Sucroferric oxyhydroxide**<br>**N = 66** | **Calcium acetate**<br>**N = 19** |
|---|---|---|
| **PA-CL-PED-01** | | |
| Study drug taken until the end of the maintenance phase (Stage 2), n (%) | 26 (39.4) | 2 (10.5) |
| Study drug discontinued, n (%) | 40 (60.6) | 17 (89.5) |
| in titration phase (Stage 1), n (%) | 23 (34.8) | 11 (57.9) |
| in maintenance phase (Stage 2), n (%) | 17 (25.8) | 6 (31.6) |
| Reasons for discontinuation, aggregated for Stage 1 and Stage 2 (multiple answers possible), n | | |
| AE | 12 | 6 |
| Kidney transplantation | 11 | 4 |
| Poor adherence | 8 | 4 |
| Parents' / legal representatives' decision | 8 | 2 |
| Lack of efficacy | 4 | 3 |
| Investigator's decision | 4 | 2 |
| Patient's decision | 3 | 4 |
| Other | 5 | 2 |
| Treatment duration, titration phase (Stage 1) [weeks] | | |
| Mean (SD) | 6.5 (3.3)[a] | 5.4 (4.1)[a] |
| Median (min; max) | 6.1 (0.4; 12.1)[a] | 5.1 (0.1; 10.6)[a] |
| Treatment duration, total (titration phase [Stage 1] and maintenance phase [Stage 2]) [weeks] | | |
| Mean (SD) | 18.1 (12.0)[a] | 10.6 (10.5)[a] |
| Median (min; max) | 18.3 (0.4; 35.0)[a] | 7.0 (0.1; 34.1)[a] |
| Follow-up period | ND[b] | ND[b] |

a. IQWiG calculations; data provided by the company converted from days to weeks.
b. As per study protocol, the follow-up observation was to finish with a final visit 14 days after the last dose of the study drug.

n: number of patients per category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

As shown in Table 10, slightly more than a third of patients in the intervention arm and slightly more than half of patients in the control arm discontinued the study drug already in the titration phase. Substantially less than half of patients continued the study drug to the end of the maintenance phase, namely about 40% in the intervention arm and even fewer, 11%, in the control arm. The early discontinuation of the study drug is reflected by the greatly shortened mean and median treatment durations. For instance, mean treatment duration (and standard deviation) was 18.1 (12.0) weeks in the intervention arm and 10.6 (10.5) weeks in the control arm. On the basis of these data and the median treatment durations (18.3 versus 7.0 weeks), fewer than 50% of patients in the intervention arm and likely even fewer than 25% of patients

in the control arm completed 24 weeks. Certainly, half of patients of the control arm are known to have had a treatment duration of no more than 7 weeks. Since, according to the study protocol, data were collected only for the period of treatment with the study drug (plus 14 days), the follow-up durations are systematically shortened for all outcomes. Drawing reliable conclusions for the entire study duration of at least 24 weeks would have required surveying the outcomes across the entire period (potentially under further treatment with subsequent therapies). In addition, due to the discontinuation of follow-up, no data are available on follow-up therapies given after the end of the study drug (see [3,5,7]).

The results on patient-relevant outcomes (fatalities and adverse events [AEs]) as well as common AEs are presented as supplementary information in Appendix A and Appendix B of the full dossier assessment. Irrespective of their relevance for patients, results on laboratory values (e.g. serum phosphorous level) are not presented as supplementary information, since the analysis did not include all patients, with a difference between treatment arms > 15 percentage points.

### 2.4.2 Central patient-relevant outcomes for the present therapeutic indication not surveyed

The PA-CL-PED-01 study surveyed only outcomes on laboratory values and side effects, with the outcome of all-cause mortality being operationalized in the company's dossier through fatal AEs. Hence, no data are available on health-related quality of life or symptoms. Furthermore, in terms of patient-relevant outcomes, no data are available which would permit a comparison of the extent to which late complications of hyperphosphataemia in CKD are prevented by sucroferric oxyhydroxide versus by calcium acetate. Potential patient-relevant outcomes (e.g. see [8,12-19]) include outcomes to survey renal osteopathy (e.g. bone and muscle pain, bone deformity and joint damage), developmental disorders, and cardiovascular events (e.g. as the result of hypercalcaemia).

For surveying the above-mentioned patient-relevant outcomes, long-term investigations with a duration of at least 12 months are recommended [12]. This would also meet a requirement of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline E1 [20], which calls for a minimum exposure for drugs intended for the long-term treatment of non-life-threatening conditions as 100 patients exposed for a minimum of 1 year.

### 2.4.3 Summary

Based on its design, the PA-CL-PED-01 study is relevant for deriving an added benefit of sucroferric oxyhydroxide in comparison with calcium acetate. However, the data from the study are unusable because the majority of patients in the PA-CL-PED-01 study did not complete the 24-week follow-up duration required for chronic disorders. This is due to the fact that a very large percentage of patients discontinued the study drug at a very early time, and as per study protocol, follow-up ended 2 weeks after discontinuation of the study drug. The percentages of

patients who discontinued study participation widely differed between the two treatment arms. In addition, the study failed to survey central patient-relevant outcomes for the present therapeutic indication.

## 2.5 Probability and extent of added benefit

The study presented by the company (PA-CL-PED-01) was conducted in comparison with calcium acetate as the only comparator among multiple treatment options in the present therapeutic indication (see next section). As discussed in Section 2.4, the data from the PA-CL-PED-01 study are unsuitable for assessing any added benefit of sucroferric oxyhydroxide in comparison with calcium acetate. Consequently, there is no hint of an added benefit of sucroferric oxyhydroxide in comparison with calcium acetate; an added benefit is therefore not proven.

Since the company's dossier provides no data on the other treatment options of the ACT (therapy upon the physician's discretion, choosing from calcium-containing phosphate binders and sevelamer carbonate), there is no hint of added benefit of sucroferric oxyhydroxide in comparison with these treatment options. An added benefit is therefore not proven.

Table 11 presents a summary of the results of the benefit assessment of sucroferric oxyhydroxide in comparison with the ACT.

Table 11: Sucroferric oxyhydroxide – probability and extent of added benefit

| **Indication** | **ACT[a]** | **Probability and extent of added benefit** |
|---|---|---|
| Control of serum phosphorous levels in children and adolescents 2 years and older in CKD stage 4 to 5 (as defined by a glomerular filtration rate < 30 mL/min/1.73 m²) or with CKD requiring dialysis | Therapy upon the physician's discretion[b] | Added benefit not proven |

a. Presented is the ACT specified by the G-BA.
b. Guidelines recommend calcium-containing phosphate binders (individually or in combination) and sevelamer carbonate for reducing phosphorous levels in children and adolescents with CKD. In the present indication, calcium-containing phosphate binders are not approved for children and adolescents. Sevelamer carbonate is approved for the treatment of hyperphosphataemia in children with CKD who are > 6 years old and have a body surface area > 0.75 m². There is a discrepancy between the drugs approved for the indication versus those used in practice and recommended by the guidelines. In clinical studies, the following drugs and drug classes may be taken into consideration as comparators: calcium-containing phosphate binders and sevelamer carbonate.

ACT: appropriate comparator therapy; CKD: chronic kidney disease; G-BA: Federal Joint Committee

The assessment described above deviates from that by the company, which derived a hint of non-quantifiable added benefit.

The approach for deriving an overall conclusion on added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

**References for English extract**

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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*The full report (German version) is published under https://www.iqwig.de/en/projects/a20-120.html.*