Medicinrådet

Bilag til Medicinrådets anbefaling vedrørende roxadustat til symptomatisk anæmi forbundet med kronisk nyresygdom

Vers. 1.0

Bilagsoversigt

1. Ansøgers notat til Rådet vedr. roxadustat
2. Forhandlingsnotat fra Amgros vedr. roxadustat
3. Ansøgers endelige ansøgning vedr. roxadustat

Att: Medicinrådet

24th february 2023

Astellas Pharma a/s' comments on the Danish Medicines Council assessment report for roxadustat for symptomatic anemia in CKD

Astellas Pharma a/s would like to thank the Danish Medicine Council's (DMC) for a thorough assessment of roxadustat and for a constructive dialogue during the process. Overall, Astellas agree with the conclusions in the report except with regard to the use of IV iron, where it is stated in section "2.4.5 Brug af IV-jern: *Medicinrådet vurderer, at behandlingen med roxadustat og komparator er ligeværdig med hensyn til bruget af IV-jern.*"

- For the ND population, the DOLOMITES study finds that time (weeks) to first use IV iron was significant longer (9.9 versus 20.6) in roxadustat patients compared with patients receiving darbepoetin (hazard ratio 0.45, 95% CI 0.26-0.78, superiority met). In patients receiving iron, the mean (SD) monthly dose of IV iron during weeks 1-36 was 34.74 (29.96) mg and 69.57 (67.34) mg in the roxadustat and darbepoetin groups respectively. [1]. During weeks 52-104, the average monthly IV dose per participant was 18.7 mg/month (95% CI: 10.4; 27) in the roxadustat group and 31.3 mg/month (95% CI: 19.4; 43.2) [2]
- Similarly, the IDD pooled analysis shows that the mean monthly IV iron dose in week 28-52 was lower in the roxadustat group compared to the ESA group (53.57 mg/month vs 70.22 mg/month; difference in mean -16.65 (95%CI: -24.8; -8.5) mg/month. [3]

We consider that there is sufficient evidence from our clinical trial programme to support the conclusion that there is a difference in IV iron use between roxadustat and ESA which is also clinically meaningful; comparable Hb levels were achieved with both treatments but with less use of IV iron in roxadustat treated group. This reduced use of IV iron is in keeping with the mechanism of action of roxadustat which, in addition to increasing endogenous EPO levels, improves the absorption of exogenous iron and the availability of endogenous iron from the body's iron store to support erythropoiesis in a coordinated manner.

When considering the added cost of roxadustat compared to current alternatives we urge the Medicines Council members to note that the cost comparison presented in the assessment report is extremely conservative:

- The statistically significant effect on use of IV iron is not reflected in the cost comparison.
- No benefits of having an oral formulation are considered in the presented analysis.
    - From a Swedish Survey conducted by TLV in Sweden we know that 18% of ESA treated patients require support in administration of subcutaneous injection of ESA in a primary care clinic or by municipality health care. [4, 5]
    - No cost of introducing patients to taking ESA injections is included in the comparative analysis. This despite training in subcutaneous technique is included in the comparative cost analyses that the Medicines Council have conducted in other disease areas.
- In addition, there are cost savings associated with roxadustat that cannot be quantified related to avoiding cold chain transport and storage of ESA and in securing that correct storage

Astellas Pharma a/s
Arne Jacobsens Allé 15, 2300 Copenhagen S, Denmark
Tel.: +45 43 43 05 33 Fax: +45 43 43 22 24
contact.dk@astellas.com – www.astellas.dk

temperature is maintained when patients are transporting and storing ESA for self-administration at home.

The cost-comparison presented in the final assessment report reflects a – from an international perspective – very competitive price for roxadustat. A national recommendation of roxadustat will allow access for patients to the first in an innovative new class of drug as an alternative to existing ESAs. The use of the HIF-PH inhibitors class will in Danish health care be managed via the tender system which will secure that the majority of patients continuously will be treated with the least costly alternative. A recommendation of roxadustat will secure competition and support Amgros in achieving low prices in future tenders.

References

1. Barratt J, Andric B, Tataradze A, Schomig M, Reusch M, Valluri U, et al. Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, open-label, active-controlled study (DOLOMITES). Nephrol Dial Transplant. 2021;36(9):1616-28. Available from: https://www.ncbi.nlm.nih.gov/pubmed/34077510.
2. ClinicalTrials.gov. Roxadustat in the Treatment of Anemia in Chronic Kidney Disease (CKD) Patients, Not on Dialysis, in Comparison to Darbepoetin Alfa (Dolomites): NIH; 2022. Available from: https://clinicaltrials.gov/ct2/show/results/NCT02021318 [Last accessed May 27].
3. Barratt J, Sulowicz W, Schomig M, Esposito C, Reusch M, Young J, et al. Efficacy and Cardiovascular Safety of Roxadustat in Dialysis-Dependent Chronic Kidney Disease: Pooled Analysis of Four Phase 3 Studies. Adv Ther. 2021;38(10):5345-60. Available from: https://www.ncbi.nlm.nih.gov/pubmed/34523074.
4. TLV. TLV omprövning av ESL (dnr 1747/2012). 2014. Available from: http://tlv.se.
5. TLV. Underlag för beslut om subvention. Evrenzo (roxadustat). DNR: 3698/2021. 2022. Available from: http://tlv.se.

Astellas Pharma a/s
Arne Jacobsens Allé 15, 2300 Copenhagen S, Denmark
Tel.: +45 43 43 05 33 Fax: +45 43 43 22 24
contact.dk@astellas.com – www.astellas.dk

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

24.02.2023

MGK/LEJ/BMC

Forhandlingsnotat

Dato for behandling i Medicinrådet	29.03.2023
Leverandør	Astellas Pharma
Lægemiddel	Evrenzo (roxadustat)
Ansøgt indikation	Til behandling af voksne patienter med symptomatisk anæmi, der er forbundet med kronisk nyresygdom.
Nyt lægemiddel / indikationsudvidelse	Nyt lægemiddel

Prisinformation

Amgros har forhandlet følgende pris på Evrenzo (roxadustat):

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke	Pakningsstørrelse	AIP (DKK)	Nuværende SAIP (DKK)	Forhandlet SAIP (DKK)	Rabatprocent ift. AIP
Evrenzo	20 mg	12 stk.	569,45	[redacted]	[redacted]	[redacted]
Evrenzo	50 mg	12 stk.	1.416,52	[redacted]	[redacted]	[redacted]
Evrenzo	70 mg	12 stk.	1.982,73	[redacted]	[redacted]	[redacted]
Evrenzo	100 mg	12 stk.	2.819,28	[redacted]	[redacted]	[redacted]
Evrenzo	150 mg	12 stk.	4.213,00	[redacted]	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling.
[redacted]

Aftaleforhold

[redacted].

Informationer fra forhandlingen

[redacted]

Konkurrencesituationen

Det nuværende valg af behandling er baseret på en behandlingsvejledning fra RADS, hvor alle erythropoietin stimulerende lægemidler (ESA-præparater) er ligestillede. Førstevalget til behandling af patienter i Danmark er på nuværende tidspunkt med Aranesp (darbepoetin alfa) og NeoRecormon (epoetin beta) er andetvalg valg.
[redacted]

Amgros forventer yderligere konkurrence på området. Vafseo (vadadustat) har 23 februar 2023 fået positiv CHMP opinion og Jesduvroq (daprodustat) forventes at få markedsføringstilladelse af EMA i 2023.

I nedenstående tabel 3 ses en sammenligning af de årlige lægemiddeludgifter for Evrenzo, Aranesp og NeoRecormon. Lægemiddeludgifterne er opgjort for patienter, som ikke er i dialyse (NDD) og for patienter, som opstartes i dialyse (IDD).

Tabel 2: Sammenligning af lægemiddeludgifter

Lægemiddel	Styrke	Pakningsstørrelse	Dosering	Pris pr. pakning (SAIP, DKK)	Antal pakninger pr. år*	Lægemiddeludgift pr. år (SAIP, DKK) **
IDD (patienter, som opstartes i dialyse						
Evrenzo IDD	150 mg	12 stk.	[redacted]	[redacted]	Opstarts år: ≈ 8 Vedligehold: ≈ 8	Opstarts år: [redacted] Vedligehold: [redacted]
Aranesp IDD	500 mikrogram	1,0 ml inj.væske, opl., pen	[redacted]	[redacted]	Opstarts år: ≈ 5 Vedligehold: ≈ 5	Opstarts år: [redacted] Vedligehold: [redacted]
NeoRecormon IDD	10.000 i.e.	6 stk.	[redacted]	[redacted]	Opstartsår: ≈ 7 Vedligehold: ≈ 8	Opstartsår: [redacted] Vedligehold: [redacted]
NDD (non-dialysis dependent)						
Evrenzo NDD	150 mg	12 stk.	[redacted]	[redacted]	Opstartsår: ≈ 6 Vedligehold: ≈ 6	Opstartsår: [redacted] Vedligehold: [redacted]
Aranesp NDD	500 mikrogram	1,0 ml inj.væske, opl., pen	[redacted]	[redacted]	Opstartsår: ≈ 4 Vedligehold: ≈ 4	Opstartsår: [redacted] Vedligehold: [redacted]
NeoRecormon NDD	10.000 i.e.	6 stk.	[redacted]	[redacted]	Opstartsår: ≈ 6 Vedligehold: ≈ 7	Opstartsår: [redacted] Vedligehold: [redacted]

*Antal pakninger er rundet op i henhold til antal åbnede pakninger.
**Lægemiddeludgiften er beregnet for det faktiske antal pakninger.

Status fra andre lande

Land	Status	Kommentar	Link
Norge	Anbefalet		https://nyemetoder.no/metoder/roksadustat-evrenzo
Sverige	Anbefalet	Tabletbehandling, er derfor vurderet af TLV	Evrenzo ingår i högkostnadsskyddet (tlv.se)
England	Anbefalet	Roxadustat is recommended as an option for treating symptomatic anemia associated with chronic kidney disease (CKD) in adults only if: they have stage 3 to 5 CKD with no iron deficiency.	Roxadustat for treating symptomatic anaemia in chronic kidney disease (nice.org.uk)

Konklusion

[redacted]

Application for the assessment of Evrenzo for treatment of symptomatic anaemia in adult patients with chronic kidney disease

Table of contents

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Color scheme for text highlighting	
Color of highlighted text	**Definition of highlighted text**
	Confidential information
[other]	**[definition of color-code]**

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

1 Basic information

Contact information	
Name	Kamilla Juhl Nørgaard
Title	Associate Director Health Economics and Outcomes Research
Phone number	+45 4062 8958
E-mail	kamilla.norgaard@astellas.com
Name	Peter Hyttinen
Title	Nordic Market Access Manager
Phone number	+46 73 448 49 02
E-mail	peter.hyttinen@astellas.com

Overview of the pharmaceutical	
Proprietary name	Evrenzo
Generic name	Roxadustat
Marketing authorization holder in Denmark	Astellas Pharma Europe B.V. Sylviusweg 62 2333 BE Leiden The Netherlands
ATC code	B03XA05
Pharmacotherapeutic group	Other anti-anaemic preparations
Active substance(s)	Roxadustat
Pharmaceutical form(s)	Film-coated tablets

Overview of the pharmaceutical	
Mechanism of action	Roxadustat is a hypoxia inducible factor, prolyl hydroxylase inhibitor (HIF-PH inhibitor). The activity of HIF-PH enzymes controls intracellular levels of HIF, a transcription factor that regulates the expression of genes involved in erythropoiesis. Activation of the HIF pathway is important in the adaptative response to hypoxia to increase red blood cell production. Through the reversible inhibition of HIF PH, roxadustat stimulates a coordinated erythropoietic response that includes the increase of plasma endogenous erythropoietin (EPO) levels, regulation of iron transporter proteins and reduction of hepcidin (an iron regulator protein that is increased during inflammation in CKD). This results in improved iron bioavailability, increased Hb production and increased red cell mass. The MOA differs fundamentally from that of erythropoietin stimulating agents which are essentially hormone replacement with modified versions of recombinant erythropoietin and which do not impact availability of iron, an essential factor for red blood cell formation.
Dosage regimen	**Treatment with Roxadustat should be initiated by a physician experienced in the management of anaemia.** The appropriate dose of roxadustat must be taken orally three times per week and not on consecutive days. The dose should be individualised to achieve and maintain target Hb levels of 10 to 12 g/dL (6.2 to 7.5 mmol/L) as described in the SmPC using step-wise dose adjustments up or down following the sequence of available doses . Hb levels should be monitored every two weeks until the desired Hb level of 10 to 12 g/dL is achieved and stabilised, and every 4 weeks thereafter, or as clinically indicated. The individualised maintenance dose ranges from 20 mg to 300 mg three times per week in NDD and 20 mg to 400 mg in DD. Dose should not exceed 3 mg/kg body weight Roxadustat treatment should not be continued beyond 24 weeks of therapy if a clinically meaningful increase in Hb levels is not achieved. Alternative explanations for an inadequate response should be sought and treated before re-starting roxadustat. No specific dose adjustment is required for patients who start dialysis while on treatment with roxadustat.
Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)	Treatment of adult patients with symptomatic anaemia associated with chronic kidney disease (CKD).
Other approved therapeutic indications	Not applicable
Will dispensing be restricted to hospitals?	Yes (Legal code BEGR)
Combination therapy and/or co-medication	Not applicable

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Overview of the pharmaceutical	
Packaging – types, sizes/number of units, and concentrations	Filmcoated tablets 20 mg × 12 unit dose blisters in carton package Filmcoated tablets 50 mg × 12 unit dose blisters in carton package Filmcoated tablets 70 mg × 12 unit dose blisters in carton package Filmcoated tablets 100 mg × 12 unit dose blisters in carton package Filmcoated tablets 150 mg × 12 unit dose blisters in carton package
Orphan drug designation	Not applicable

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

2 Abbreviations

ACM	All-cause mortality
CFB	Change from baseline
CI	Confidence interval
CKD	Chronic kidney disease
CRP	C-reactive protein
CV	Cardiovascular
DA	Darbepoetin alfa
DBP	Diastolic blood pressure
DD	Dialysis dependent
eGFR	Estimated glomerular filtration rate
EPO	Erythropoietin
ESA	Erythropoiesis-stimulating agents
ESRD	End-stage renal disease
FAS	Full analysis set
Hb	Haemoglobin
HHD	Home haemodialysis
HIF	Hypoxia inducible factor
HIF-PH	Hypoxia inducible factor, prolyl hydroxylase
HR	Hazard rate
HRQoL	Health-related Quality of life
hs-CRP	High-sensitivity C-reactive protein
IC-HD	In-center haemodialysis
ID-DD	Incident Dialysis Dependent
ITT	Intention to treat
IV	Intravenous
LDL	Low-density lipoprotein
LSM	Least-square means
MACE	Major cardiovascular event
MAP	mean arterial pressure
MDRD	Modification of Diet in Renal Disease Study
MPG-EPO	methoxy polyethylene glycol-epoetin
NDD	Non-dialysis dependent
PBO	Placebo
PD	Peritoneal dialysis
PPS	Per protocol set
RBC	Red blood cell
Roxa	Roxadustat
RR	Relative Risk
SBP	Systolic blood pressure
SD	Standard deviation
SF-36 PF	Short-Form 36 health survey questionnaire. Physical Functioning
SF-36 VT	Short-Form 36 health survey questionnaire. Vitality
SmPC	Summary of product characteristics
TSAT	Transferrin saturation
US	United States

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

3 Tables and Figures

3.1 List of tables

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

3.2 List of figures

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

4 Summary

Anaemia of CKD

Chronic kidney disease (CKD) is a global public health challenge characterised by the progressive loss of kidney function, resulting in premature death or need for renal replacement therapy (kidney transplant or dialysis). Anaemia is an important complication of CKD resulting from significantly reduced erythropoietin (EPO) synthesis relative to the body's needs, and significant disturbances in iron metabolism, often exacerbated by chronic inflammation. Anaemia requires careful management in CKD patients to avoid the clinical consequences associated with prolonged low haemoglobin (Hb) levels.

Current treatment

Current treatment of anaemia of CKD is based on guidelines, published by Kidney Diseases: Improving Global Outcomes (KDIGO) in 2012 and involves raising and maintaining Hb levels with erythropoiesis-stimulation agents (ESA), iron - oral or intravenous (IV) - or red blood cell transfusions (RBC). Although iron (in IV form) and ESA are very effective and the mainstays of current treatment of anaemia of CKD, there are nevertheless shortcomings relating to convenience (route of administration is by injection), efficacy (higher doses of ESA are required in some patients possibly related to functional iron deficiency and inflammatory status) and safety (attempting to normalize Hb levels with ESA has been associated with increased CV risk).

Roxadustat

Roxadustat, is the first in a new class of drugs - hypoxia inducible factor prolyl hydroxylase (HIF-PH) inhibitors - for the treatment of anaemia by the oral route and via a completely different mechanism of action compared with current standard of care. The drug mimics the body's natural response to hypoxia and stimulates erythropoiesis using the body's own erythropoietin and by improving endogenous iron supplies. Of note, roxadustat reduces hepcidin, a hormone controlling iron availability which is elevated by inflammation frequently occurring in CKD patients; hepcidin locks iron into storage cells thereby restricting erythropoiesis, since iron is an essential component of RBC production. The safety and efficacy of roxadustat has been explored in an extensive clinical trial programme in approximately 9600 patients, spanning the disease spectrum of CKD in non-dialysis, incident dialysis and stable dialysis settings. The clinical advantages of roxadustat include oral administration, correction and maintenance of haemoglobin within the target range (10-12g/dL) but with less use of IV iron, and fewer RBC transfusions in the dialysis setting, compared with ESA. LDL levels are also reduced which may be a benefit since dyslipidaemia is linked to cardiovascular morbidity in CKD patients. The Hb response with roxadustat is achieved with lower EPO levels than with ESA and also at a stable mean dose in the population over time. Adverse reactions are, however, similar in nature and frequency to ESA overall with a similar cardiovascular risk profile. Thus, roxadustat offers a new approach to managing anaemia of CKD overcoming some of the complexities of current standard of care and addressing the multifaceted nature of anaemia of CKD.

In addition to the clinical benefits, the fact that roxadustat is an oral treatment option may be considered a benefit by the patient. Oral treatments also require less healthcare resource, as practitioners need to train patients to administer ESA subcutaneously to ensure this is done properly.

Cost of treatment

The economic evaluation of roxadustat for treatment of symptomatic anaemia in chronic kidney disease was conducted as a cost-comparison. Total cost was estimated from a direct health care perspective. Cost was estimated as net-present cost per patient for roxadustat and the relevant comparators (darbepoetin alfa, methoxy polyethylene glycol-epoetin beta, and epoetin beta). Costs considered were drug acquisition costs, administration cost and cost of IV iron. The cost analysis was conducted separately for ESA-naïve patients who are NDD and ESA-naïve patients

starting dialysis (incident dialysis-dependent, IDD, patients). [redacted]

Budget impact

Roxadustat gives the possibility of a new approach to treating anaemia in patients with CKD, and in alignment with available evidence and the prescribing information (Evrenzo Summary of Product Characteristics, SmPC) is most likely to be introduced in new patients previously untreated with ESA who are not yet on dialysis or who are initiating dialysis. [redacted]

5 The patient population, the intervention and choice of comparator(s)

5.1 The medical condition and patient population

All patients with chronic kidney disease (CKD) are at risk of anaemia; anaemia is a serious condition that refers to abnormally low levels of Hb and/or circulating red blood cells (RBC) that are insufficient to meet the body's physiological oxygen-carrying needs. The prevalence of anaemia is recognised to increase as kidney function declines, presenting more frequently and with more severity in advanced stages of CKD [1-3]. Data from the Swedish Renal Registry including 14 415 (NDD, 11 370; DD, 3045) patients under the care of nephrologists have shown the patterns of anaemia across Stages 3b–5 in non-dialysis (NDD) and dialysis-dependent (DD) CKD patients during 2015. These data suggest that anaemia was present in 60% of nephrology-referred NDD and 93% of DD patients.[2]

The hormone erythropoietin (EPO) regulates the development of RBCs, which contain oxygen-binding Hb molecules, and is itself regulated by hypoxia-inducible transcription factors (HIFs).[3-5] A breakdown of this HIF-mediated oxygen sensing mechanism directly contributes to insufficient EPO production, and lack of iron availability, an effect which is exacerbated by inflammation-associated increases in the iron regulatory protein hepcidin.[5-8]

Anaemia of CKD is associated with an increased risk of CKD progression; the RENAAL trial showed that lower levels of Hb correlated with a higher risk of progression to end-stage renal disease (ESRD) compared with normal Hb levels and patients with severe anaemia (Hb <11.3g/dL) were almost twice as likely to progress to ESRD compared with patients with high Hb levels (≥13.5g/dL)).[9]

In addition, anaemia of CKD is associated with a doubling of the risk of all-cause mortality, as demonstrated by the ARIC Study, where adjusted relative hazards of all-cause mortality associated with moderately decreased versus normal kidney function were 1.7 (95% confidence interval [CI]: 1.3, 2.2) in the absence of anaemia and 3.5 (95% CI: 2.4, 5.1) in the presence of anaemia.[10] This is supported by another study on patients with CKD where anaemia increased the risk of all-cause mortality by 65% compared with patients without anaemia (hazard ratio [HR] 1.65 [95% CI, 1.35–2.02]).[11] Anaemia of CKD is also associated with CV events and associated mortality. In a US retrospective cohort study in patients with stage 3 or 4 CKD, the presence of severe anaemia (Hb <10.5g/dL) was associated with increased risk of hospitalisations due to CV events (HR: 2.18; 95% CI: 1.76, 2.70) and increased risk of mortality (HR: 5.27; 95% CI: 4.37, 6.35.[12]

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Prevalent patient population

Dialysis dependent population

According to the Danish Renal Registry, there are approximately 2700 dialysis dependent CKD patients under the care of a nephrologist in Denmark [13]. Most of these patients are expected to have anaemia and approximately 80% are assumed to be ESA treated in the prevalent dialysis dependent population (Evans et al, 2020), see Table 1.

Table 1. Prevalent dialysis dependent population

Population	
Dialysis dependent patients	2700
Dialysis dependent patients currently treated with an ESA (80% of the overall DD population)	2160

Non-dialysis dependent population

Currently, the Danish Renal Registry does not include information on non-dialysis patients. By extrapolating information from the Swedish Renal Registry on the proportional relationship between the dialysis-dependent and non-dialysis dependent patient populations, we assume that approximately 10000 patients are under the care of a nephrologist in Denmark, and that 2400 of these are ESA-treated [2, 13], see Table 2.

.

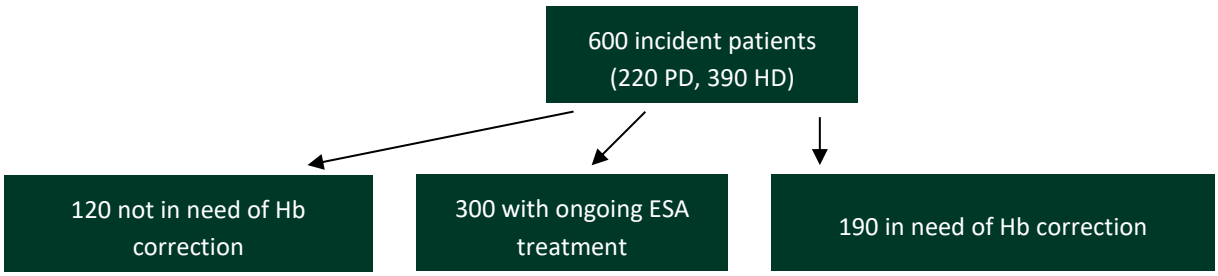
Table 2. Prevalent non-dialysis dependent population

Population	
Non-dialysis dependent patients	10000
Non-dialysis dependent patients with anaemia (60% of the overall NDD population)	6000
Non-Dialysis dependent patients currently treated with an ESA (24% of the overall NDD population)	2400

Incident patient population

Dialysis dependent population newly initiating dialysis

According to the Danish Renal Registry approximately 610 patient initiate dialysis per year. It is estimated that there will be a minor share of patients entering dialysis who are not previously treated with ESA. By combining information from the Swedish Renal Registry and the Danish Renal Registry, we assume that 80% of dialysis-dependent patients would eventually need ESA treatment and that about 60% are already ESA-treated at initiation of dialysis (490).



Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Non-dialysis dependent population
The number of incident (new) ND patients developing anaemia each year to the degree warranting treatment with roxadustat (symptomatic with Hb < 10g/dL as for ESA initiation) is estimated based on prior studies of incidence to be in the region of 10% of the prevalent population – i.e., 240 ND-CKD patients in need of Hb correction.

5.1.1 Patient populations relevant for this application

In Denmark, we anticipate that roxadustat will be used mostly in patients not on dialysis who need anaemia treatment to correct Hb levels to within the target range, and in patients new to dialysis not already on ESA at the time of starting dialysis treatment (i.e., a first line treatment position). Patients (whether NDD or DD) already on stable ESA treatment are not expected to be switched to roxadustat. Indeed, the prescribing information for Evrenzo recommends that patients on dialysis should only be converted from ESA to roxadustat if there is a valid clinical reason, and conversion of NDD patients from ESA to roxadustat was not studied in the clinical trial programme. Physicians should generally apply the same risk benefit considerations as apply to ESA when considering initiation of roxadustat treatment in NDD patients.

Table 3 Estimated number of patients eligible for treatment

Year	2022	2023	2024	2025	2026
Incident patient population	430	430	430	430	430

5.2 Current treatment options and choice of comparator(s)

5.2.1 Current treatment options

Current treatments recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines for treating anaemia of CKD include traditional erythropoiesis-stimulating agents (ESA), iron and RBC transfusion.[14] The management of anaemia in CKD in Denmark are in broad terms in line with the KDIGO guidelines. [15]

ESA treatment provides hormone replacement of EPO, often at non-physiological levels, in combination with separate administration of adjuvant iron as needed to sustain erythropoiesis. The available ESA treatment options include short-acting epoetin (EPO-alfa, -beta, -zeta) as well as long-acting (darbepoetin alfa, and methoxy polyethylene glycol-epoetin beta (MPG-EPO)). They can be administered either intravenously or subcutaneously and the route of administration has limited influence on achieving or maintaining Hb levels. IV administration requires IV access and may be preferred in the HD setting.

In Denmark, RADS assessed the available treatment options in 2015[15] which have formed the basis for national treatment recommendation.[16] The treatment recommendation focuses on new patients needing Hb correction and does not cover patients on existing ESA treatment, given the complications and risks associated with switching patients on stable treatment between the various treatment options. Eligible patients are divided in two main categories based on the need for, and type of, renal replacement therapy. The first group includes patients who are NDD or DD and receiving dialysis at home either as peritoneal dialysis – (PD or as home haemodialysis – HDD. The second group consists of DD patients receiving in-center haemodialysis (IC-HD). The national treatment guideline recommends using long-acting ESA (darbepoetin alfa or MPG-EPO) for patients in the NDD/PD/HHD setting and short-acting EPO or long-acting ESA in the IC-HD setting.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

All currently used ESAs have a common mechanism of action (i.e., stimulation of the EPO receptor), the only difference between them being modification of the amino acid chain and carbohydrate moiety of the erythropoietin molecule to alter half-life resulting in changes to dosing frequency. The RADS comparison of ESAs concluded that there is no evidence that any given ESA brand is superior to another in terms of patient outcomes[15] and according to the KDIGO guidelines, the likelihood of differences in clinical outcomes between ESA brands is low[14]. Furthermore, a recent randomized controlled study of methoxy polyethylene glycol-epoetin beta versus other ESAs (darbepoetin alfa and short-acting ESAs) with an 8-year follow-up showed no difference in outcomes[17]. Thus, the choice of ESA is dependent on price and convenience in relation to frequency of administration, and not on any expected difference in clinical outcomes.

5.2.2 Choice of comparator(s)

Five out of the 8 studies in the global phase 3 programme for roxadustat, evaluated efficacy and safety versus ESA as an active comparator. Depending on the particular study, the selected ESA comparator was either solely darbepoetin alfa (NDD) or solely epoetin alfa (IDD, SD) or either darbepoetin alfa or epoetin alfa (SD). Since there is no evidence to support a difference in efficacy or safety of one ESA compound over another, we consider that the results for a specific ESA are considered as representative of the ESA class.

Given the target patient population, roxadustat is more likely to displace long-acting ESAs in Denmark than short acting ESAs. Hence, in the economic analysis, the long-acting ESAs – DA and MPG-EPO – are considered the main comparators. The short-acting ESA, epoetin beta (NeoRecormon®) was included as a point of reference as this short-acting ESA has an AMGROS tender price and because the clinical comparison and comparative dosing data in ID-DD is from clinical studies where short-acting ESA was the comparator.

5.2.3 Description of the comparator(s)

	Darbepoetin alfa	Methoxy polyethylene glycol-epoetin beta	Epoetin beta
Generic name(s) (ATC-code)	B03XA02	B03XA03	B03XA01
Mode of action	Darbepoetin alfa stimulates erythropoiesis by the same mechanism as the endogenous hormone.	MPG-EPO beta a is continuous erythropoietin receptor activator with increased half-life compared to erythropoietin.	Erythropoietin is a glycoprotein that stimulates the formation of erythrocytes from its committed progenitors.
Pharmaceutical form	Solution for injection		
Posology	See dosing		
Method of administration	Subcutaneous or intravenously injection. Subcutaneous use is preferable in patients who are not receiving haemodialysis to avoid the puncture of peripheral veins.		
Dosing	Patients should be monitored closely to ensure that the lowest approved effective dose is used to provide adequate control of the symptoms of anaemia whilst maintaining a haemoglobin	Patients should be monitored closely to ensure that the lowest approved effective dose is used to provide adequate control of the symptoms of anaemia whilst maintaining a	Patients should be monitored closely to ensure that the lowest approved effective dose is used to provide adequate control of the symptoms of anaemia whilst maintaining a haemoglobin concentration below to 12 g/dl

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

	Darbepoetin alfa	Methoxy polyethylene glycol-epoetin beta	Epoetin beta
	concentration below or at 12 g/dL. The initial dose by subcutaneous or intravenous administration is 0.45 mcg/kg body weight, as a single injection once weekly. Alternatively, in patients not on dialysis, the following initial doses can also be administered subcutaneously as a single injection: 0.75 mcg/kg once every two weeks or 1.5 mcg/kg once monthly. In maintenance treatment, dialysis patients, may continue to have darbepoetin alpha administrated as a single injection once weekly or once every two weeks. In patients not on dialysis, Aranesp may continue to be administered as a single injection once weekly or once every two weeks or once monthly Non-response to therapy with DA should prompt a search for causative factors	haemoglobin concentration below or at 12 g/dl. The initial dose in patients not on dialysis is 1.2 microgram/kg body weight, administered once every month as a single subcutaneous injection. Alternatively, a starting dose of 0.6 microgram/kg bodyweight may be administered once every two weeks as a single intravenous or subcutaneous injection in patients on dialysis or not on dialysis. Patients treated once every two weeks whose haemoglobin concentration is above 10 g/dl may be switch to once-monthly using the dose equal to twice the previous once-every-two-week dose. In patients with a poor haemoglobin response to epoetin, alternative explanations for the poor response should be considered	The initial dosage by sc administration is 3 x 20 IU/kg body weight per week. In the case of subcutaneous administration, the weekly dose can be given as one injection per week or in divided doses three or seven times per week. Patients who are stable on a once weekly dosing regimen may be switched to once every two weeks administration. The maximum dose should not exceed 720 IU/kg per week. Caution should be exercised with escalation of epoetin beta doses in patients with chronic renal failure. In patients with a poor haemoglobin response to treatment, alternative explanations for the poor response should be considered
Should the pharmaceutical be administered with other medicines?		No	
Treatment duration/criteria for end of treatment	Treatment for anaemia, once initiated, is generally life long		
Necessary monitoring, both during administration and during the treatment period	Haemoglobin should be measured every one or two weeks until levels are stable. Thereafter haemoglobin can be measured at longer intervals.	It is recommended that haemoglobin is monitored every two weeks until stabilized and periodically thereafter.	
Need for diagnostics or other tests (i.e. companion diagnostics)	Not applicable	Not applicable	No applicable
Packaging	Strength in the range 10-500 mcg in pre-filled syringes or prefilled pens. Packs with 1 prefilled pen or 1 or 4 prefilled syringes available.	Strengths in the range 30-360 mcg in pre-filled syringes (pack size of 1 pen) are available.	Strengths of 4000 IU or 10000 IU in prefilled syringes (packs of 6 syringes)

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

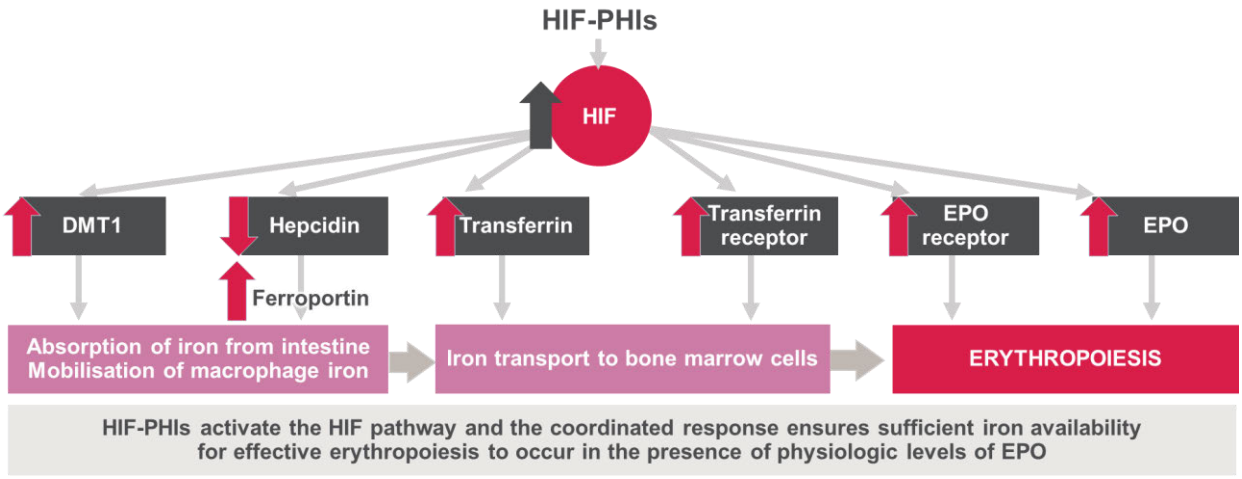
5.3 The intervention

Roxadustat is a new oral treatment for anaemia of CKD and belongs to a new class of drugs called hypoxia inducible factor (HIF) prolyl hydroxylase (PH) inhibitors[18]. Roxadustat is the first drug in this class to receive a marketing authorisation in Europe (as of 18 August 2021). The clinical development programme has been a tripartite collaboration between the molecule's originator Fibrogen, together with AstraZeneca, and Astellas.

Mechanism of action

The development of the HIF PH inhibitor class of drugs is based on research to unravel the mechanism by which the kidney senses oxygen (as described in section 5.1). Essentially, roxadustat mimics the effect of hypoxia in the body, by inhibiting the enzyme HIF prolyl hydroxylase (also inhibited when oxygen levels are low). Like hypoxia, roxadustat results in stabilization of HIF-α in the cell, allowing HIF-α to form a complex with HIF-β in the cell nucleus; this HIF complex then transcribes multiple genes for erythropoiesis including up-regulation of the genes for erythropoietin and iron metabolism. The resulting coordinated response involves increase in endogenous erythropoietin levels, the regulation of iron-transport proteins and the reduction of hepcidin (see Figure 1). The mechanism of action of roxadustat therefore involves multiple co-ordinated actions in the body whereas the primary effect of ESA is the direct replacement of EPO (the action shown at far right of Figure 1). The novel mechanism of action of roxadustat aids restoration of the body's natural ability to stimulate erythropoiesis: notably, EPO is endogenous and generated to at or near physiological levels, and erythropoiesis is efficient by enhancing endogenous iron availability. Treatment with roxadustat provides an alternative to raising Hb levels via hormone replacement of injectable EPO analogues.

Figure 1. Treatment with roxadustat delivers coordinated erythropoietic response



Dosing

Roxadustat is administered in tablet form. The appropriate dose of roxadustat must be taken orally three times per week and not on consecutive days. Doses are initiated based on a patient's weight (in those with no prior ESA use; 70mg 3 times a week > 100kg and 100mg 3 times a week > 100kg) or based on the mean ESA dose taken during the previous 4 weeks in patients converting from ESA. The dose should be individualised thereafter to achieve and maintain target Hb levels of 10 to 12 g/dL as described in the SmPC. Roxadustat treatment should not be continued beyond 24 weeks of therapy if a clinically meaningful increase in Hb levels is not achieved. Alternative explanations for an inadequate response should be sought and treated before re-starting roxadustat.

The individualised maintenance dose ranges from 20 mg to 300 mg three times per week in NDD and 20 mg to 400 mg in DD. The dose should not exceed 3 mg/kg body weight or the maximum total dose for NDD or DD, whichever is lower. Hb levels should be monitored every two weeks until the desired Hb level of 10 to 12 g/dL is achieved and stabilised, and every 4 weeks thereafter, or as clinically indicated. No specific dose adjustment is required for patients who start dialysis while on treatment with roxadustat.

Roxadustat are available in the following strengths: 20mg, 50mg, 70mg, 100mg, 150mg (12 tablets packs).

Treatment duration

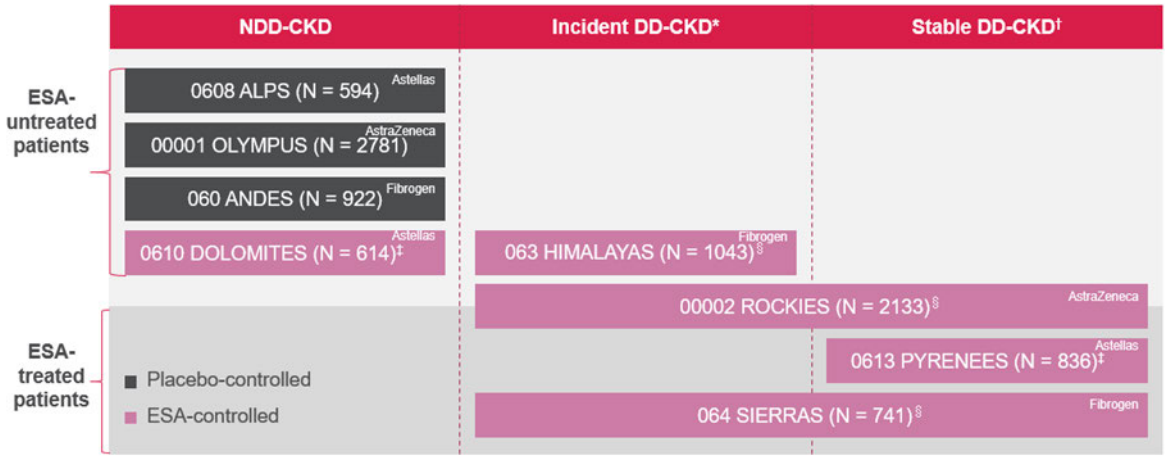
Treatment for anaemia, once initiated, is generally life-long and patients initiated on treatment with roxadustat can be expected to stay on treatment whether or not they initiate dialysis or switch type of dialysis, unless they are transplanted. Providing a patient is stable, although not directly studied, it would probably not be appropriate to switch treatment away from roxadustat to ESA without due cause (as exemplified by the design of roxadustat trials where there was an elevated risk of switching patients stable on ESA to roxadustat). Median life expectancy on dialysis, also taking into consideration that this is an elderly population, is in the region of 4-5 years; note some patients survive without transplant for >10 years. Males and females not on dialysis at stage 4 or 5 CKD can be expected to live for a median 4-6 years or 4-8 years respectively [19]. Most patients die from cardiovascular events related to CKD before they reach dialysis.

6 Literature search and identification of efficacy and safety studies

6.1 Identification and selection of relevant studies

The global phase 3 clinical development programme (called ALPINE) for roxadustat included eight studies conducted to support regulatory submissions to the FDA, EMA and several other countries (see Figure 2). These studies enrolled approximately 9600 patients and provided evidence on the efficacy and safety of roxadustat for treatment of anaemia across the CKD spectrum from non-dialysis, incident dialysis and stable dialysis.

Figure 2. Overview of studies by disease stage, comparator and prior ESA exposure



All studies were multi-centre and randomised and evaluated the efficacy and safety of roxadustat in correcting and/or maintaining Hb levels for at least 52 weeks.

Dialysis status and comparators

Four studies were conducted in patients not on dialysis (NDD), of which 3 were placebo-controlled (ALPS, OLYMPUS, ANDES) and one was an active controlled study versus darbepoetin alfa (DOLOMITES).[20] Four studies were conducted in dialysis (DD) patients where patients were either new to dialysis (on dialysis > 2 weeks but less than 4 months) (ID-DD) or on stable dialysis (dialysis for > 4 months).[21-24] Of these, the HIMALAYAS study [24] included only incident dialysis patients and the PYRENEES study [22] included only stable dialysis patients. The ROCKIES [23] and SIERRAS studies [21] included a mix of these two categories of dialysis patient, incident and stable. These DD studies were ESA-controlled and in HIMALAYAS, ROCKIES and SIERRAS, the comparator was epoetin alfa, i.e., the comparator in the integrated analysis of studies in incident dialysis patients was epoetin alfa.

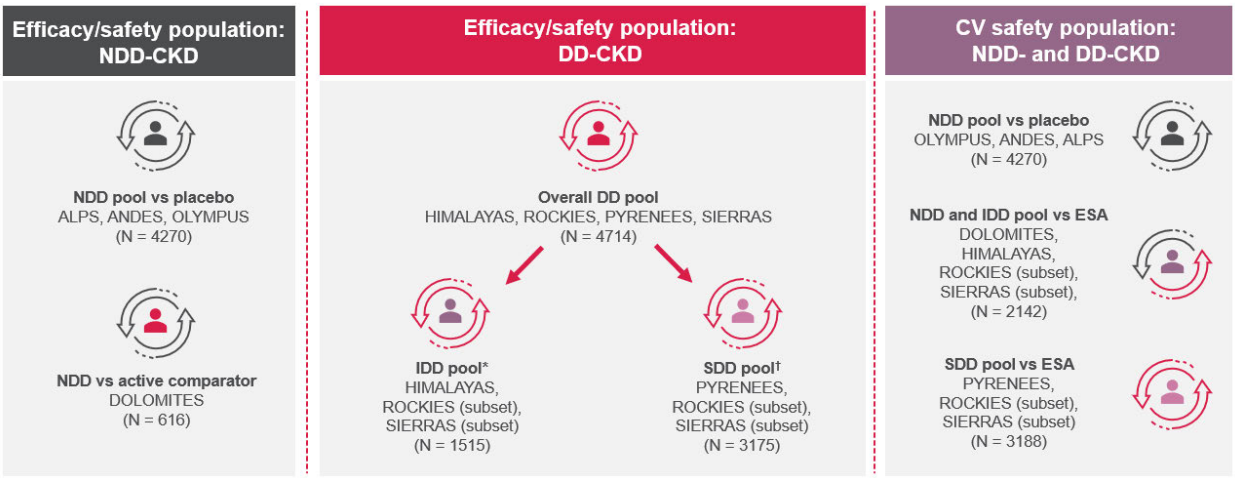
Prior ESA treatment

In all 4 NDD studies, patients were "ESA untreated" (ESA-naïve) prior to randomisation. In these studies, patients were therefore newly initiated on either roxadustat or ESA for correction of Hb. The same is true of the HIMALAYAS study in IDD patients. The PYRENEES and SIERRAS studies in contrast included only patients converted from prior ESA, whereas the ROCKIES study included a mix of patients with prior ESA treatment and ESA-naïve patients.

Pre-specified integrated analyses

The ALPINE program was designed to facilitate various pre-specified integrated analyses: these pre-specified analyses included an evaluation of safety and efficacy of roxadustat in NDD versus placebo (by pooling the data from the ALPS, OLYMPUS and ANDES studies), and of roxadustat in DD versus ESA (by pooling data from HIMALAYAS, ROCKIES, PYRENEES and SIERRAS); the DD patient pool was also further sub-divided into incident DD and stable DD patients and data analysed separately for each sub-group.[25]

Figure 3. Overview of pooled data sets for analysis of efficacy, safety and CV safety



Selection of studies for the application

The RADS Expert Committee review and comparison of ESA with respect to efficacy and safety, concluded that the 5 included ESAs (epoetin alpha, beta, zeta; darbepoetin alfa and methoxy polyethylene glycol-epoetin beta) are all effective in treating anaemia. The review furthermore concluded that the five products were equally efficacious and had a similar side-effect profile[15]. Furthermore, according to the KDIGO guidelines, the likelihood of differences in clinical outcomes among ESA brands is low[14]. Based on these observation, it is fair to conclude that further literature search and meta-analysis of ESA studies will not provide additional relevant documentation for efficacy and

safety for specific comparators and that the darbepoetin alfa-controlled trial (NDD) and epoetin alfa-controlled (ID-DD) trials in ALPINE may be used as full documentation for all ESAs - irrespective of brand - as the relevant comparator in Danish clinical practice.

In this application, evidence of the efficacy and safety of roxadustat compared with ESA for Hb correction is presented for NDD based on the DOLOMITES study. Comparative evidence for roxadustat versus ESA for Hb correction in ID-DD is based on the relevant sub-group of patients (incident dialysis patients) in the integrated analysis of DD patients (sub-group comprises HIMALAYAS study and the ID-DD patients in ROCKIES and SIERRAS). The comparative data for roxadustat versus ESA for NDD and IDD patients are presented separately (section 7.1 for NDD and section 7.2 for ID-DD). Section 7.3 presents additional evidence for roxadustat in stable dialysis as well as cardiovascular safety in all patients receiving Hb correction treatment in the ALPINE clinical trial programme (NDD and ID-DD).

6.2 List of relevant studies

Table 4 Relevant studies included in the assessment

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, open-label, active-controlled study (DOLOMITES). **Barratt et al.** Nephrol Dial Transplant. 2021;36(9):1616-28. [20]	DOLOMITES	NCT02021318	March 2014 – November 2019	Roxadustat vs ESA in NDD
Efficacy and Cardiovascular Safety of Roxadustat in Dialysis-Dependent Chronic Kidney Disease: Pooled Analysis of Four Phase 3 Studies. **Barratt et al.** Adv Ther. 2021;38(10):5345-60. [25]	Integrated analysis of efficacy and safety in ID-DD patients:			Roxadustat vs ESA in ID-DD
	HIMALAYAS	NCT02052310	February 2014 – September 2018	
	ROCKIES (ID-DD sub-group)	NCT02174731	July 2014 – September 2018	
	SIERRAS (ID-DD sub-group)	NCT02273726	January 2015 – September 2018	

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Reference (title, author, journal, year)	Trial name	NCT number	Dates of study (start and expected completion date)	Used in comparison of*
Roxadustat Public assessment report. EMA. 2021	Integrated analysis of CV safety in correction treatment: DOLOMITES HIMALAYAS ROCKIES (ID-DD sub-group) SIERRAS (ID-DD sub-group)	See above	See above	Roxadustat vs ESA in NDD and ID-DD (Cardiovascular safety only)

For detailed information about included studies, refer to appendix B.

7 Efficacy and safety

7.1 Efficacy and safety of roxadustat compared to ESA for ESA-naïve NDD patients

7.1.1 Relevant studies

As outlined in section 6.1, DOLOMITES is the main source for comparative evidence of efficacy and safety of roxadustat compared to ESA in NDD patients.

DOLOMITES is a phase 3, multicentre, randomised, open-label, active-controlled study. Eligible patients were randomised (1:1) to receive roxadustat or DA for up to 104 weeks during the treatment period. An initial correction period to achieve Hb ≥11.0 g/dL and Hb change from baseline (CFB) ≥1.0 g/dL (measured at two consecutive visits separated by ≥5 days) occurred in both groups. This was followed by a maintenance period with dosing aimed at achieving Hb levels between 10.0–12.0 g/dL. During a 4-week follow-up period, anaemia treatment was at the discretion of study investigators. Randomization (1:1) was conducted according to stratification factors (region; Hb values at screening; history of cardiovascular, cerebrovascular, or thromboembolic diseases; and eGFR values at screening).

For a detailed study description, see appendix B.

The baseline characteristics of patients in the DOLOMITES study are shown in Table C1. The DOLOMITES study population consisted primarily of Caucasians and the study enrolled slightly more women than men, patients were on average above 60 years of age; most patients were in stage 4 and 5 CKD with mean eGFR reflecting this. The proportion of patients considered iron-replete based on iron status parameters (TSAT and ferritin) was around 55%. Between 35% and 40% of patients had elevated CRP levels across study arms. Around 40% of patients had diabetes as most likely CKD aetiology. Patient characteristics were generally comparable between the respective roxadustat and darbepoetin alfa arms.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

7.1.2 Efficacy and safety – results per study

Detailed efficacy and safety results are tabulated in Table D2 and Table E1, respectively.

Hb response

The DOLOMITES study met the primary endpoint showing non-inferiority of roxadustat compared with darbepoetin alfa with regard to the proportion of patients achieving a Hb response during the first 24 weeks of treatment without rescue therapy. More patients in the roxadustat group met the criteria for Hb response (89.5%) compared to the DA group (78.0%). (Figure 3). Roxadustat maintained Hb levels within the target range for the duration to the study (Figure 4).[20]

Figure 3 Primary endpoint: Hb response during the first 24 weeks of treatment without rescue therapy

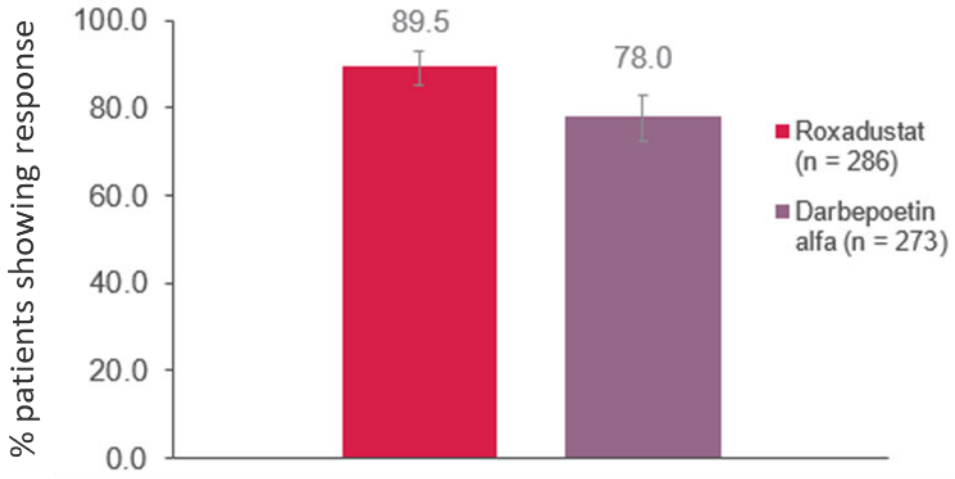
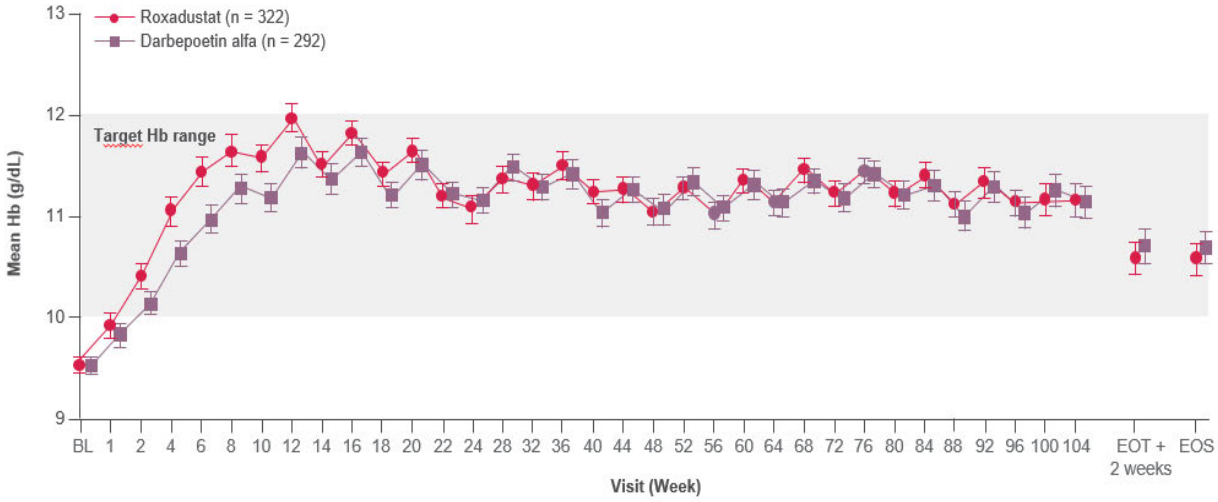


Figure 4 Achievement and maintenance of Hb levels within the target range (10-12 g/dL)



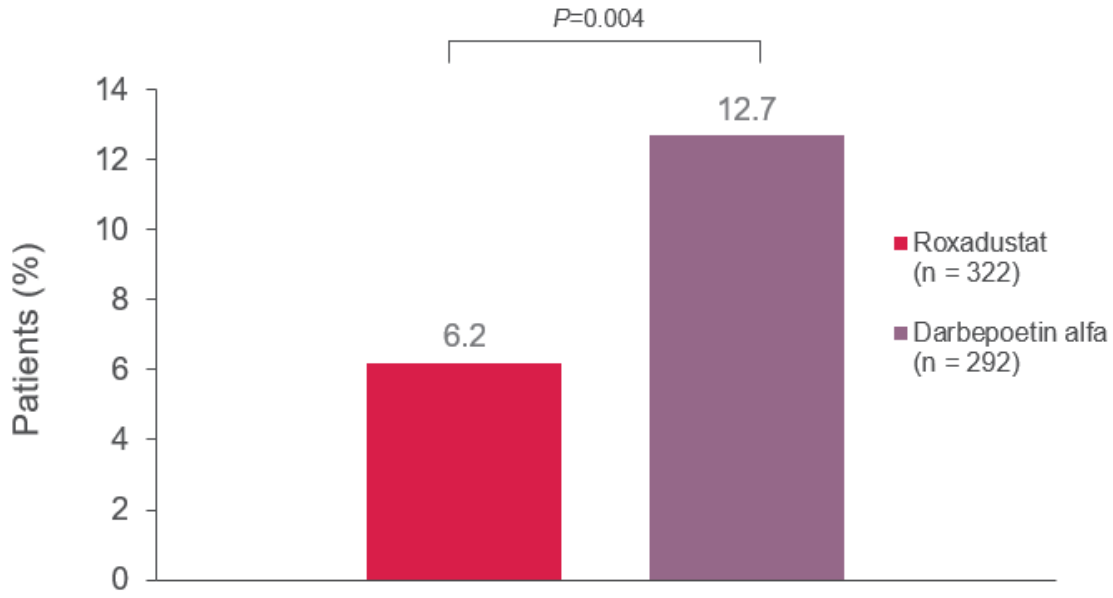
Furthermore, non-inferiority of roxadustat to darbepoetin was demonstrated for key secondary efficacy endpoints, including Hb change from baseline to average of weeks 28-36, SF-36 Physical Functioning (PF) and SF-36 Vitality (VT) scores.[20, 26]

Use of intravenous iron

Time to first use IV iron was significant longer in roxadustat patients compared with patients receiving darbepoetin (hazard ratio 0.45, 95% CI 0.26-0.78) (Figure 5). In patients receiving iron, the mean (SD) monthly dose of IV iron during weeks 1-36 was 34.74 (29.96) mg and 69.57 (67.34) mg in the roxadustat and darbepoetin groups respectively.[20]. During weeks 52-104, the average monthly IV dose per participant was 18.7 mg/month (95% CI: 10.4; 27) in the roxadustat group and 31.3 mg/month (95% CI: 19.4; 43.2) [27]

Interestingly the use of oral iron preparations was also lower (bivalent preparations: roxadustat: 43.7%; DA: 49.8%) and trivalent preparations: roxadustat: 35.3%; DA: 44.7%) in the roxadustat group compared with the darbepoetin group [20]. These data indicate that the increase in Hb levels and maintenance within the target range was achieved with lower use of supplemental IV iron in roxadustat-treated patients than those receiving darbepoetin. This is keeping with the mechanism of action of roxadustat, stimulating efficient erythropoiesis through a coordinated increase in endogenous erythropoietin production and enhanced mobilization of endogenous iron supplies.

Figure 5: Proportion of patients requiring IV iron vs ESA group (%) during Weeks 1–36



Other secondary endpoints

RBC transfusions: No differences was observed in RBC transfusions (Number of patients receiving transfusion in treatment-emergent period or number of packs transfused) between roxadustat and DA groups.[27]

Progression to ESRD: 34.2% of patients in the roxadustat group and 36.6% in the DA group developed ESRD between randomization and end-of-study (up to week 108) (RR: 0.93; 95%CI: 0.75; 1.15). [27]

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Safety outcomes

Table E1 provides a summary of safety outcomes in DOLOMITES. Treatment Emergent adverse events (TEAEs) occurrence was comparable between the roxadustat (91.6%) and DA (92.5%) groups. TEAEs leading to treatment withdrawal, drug-related AEs, serious AEs, and drug-related serious AEs occurred with a higher incidence for roxadustat than DA. The CHMP public assessment report conclusion on the safety data from the DOLOMITES study is that substantial differences for increased frequency of AEs for roxadustat vs ESA were not found (CHMP Public Assessment Report, p 132).[28] Table E2 presents the incidence of common SAEs by MedDRA preferred term in both treatment arms. The authors conclude that the safety profiles of roxadustat and DA were generally comparable over the study duration with no new safety signals observed.

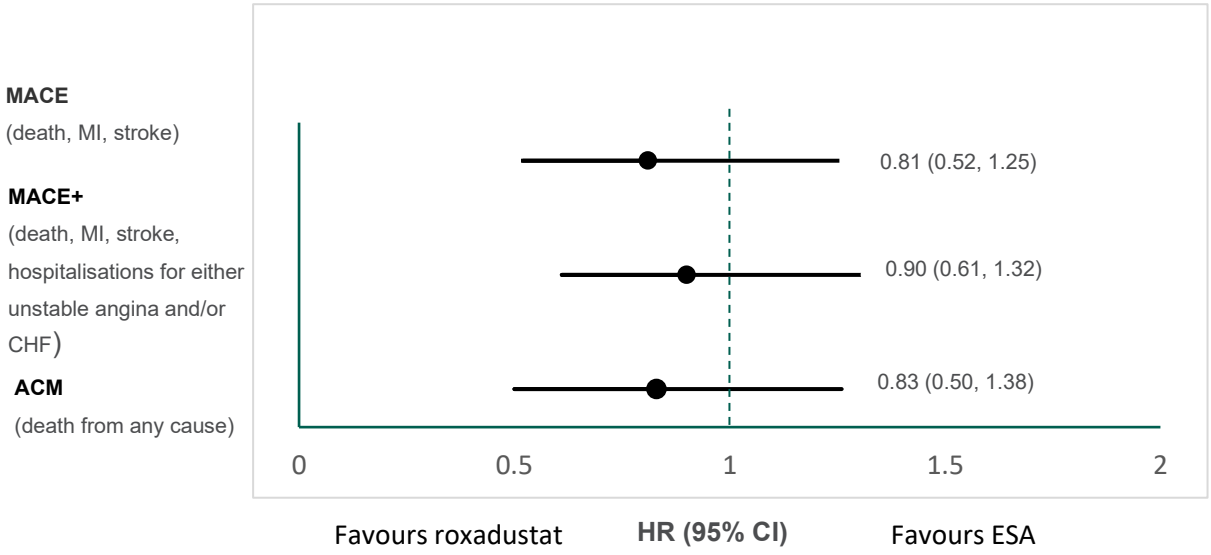
Cardiovascular safety is a key consideration with erythropoiesis-stimulating agents and has been assessed in the ALPINE clinical programme using the composite endpoint of major adverse cardiovascular events (MACE) and MACE+, the definitions of which are given in Table 5: in summary, MACE is the composite endpoint of all-cause mortality, myocardial infarction and/or stroke. The five-point MACE (MACE+) furthermore included unstable angina requiring hospitalisation and/ or congestive heart failure requiring hospitalisation.

Table 5 Definition of major adverse cardiovascular composite endpoints applied in ALPINE safety analyses

Individual event endpoints	Composite event endpoints	
Adjudicated individual events	**MACE**	**MACE+**
Death – any reason (all cause)	Y	Y
Myocardial infarction	Y	Y
Stroke	Y	Y
Unstable angina that requires hospitalisation	-	Y
Congestive heart failure that requires hospitalisation	-	Y

Analysis of MACE, MACE+ and all-cause mortality (on-treatment analysis + 28 days) in NDD (DOLOMITES) showed a favourable numerical trend in favour of roxadustat (HR (95%CI): 0.81 (0.52; 1.25), 0.90 (0.61; 1.32) and 0.83 (0.50; 1.38), respectively) (Figure 6). [20]

Figure 6: MACE and MACE+, ACM: on-treatment analysis*



* Included the treatment period and the following 28 days

That said, the results should be interpreted appropriately since the DOLOMITES study was in itself not powered for non-inferiority or superiority between roxadustat and ESA in terms of MACE. An analysis of the comparative CV risk of roxadustat versus ESA in the entire pool of patients in need of Hb correction (NDD patients from DOLOMITES, ID-DD patients from HIMALAYAS, ROCKIES and SIERRAS) is presented in Section 7.3.2

7.1.3 Comparative analyses of efficacy and safety

Not applicable. The clinical evidence for roxadustat compared to ESA based on a single head-to-head study is presented in section 7.1.2 (DOLOMITES study).

7.2 Efficacy and safety of roxadustat compared to ESA for ID-DD patient pool

7.2.1 Relevant studies

As outlined in section 6.1, the integrated analyses of ID-DD patients from the ALPINE programme provides the totality of comparative efficacy and safety of roxadustat compared to ESA in this patient group.

The pre-specified integrated analyses are described in Appendix B together with the design of the individual studies. Baseline characteristics for the pooled ID-DD and stable dialysis (SD) populations are presented in appendix C together with an overview of characteristics for the total pool of dialysis patients (ID-DD plus SD).

In the integrated analysis of DD studies, the sub-pool of ID-DD patients consisted of 1043 patients from the HIMALAYAS study, 283 from the ROCKIES study, and 71 from the SIERRAS study. By far the majority to these 1,397 patients were ESA naïve at the time of study enrolment and in need of anaemia correction; the small group of 71 patients in the SIERRAS study, although pre- treated with ESA for 4 weeks or more, were nevertheless deemed in need

of anaemia correction. Thus, the pooled analysis of ID-DD patients in ALPINE represents a group of patients in need of anaemia correction (most of whom were ESA naïve).

Overall, there was no difference in demographics and anaemia baseline characteristics between the roxadustat and ESA treatment groups (Table C2) in the ID-DD sub-group. The ID-DD patient population had a mean age of 54 years, with approximately 25% of patients (in both arms) aged 65 or over. The mean Hb at baseline was < 9g/dl in both arms, and approximately 80% of patients were iron replete (ferritin ≥100 ng/mL and TSAT ≥20%). The most likely aetiolgy of CKD was diabetic nephropathy accounting for more than one third of patients in both arms.

7.2.2 Efficacy and safety – results per study

The results in the ID-DD pool with respect to efficacy and CV safety are tabulated in appendix D.

Hb

In incident dialysis patients, non-inferiority of roxadustat to ESA with respect to change in Hb was confirmed (Figure 7). [25]- Changes from baseline to weeks 28-36 without rescue therapy were, mean (SD) 2.37 (1.57) for roxadustat versus 2.12 (1.46) for ESA; LSMD (95% CI) 0.28 (0.11, 0.45). With respect to the secondary endpoint of Hb response (proportion of patients achieving Hb response at weeks 28-36), noninferiority was also met: 59.9% of patients in the roxadustat group achieved Hb response (without rescue therapy) compared to 59.6% of patients in the ESA group (difference 0.3 percentage points, 95% CI -4.5; 5.1). Figure 8 provides the weekly mean Hb over time for up to 52 weeks.

Figure 7 Mean change in Hb from baseline to weeks 28-36 (Per protocol set, ID-DD pool)

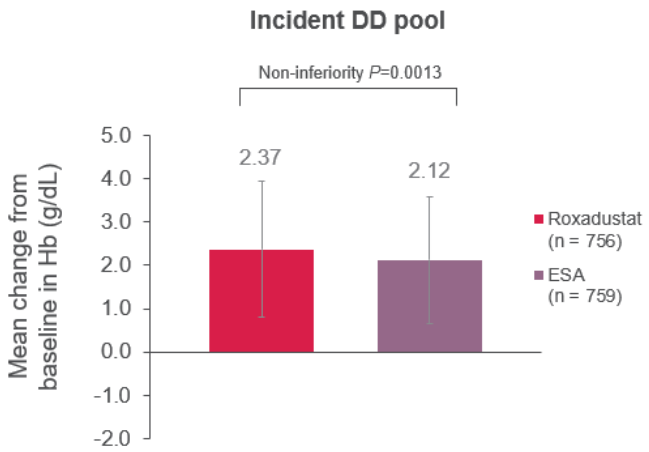
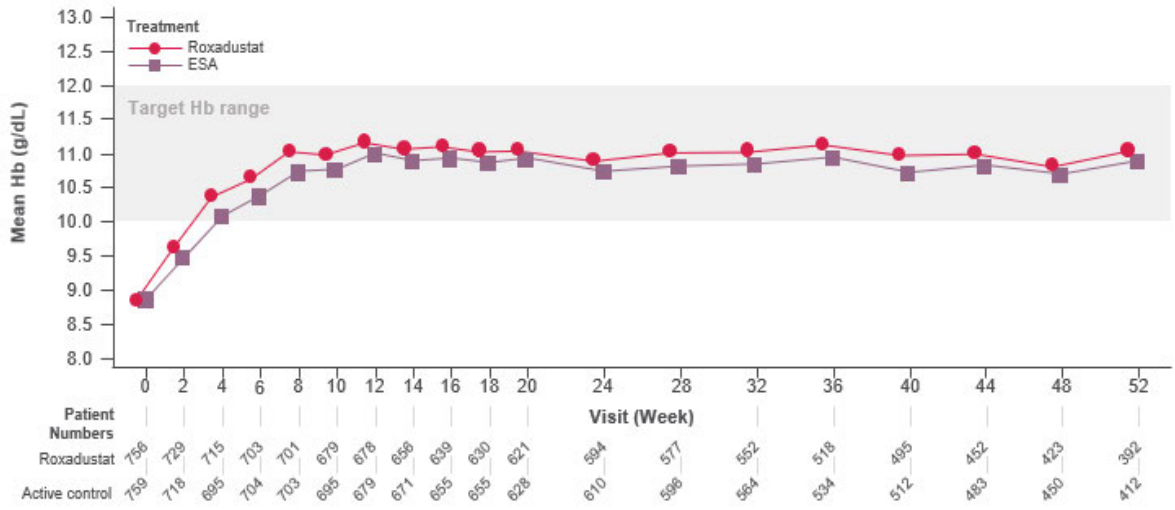


Figure 8. Mean Hb (g/dL) over time up to Week 52 in ID-DD pool (FAS population)

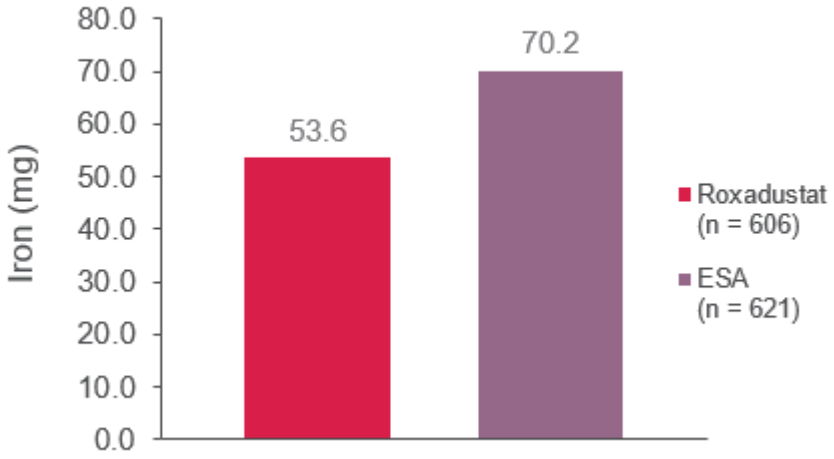


Abbreviations: DD: dose dependent; FAS: full analysis set; Hb: haemoglobin; ID: incident dialysis

IV iron and other secondary endpoints

Mean monthly IV iron dose in week 28-52 was lower in the roxadustat group compared to the ESA group (53.57 mg/month vs 70.22 mg/month; difference in mean -16.65 (95%CI: -24.8; -8.5) mg/month.[25]

Figure 9: Mean monthly IV iron (weeks 28-52)



In the ID-DD sub-pool, no differences were observed in rate of RBC transfusions (HR 0.99, 95%CI: 0.66;1,47).
No comparative analysis of health related quality of life outcomes were included in the integrated analysis of DD trials in ALPINE but were evaluated in each individual study supporting non-inferiority between roxadustat and ESA.[26]

Safety

The summary of safety outcomes is tabulated in Table E3. TEAE occurrence was comparable between the roxadustat (80.4%) and ESA (80.4%) groups. Drug-related TEAEs (9.3% vs 5.6%) , serious AEs (41.8% vs 41.5%), TEAEs leading to treatment withdrawal (33.8% vs 31.6%), and drug-related treatment discontinuation (1.3% vs 0.3%) occurred with a

somewhat higher incidence for roxadustat than ESA. [26]. Incidence and incidence rates per patient year of common SAE by MedDRA preferred term can be found in Table E4.[26] These AEs are generally in keeping with patients' condition, and without major differences between treatment arms.

Cardiovascular safety

Patients who received roxadustat compared with ESA in the incident dialysis subgroup had a numerically lower risk of all-cause mortality (HR 0.83, 95% CI 0.57; 1.19) as well as time to first event for MACE (HR: 0.83, 95% CI: 0.61;1.13) and MACE+ (HR: 0.76, 95%CI: 0.57;1.00) (Appendix D3). [25]

7.2.3 Comparative analyses

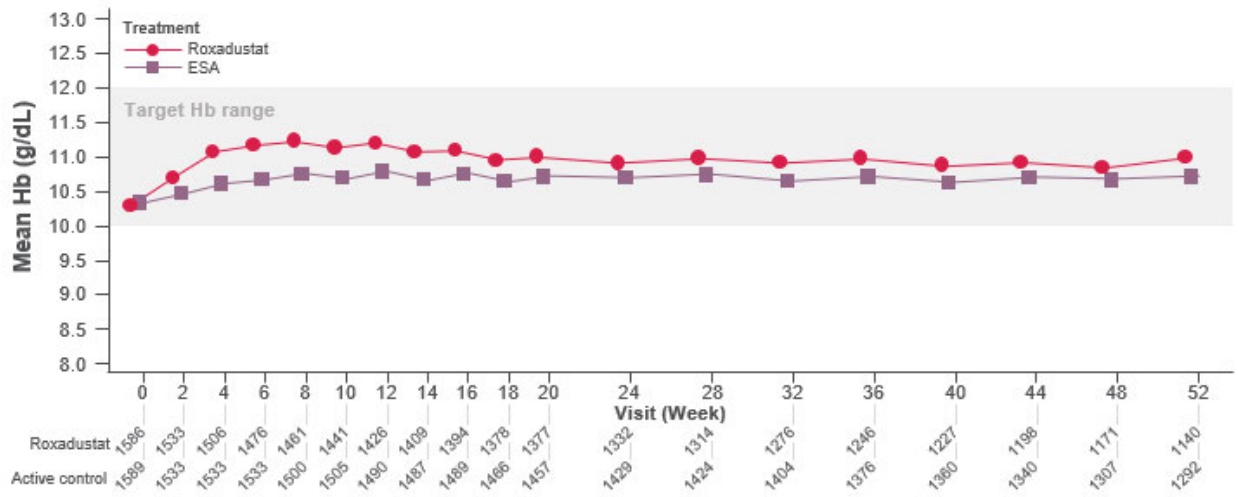
Not applicable. The clinical evidence for roxadustat compared to ESA based on a pre-specified integrated analysis of ID-DD patients in the ALPINE program is presented in section 7.2.2.

7.3 Additional evidence of efficacy and safety

7.3.1 Efficacy in stable dialysis

In the integrated analysis of patients in the stable dialysis sub-group, the change from baseline Hb to average Hb in weeks 28 to 36, without use of rescue therapy, was comparable between the roxadustat and ESA treatment groups: mean (SD) was 0.65 (1.15) in the roxadustat group versus 0.36 (1.23) in the ESA group, giving a LSM difference of 0.30 (95% CI: 0.228, 0.374; p<0.0001) in the SD pool. [25] Mean Hb over time in the SD pool remained within the target Hb range over the duration of the study for both roxadustat and ESA and is depicted in Figure 10.[25]

Figure 10. Mean Hb (g/dL) over time up to Week 52 in SD pool (FAS population)



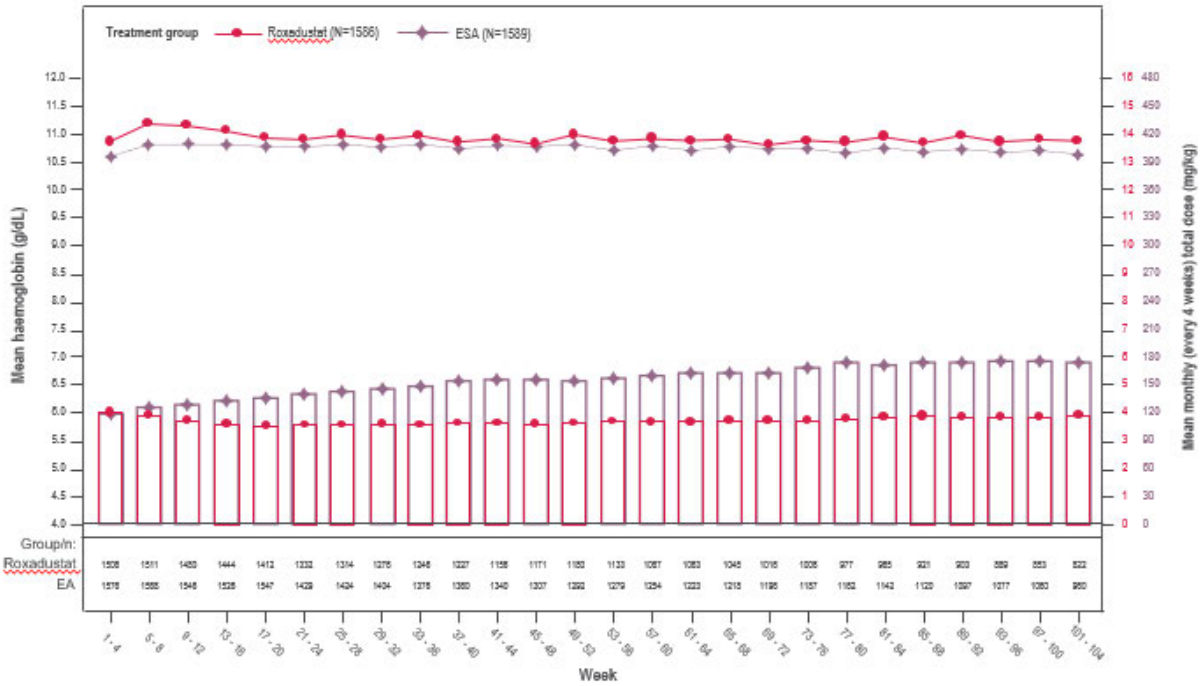
Abbreviations: FAS: full analysis set; Hb: haemoglobin; SDD: stable dialysis dependent

The mean monthly IV iron use was lower in patients receiving roxadustat compared to those receiving ESA (42.5 ± 229.8 versus 62.0 ± 148.0).[25] Furthermore in the SD pool, fewer patients in the roxadustat required RBC transfusion compared to patients treated with ESA (HR: 0.80 (95% CI: 0.66, 0.97)).[26]

The mean weekly dose of roxadustat required to maintain Hb levels within the target range in patients on stable dialysis remained fairly constant throughout the duration of the study (mean dose over weeks 1-4: 4.01 mg/kg; mean

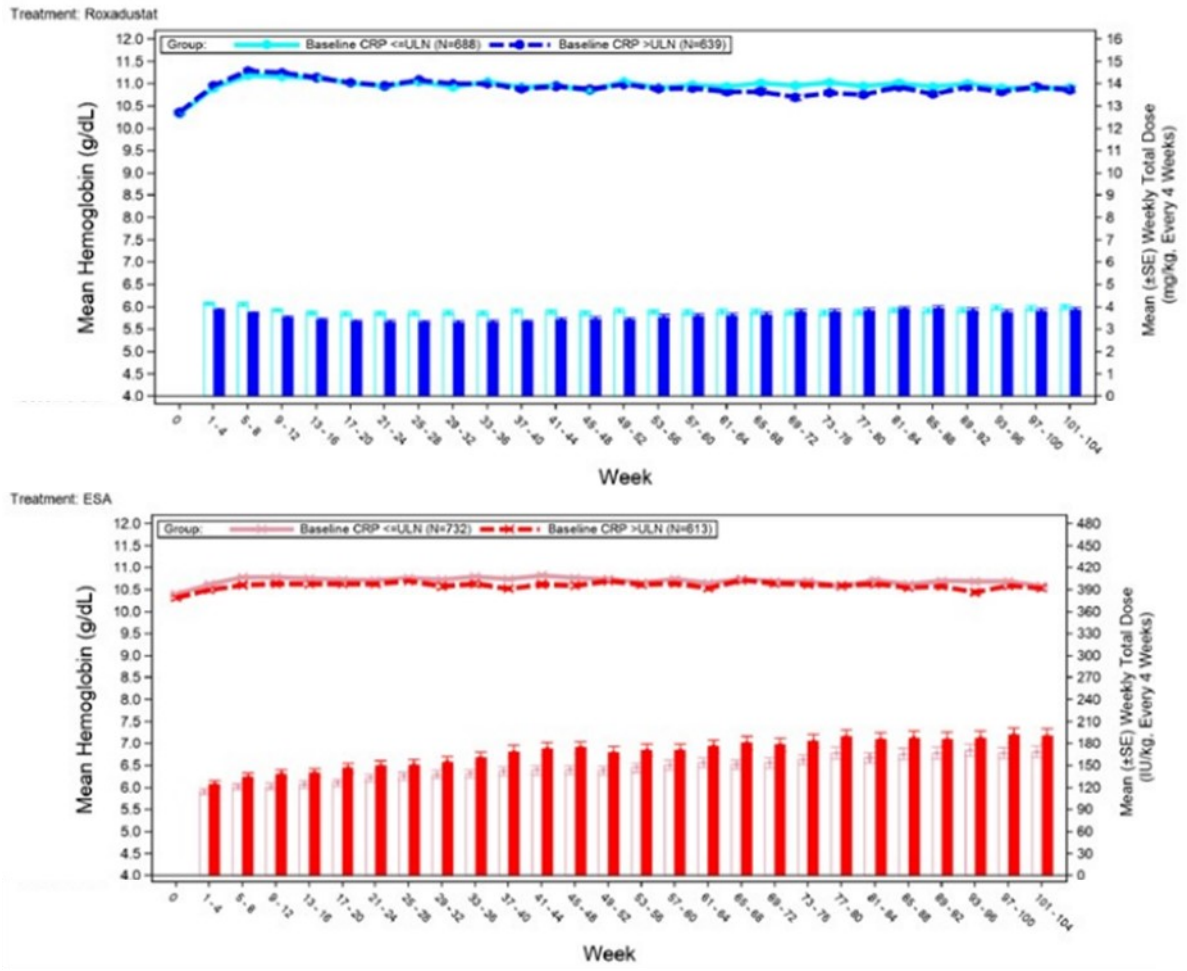
dose over weeks 101-104:3.90 mg/kg). In contrast, the mean weekly dose of ESA required to maintain target Hb levels increased by 48% from start to end of study (mean dose over weeks 1-4: 117.9 IU/kg; mean dose over weeks 101-104: 174.5 IU/kg) (Figure 11).

Figure 11. Mean dose of roxadustat versus ESA and mean achieved Hb level over 104 weeks in stable dialysis patients



Interestingly, in an analysis of dose requirements in stable dialysis patients with or without inflammation (based on a stratification of baseline hs-CRP levels above or below the upper limit of normal with cut off at > 5mg/L), the mean dose of roxadustat needed to achieve Hb levels in the target range was the same in both groups. In contrast, the ESA dose requirements to achieve target Hb were higher in patients with inflammation compared to those without (see Figure 12). This illustrates the use of higher ESA doses in patients with inflammation, where hepcidin levels are elevated restricting the availability of iron and reducing the response to erythropoietin. The observation that doses of roxadustat were the same in patients with or without inflammation is consistent with the mechanism of action of roxadustat, whereby hepcidin levels are reduced, improving absorption of iron, and mobilisation of iron from the body's iron store promoting efficient, co-ordinated erythropoiesis.

Figure 12. Mean Hb level and weekly total dose by baseline hs-CRP status for roxadustat (upper panel) and ESA (lower panel) stable dialysis patients

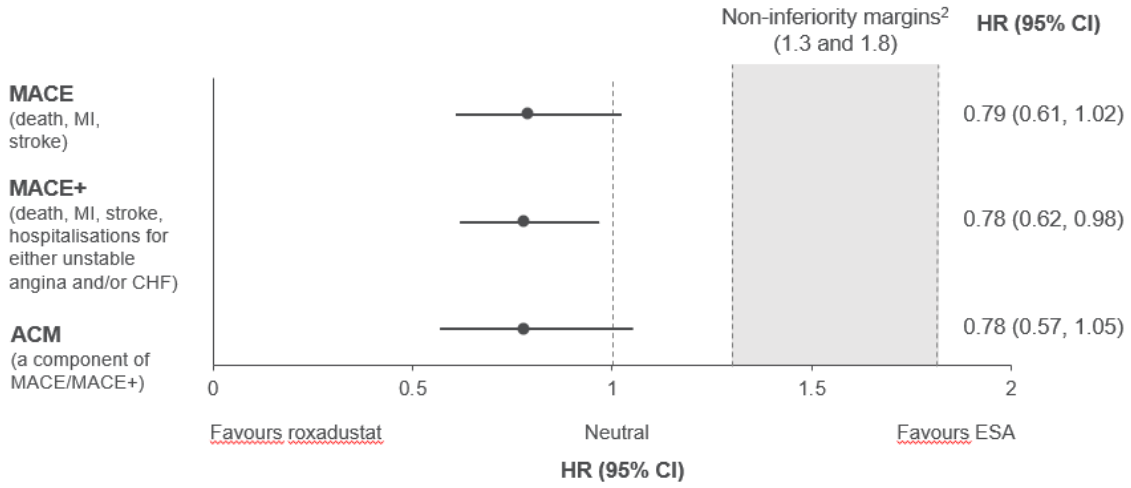


Abbreviations: Hb: haemoglobin; hs-CRP: high-sensitivity C-reactive protein; Q4W: Every 4 weeks; SE: Standard error; ULN: Upper limit of normal

7.3.2 Cardiovascular safety in Hb correction setting and SD setting

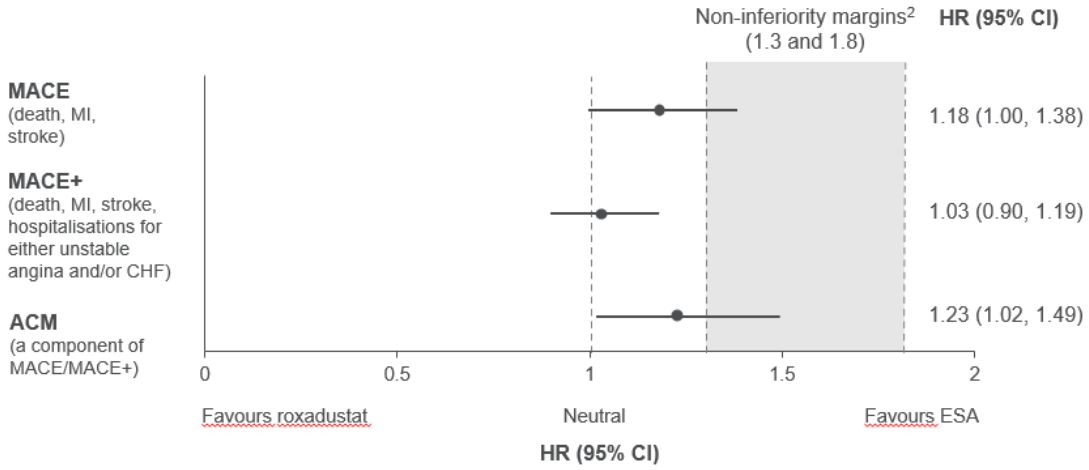
In the Hb correction setting (which includes both NDD and ID-DD patients), the analysis for MACE, MACE+ and ACM observed on treatment showed HRs of 0.79, 0.78 and 0.78, with upper limits of the 95% CIs of 1.02, 0.98 and 1.05, respectively (Figure 13). These data indicate no increased cardiovascular safety or mortality risk with roxadustat compared with ESA. Indeed, there is a consistent trend in favour of roxadustat. These data reflect CV outcomes in patients not considered stable on ESA, since essentially most were ESA-naïve at study inclusion.

Figure 13 MACE, MACE+ and ACM in patients in need of Hb correction



In the stable dialysis sub-group, all patients were stable on ESA when converted to treatment with roxadustat. Analysis of MACE, MACE+, and ACM observed on-treatment for roxadustat versus ESA showed numerically higher hazard ratios for roxadustat compared to ESA (MACE HR: 1.18 (95% CI: 1.00–1.38); MACE+ HR: 1.03 (95% CI: 0.90; 1.19), and all-cause mortality (HR 1.23, 95% CI 1.02; 1.49) (Figure 14) than those observed in the Hb correction setting:

Figure 14: MACE, MACE+ and ACM in patients on SD



As commented in the European Assessment Report for roxadustat, these hazard ratios should be interpreted with caution as they reflect a bias of switching patients stable on a treatment (ESA) to a new treatment. [28]

Such a bias is not present in the analysis of CV risk in the ID-DD pool or in the Hb correction pool (DOLOMITES and ID-DD pool) as patients were not stable on ESA treatment, being ESA-naïve at inclusion. Taken together these data are informative regarding the use of roxadustat in clinical practice and indicate that conversion of dialysis patients otherwise stable on ESA treatment is only to be considered when there is a valid clinical reason.[29]

7.3.3 LDL cholesterol

A consistent finding in all studies and integrated analyses was a lowering of LDL cholesterol with roxadustat compared with placebo or ESA. This effect was maintained throughout the duration of the study.

In the DOLOMITES study, the change from baseline in LDL cholesterol (mmol/L) to weeks 12 to 28 (LSM, 95% CI) was -0.356 (-0.432, -0.280) for roxadustat versus 0.047 (-0.033,0.127) for darbepoetin alfa, giving a LSM difference of -0.403 (0.510, 0.127) (p<0.001). [20] In the integrated analysis of ID-DD patients, the change from baseline in LDL cholesterol (mmol/L) to weeks 12 to 28 (LSM, 95% CI) was -0.610 (-0.700, -0.520) for roxadustat versus 0.157 (-0.265, 0.069) for ESA, giving a LSM difference of -0.453 (-0.575, -0.331) (p<0.0001). [25] The potential cholesterol-lowering effect of roxadustat may be mediated, in part, by the effects of HIF on degradation of the rate-limiting enzyme, 3-hydroxy-3-methylglutaryl-CoA reductase. [30]

8 Health economic analysis

8.1 Model

The economic evaluation of roxadustat for treatment of symptomatic anaemia in chronic kidney disease was conducted as a cost-comparison. Total cost was estimated from a limited societal perspective. Cost was estimated as net-present cost per patient for roxadustat and relevant comparators.

The cost-comparison approach was chosen based on the fact that the purpose of treatment is to keep patients within a target range of Hb, which is also reflected in the non-inferiority design of the trials with respect to Hb correction and maintenance.

ESAs are currently used for treatment of symptomatic anaemia in CKD in Denmark and these drugs have been the standard of care for more than 25 years. Given the long history of ESA in Denmark, none of the products has been assessed by the DMC and indeed ESA became standard of care in CKD before health technology assessment of new drugs were implemented. As a consequence, no assessments of ESA compared to no ESA treatment have been carried out in Denmark or by the UK National Institute for Health and Care Excellence. In Denmark, first sales of ESA (ATC B03XA) was recorded in MEDSTAT in 1997 and the sales volume reached 1 million DDD after approximately 5 years. Sales to the hospital sector peaked in 2007 (145 MDKK). While sales volumes have remained stable over the years 2008-2020 at around 2.6 MDDD/year, sales amounts have decreased substantially over the period. In 2017 sales amounts were smaller (59.7 MDKK) than in the first year of sales (62.0 MDKK in 1997). Given ESAs have been standard of care of symptomatic anaemia in CKD for more than 25 years and the area has been increasingly competitive, no cost-effectiveness analysis comparing roxadustat to rescue treatment alone was attempted.

As described in section 6, the expected patient population for roxadustat is patients in need of Hb correction not on dialysis or those initiating dialysis (ID-DD) without prior ESA treatment. The largest patient population is expected to be the NDD patient population based on epidemiological data of patient numbers in each segment. In order to inform the cost comparison, dosing will be based on observed comparative dosing in ALPINE.

The cost comparison is performed separately for ESA-naïve patients who are NDD (NDD-comparison) and patients starting on dialysis (ID-DD comparison).

The relevant comparators for the above patient populations are the long-acting or continuous receptor activators (darbepoetin alfa (Aranesp) or Methoxy polyethylene glycol-epoetin beta (Mircera)). The use of ESAs in Denmark is in most cases patient-administrated (or administrated during haemodialysis sessions). According to the MR treatment recommendation, the primary product is darbepoetin alfa. Methoxy polyethylene glycol-epoetin beta (MPG-EPO) is recommended as a clinical equivalent but is currently ranked as second choice based on the product's list price. Among the short acting ESAs, epoetin beta is recommended based on tender prices.

In the economic model, the cost of treatment when using roxadustat is compared to DA, MPG-EPO and epoetin beta. The long-acting ESAs are probably the most relevant comparators because these products have a more patient convenient dosing than short-acting ESAs. Short-acting epoetin beta is included as a reference treatment because comparative data on dosing of roxadustat and long-acting epoetin beta is not available for patients starting on dialysis (ID-DD comparison).

The DOLOMITES study is the only comparative study between roxadustat and ESA (darbepoetin alfa) conducted in the NDD setting. The study is furthermore conducted in a European setting; the data are therefore relevant for the main target population for roxadustat. The integrated analysis of ID-DD patients in ALPINE was used as the source for comparative data in the ID-DD subgroup. The comparator here was epoetin-alpha.

Doses in the study are comparable between study arms because the achieved Hb-levels are comparable; doses can only be fairly compared in context of outcomes in the same population.

The outcome considered in the economic evaluation is net-present value of total cost per patient. A 3.5% discount rate per year is applied for all cost accrued after year 1 using discrete discounting. Cost elements included in the analysis are regional and patient cost of medication, drug administration and i.v. iron treatment.

The duration of treatment and the time horizon is set to 5 years in both comparisons (NDD and ID-DD). Treatment for anaemia, once initiated, is generally life long and patients initiated on treatment with roxadustat can be expected to stay on treatment (unless transplanted) whether or not they initiate dialysis or switch type of dialysis. Median life expectancy on dialysis, also taking into consideration that this is an elderly population, is in the region of 4-5 years; note some patients survive without transplant for >10 years. Males and females not on dialysis at stage 4 or 5 CKD can be expected to live for a median 4-6 years or 4-8 years respectively [19]. Most patients die from cardiovascular events related to CKD before they reach dialysis.

8.2 Relationship between the data for relative efficacy, parameters used in the model and relevance for Danish clinical practice

The purpose of treatment of symptomatic anaemia in CKD is to keep patients within a target range of Hb, which is also reflected in the non-inferiority design of the trials with respect to Hb correction and maintenance. Treatment in Denmark follows the KDIGO guidelines with respect to initiation of treatment and target Hb level. The protocols for treatment in ALPINE also reflect the KDIGO guidelines. In the management of anaemia, dosing of treatments is adjusted on an individual basis and based on treatment response to reach and maintain the target Hb level.

This means that the key driver of the cost of treating symptomatic anaemia is the comparative dosing. The actual doses observed in the ALPINE programme were the source for estimating comparative dosing of roxadustat versus ESA in the cost analysis.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

In this section the relationship between trial data and model assumptions are presented with respect to comparative dosing of roxadustat, ESA and I.V. iron.

8.2.1 Presentation of input data used in the model and how they were obtained

Table 6 Input data used in the model:

Name of estimates	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated
Dose during Hb correction	Starting dose stipulated by study protocols with individually adjusted dose (every 4 weeks) for 24 weeks NDD: Average dose week 1-24 was xx mg roxadustat and xx mcg DA ID-DD: Average dose not reported	Recommended starting dose in SmPC. Linearly adjusted to starting dose of maintenance treatment (see below).	In lack of a source to estimate the dose of roxadustat during the correction phase a linear approximation was applied. The same dose model was applied for the comparators.
Dose during Hb maintenance	Weekly dose by follow-up (4 week cycles) for weeks 25-102 in DOLOMITES FAS population (NDD) and in FAS integrated ID-DD population in ALPINE (ID-DD) and SD. In DOLOMITES dosing of roxadustat and DA was available for NDD patients In the integrated ID-DD analysis dosing of roxadustat and epoetin-alfa was available. Dosing data from the maintenance phase of SD trials were applied in the extrapolation of the ID-DD dosing. The dose in the SD pool in the integrated analysis was reported in EPO IU	Weekly dose by time in maintenance treatment with extrapolation from end of observation period (102 weeks). Comparator dosing data was converted to relevant comparators using the following conversion factors EPO:DA 200 IU/mcg[31] MPG-EPO beta: DA 1.14 mcg/mcg. [32] For dosing in IU, the dose was first converted to DA then to MPG-EPO using the two conversion factors above.	**NDD:** Week 25-104. Weighted average of weekly dose in DOLOMITES week 25-104 Week 105-: Weighted average of weekly dose in DOLOMITES week 92-104 **ID-DD:** Week 25-104. Weighted average of weekly dose in DOLOMITES week 25-104 Week 105-186: Weighted average of weekly dose in ALPINE SD pool week 25-104 Week 187-: Weighted average of weekly dose in DOLOMITES SD pool week 92-104

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Name of estimates	Results from study or indirect treatment comparison (ITC), (clarify if ITT, per-protocol (PP), safety population)	Input value used in the model	How is the input value obtained/estimated
Iron use	NDD: Average weekly dose of iv iron during weeks 52-104 in DOLOMITES FAS population ID-DD Average weekly dose in weeks 28-52 in FAS integrated ID-DD population	Equivalent weekly dosing to those observed in clinical program assumed administrated regularly over time horizon.	Annual cumulative dose estimated from weekly dose in studies multiplied by 52 The cumulative annual dose was assumed administrated as 1,000 mg IV iron infusions

8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

8.2.2.1 Patient population

The Danish patient population: ESA-naïve patients who are NDD and ESA-naïve patients incident to dialysis

Patient population in the clinical documentation submitted: ESA-naïve patients who are NDD and patients incident to dialysis

Patient population in the health economic analysis submitted: ESA-naïve patients who are NDD and patients incident to dialysis

Comparability of the study population to the Danish health care setting is discussed in appendix C.

8.2.2.2 Intervention

Intervention as expected in Danish clinical practice : Roxadustat. Individually titrated dose to correct and maintain Hb levels.

Intervention in the clinical documentation submitted: Roxadustat. Individually titrated dose to correct and maintain Hb levels. In ALPINE treatment follow-up was up to 104 weeks.

Intervention as in the health economic analysis submitted: Roxadustat. Individually titrated dose to correct and maintain Hb levels. Treatment duration was assumed to be 5 years for both sub-groups (NDD and ID-DD) and assumed to be the same for the intervention and comparator.

8.2.2.3 Comparators

The current Danish clinical practice: ESA. Individually titrated dose to correct and maintain Hb levels. Treatment is considered life-long.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Comparator(s) in the clinical documentation submitted: ESA. Individually titrated dose to correct and maintain Hb levels. In NDD, the ESA used was darbepoetin alfa and in ID-DD it was epoetin alfa. Treatment follow-up was up to 104 weeks.

Comparator(s) in the health economic analysis submitted: ESA. Individually titrated dose to correct and maintain Hb levels. Costs are calculated using the observed dosing in ALPINE and calculated to the two long-acting ESAs darbepoetin alfa and MPG-epoetin beta and the short-acting ESA epoetin beta. When applicable, dosing observed in ALPINE was converted between ESA using fixed conversion factors. Treatment duration was assumed to be 5 years for both sub-groups (NDD and ID-DD) and assumed to be the same for the intervention and comparator.

8.2.2.4 Relative efficacy outcomes

The cost comparison does not consider relative efficacy. The treatment goal is to maintain patients within a target range of Hb which is also reflected in the non-inferiority designs of the trials in the ALPINE clinical programme. This means that the dosing needed to correct and maintain Hb over time is the key comparative parameter. This is presented in section 9.5. The clinical studies and the RADS guidelines builds on the international guidelines for initiation and maintenance of treatment. The means that the comparative dosing data from ALPINE is relevant for the predicted dosing in Danish clinical practice with no need to adjust for differences in target Hb range.

8.2.2.5 Adverse reaction outcomes

Cost of side-effects are not considered in the cost-analyses for the intervention or the comparators.

8.3 Extrapolation of relative efficacy

The analysis is based on the documented non-inferior efficacy of roxadustat and ESA based on head-to-head trials. The clinical documentation and the implementation in the cost analysis is presented in section 8.

8.3.1 Time to event data – summarized:

Not applicable. No time to event data is applied in the model.

8.4 Documentation of health-related quality of life (HRQoL)

Not applicable. No cost utility analysis performed.

8.5 Resource use and costs

Pharmaceutical costs

The estimation of pharmaceutical cost is divided into cost during Hb correction and Hb maintenance.

Dosing in the population of ESA-naïve NDD patients were based on data from the DOLOMITES trial comparing roxadustat and darbepoetin alfa. The multicentre, European DOLOMITES trial provides robust data on comparative dosing of roxadustat and darbepoetin alfa in patients who were ESA-naïve and NDD at the time of treatment initiation.

In DOLOMITES, the average weekly dosing during the first 24 weeks was 267mg/week for the correction period and 205 mg/week for the maintenance period. For darbepoetin alfa the average weekly dose during correction period was 33.3 mcg/week and during maintenance 36.0 mcg/week.

Dosing in the ID-DD population was estimated from the integrated analysis of studies of patients on dialysis in ALPINE. In the sub-pool of ID-DD patients the common comparator was EPO-alfa.

Data are available as data on file (02). [33]. Table 7 presents the overview of mean weekly dosing by study arm and time since start of treatment.

Table 7 Average weekly dose (95% CI) by treatment phase and product in ALPINE

	Week 1- 24	Week 25-104	Week 92-104
NDD. Roxadustat	[redacted]	[redacted]	[redacted]
NDD. DA	[redacted]	[redacted]	[redacted]
ID-DD. Roxadustat	[redacted]	[redacted]	[redacted]
ID-DD. EPO alfa	[redacted]	[redacted]	[redacted]
SD. Roxadustat	[redacted]	[redacted]	[redacted]
ID-DD. ESA (IU*)	[redacted]	[redacted]	[redacted]

For the economic model, the roxadustat dosing in the correction period in ALPINE is believed to overestimate the dosing in clinical practice. According to the initial protocols, the starting dose should be 300mg/week for patient with a body weight above 70.0 kg and 210 mg/ week for patients with a lower body weight. However, according to the SmPC, the starting dose should be 210 mg/week for patients with a body weight below 100 kg.[29] The mean body weight in the roxadustat arm was 76.9 kg in DOLOMITES[20]. This suggest that the average dosing in the trial would overestimate dosing in clinical practice. The following approach was taken to estimate the dosage during the correction period:

- The standard starting dose from the SmPCs were applied for week 1 and weekly dosing was assumed to be adapted linearly to the maintenance dose. This means that the average weekly dose during the correction phase was the mid-point between the starting dose and the maintenance dose. For roxadustat, the starting dose is 210mg/week and for darbepoetin alfa the recommended starting dose is 0.75 mcg/kg every second week. At an average body weight of 77.61 kg[20], this gives a recommended starting dose for darbepoetin alfa of 58.2mcg per 2 weeks or 29.1 mcg/week.

- The starting dose for the maintenance phase was sourced from the ALPINE programme. For NDD, the average weekly dose during week 25-104 in DOLOMITES were applied for the maintenance phase. For the IDD, the average maintenance dose (week 25-104) was sourced from the ALPINE incident dialysis subgroup. Long-term dosing was estimated as follows:

    - For NDD, the mean weekly dose from the last 12 weeks of observation (week 92-104) in DOLOMITES was applied from week 105 in the model for the remaining weeks of the analysis

    - For IDD, the average maintenance dose (week 25-104) from ALPINE stable dialysis subgroup was applied for weeks 105-184 in the model. The average weekly dose from the last 12 week of observation in the SD maintenance period (week 92-104 in the trials) was then applied from week 187 and for the remaining weeks in the cost-calculation.

- For MGP-EPO and epoetin beta, dosing in the correction phase was estimated from the SmPC starting dose and the converted starting maintenance dose using the following conversion rates. Conversion from DA to MPG-EPO was estimated from an European MPG-EPO to DA conversion study. After 6 month the conversion ratio relative to pre-switch MPG-EPO dosing was 0.88 mcg DA: 1 mcg MPG-EPO. [32]. Conversion from EPO to DA was done using the SmPC conversion factor in the Aranesp SmPC [31] and in line with the TLV assessment of roxadustat[34].

The resulting accumulated dose using the above assumption over a 5-year horizon is shown in Table 8. The ratio of DA to roxadustat dosing is 0.178 (mcg/mg) in NDD and 0.173 (mcg/mg) in ID-DD and the ratio of EPO to roxadustat dosing is 33 IU/mg in NDD and 32 IU/mg in ID-DD.

Table 8 Cumulative dose by treatment arm in the model (undiscounted)

	Cumulative dose		
	Units	Ratio	
NDD			
Roxadustat (mg)	[redacted]		
Darbepoetin alfa (mcg)	[redacted]	0.178	mcg/mg
MPG Epoetin beta (mcg)	[redacted]	0.202	mcg/mg
Epoetin beta (IU)	[redacted]	33	IU/mg
ID-DD			
Roxadustat (mg)	[redacted]		
Darbepoetin alfa (mcg)	[redacted]	0.173	mcg/mg
MPG Epoetin beta (mcg)	[redacted]	0.196	mcg/mg
Epoetin beta (IU)	[redacted]	32	IU/mg

No drug wastage was included in the economic calculation. All the products are available in multiple dose strengths to fit the dose titration schedules suggested in the SmPCs. Furthermore, dose changes are not recommended at a frequency of less than once per 4 weeks. This means that patients on subcutaneous ESA will always use a 1 or 2 full syringes/ pens per four-week period and patients on roxadustat will use a full pack (or combination of two packs) during a four-week period.

The estimated weekly dose was multiplied by the cost per dose unit (Table 9) estimated from the DkMA price database (Medicinpriser.dk price period 20220321). The overall price per dose unit was estimated as the average of the minimum cost per unit across available dose strengths. The model allows for estimating using Amgros purchase prices where different unit cost apply for darbepoetin alfa in strength up to 80 mcg and above 80 mcg. In DOLOMITES, [redacted] of ESA administrations in maintenance were 40 mcg/week or less (which – if assumed administrated every 2 weeks - would require a syringe of 80 mcg or less).

Administration cost

Roxadustat is assumed to be administrated by the patients three times per week. Darbepoetin alfa was assumed to be administrated every two weeks and MPG-EPO every four weeks. The subcutaneous formulation was assumed to be mainly administrated by patients themselves and administration cost was assumed to consist of patient cost only (10 minutes per administration) – see Table 11. This is a conservative assumption as some patients may need support in administration of injection from municipality nurses. In a review of ESA, TLV in Sweden estimated that 18% of patients treated with ESA would need some form of support with injections from municipality nurses. [34]

For patients on ESA, cost associated with training in self-injection technique for the sub-cutaneous injection was included in the calculations. The training is assumed to take place at the first initiation of treatment (no additional cost) and at the second injection (1 to 2 weeks later). For the first training session, only patient cost (30 minutes patients time) is considered. For the second training session one additional outpatient visit was assumed for this session (Table 10) as well as patient time and travel cost – see Table 11.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

ESA should be distributed in cool-chain. No cost associated with transport or storage of the product was included.

IV iron cost

Iron doses required by treatment arm were informed by long-term average doses observed in ALPINE. In the NDD population, average monthly dosing during week 52-104 was available in DOLOMITES. For ID-DD, the average monthly dose during weeks 28-52 was available. The observed monthly dosages was multiplied by 12 to form an estimate of cumulative annual IV iron need.

Based on the RADS recommendations for IV iron administration in NDD, HHD, and PD, dosages are assumed to be given as 1,000 mg doses. The number of administrations of IV iron per year was calculated by dividing the cumulative annual dose by 1,000 mg.

Cost of IV iron was estimated using Diafer pharmaceutical purchase price per mg multiplied by 1,000 per administration session (Medicinpriser.dk price period 20220321)). No wastage was assumed. Regional cost was estimated using DRG tariff for an outpatient visits – see Table 10.

Patient cost associated with IV iron infusion was calculated based on 1 hour clinic time plus transportation time and cost (Table 11).

Summary tables

Table 9 Pharmaceutical costs used in the model

Costs	Average of lowest price per dose unit across strengths	
Roxadustat	2.479	per mg
ESA		
Darbepoetin alfa	14.286	per mcg
MPG epoetin beta	14.924	per mcg
Epoetin beta	0.095	per IU

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 10 Hospital costs used in the model

Costs	Number of units		DKK (per unit of measurement used in the model)
	Intervention	ESA	
Additional outpatient visit for training sc injection technique	0	1	2,038 DKK (per visit)
Administration of iv iron			2,038 DKK (per administration)
NDD	[redacted]	[redacted]	
ID-DD	[redacted]	[redacted]	
IV Iron (Diafer)	1000 mg / administration		2.723 DKK/mg

Table 11 Patient costs used in the model

	Unit cost	Cost of training in SC technique (total)	ESA administration (per administration)	Iron administration (per administration)
Patient time	181.00	1.00	0.17	1.00
Travel time	181.00	1.00	0.00	1.00
Travel distance (km round-trip)	3.51	40	0	40
Total patient cost		**502.40**	**30.17**	**502.40**

8.6 Results

8.6.1 Base case overview

Table 12 Base case overview

Comparator	ESA
Type of model	Cost-comparison
Time horizon	5 years
Treatment line	1st line. Subsequent treatment lines not included.
Measurement and valuation of health effects	Not applicable
Included costs	Pharmaceutical costs Administration costs Cost iv iron treatment Patient costs

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Dosage of pharmaceutical	Individual titrated dose needed for Hb correction and maintenance
Conversion factors for ESA	1 mcg darbepoetin alfa = 1.14 mcg MPG epoetin beta 1 mcg darbepoetin alfa = 200 IU epoetin beta
Average time on treatment	5 years
Parametric function for dosing	Intervention: log-log linear function of time on treatment Comparator: log-log linear function of time on treatment
IV iron dose	Annual dose as observed in clinical program. Assumed administrated as infusions of 1,000 mg iron per infusion.

8.6.2 Base case results

Table 13 presents the base case cost comparisons of roxadustat to ESAs in the ID-DD population. Evaluated at list prices, roxadustat is associated with a lower cost than all three comparators. Table 14 presents the break-down of incremental cost (roxadustat compared to each of the ESAs) by cost-elements. Cost and incremental costs are mainly driven by the drug acquisition cost of products.

Table 13 Base case results (NDD)

	Roxadustat	Darbepoetin Alfa	MPG epoetin alfa	Epoetin beta
Drug acquisition costs	121,562	131,047	149,168	166,562
Administration costs	0	2,038	2,038	2,038
IV iron costs	5,067	8,483	8,483	8,483
Total regional cost	**126,629**	**141,568**	**159,690**	**177,083**
Patient cost	527	5,050	3,398	8,715
Total cost	**127,156**	**146,618**	**163,088**	**185,798**
Incremental cost		**-19,463**	**-35,932**	**-58,642**

Table 14 Incremental cost (roxadustat compared to comparator) by cost element (NDD)

	Darbepoetin Alfa	MPG epoetin alfa	Epoetin beta
Drug acquisition costs	-9,485	-27,606	-44,999
Administration costs	-2,038	-2,038	-2,038
IV iron costs	-3,417	-3,417	-3,417
Regional cost	**-14,940**	**-33,061**	**-50,454**
Patient cost	-4,523	-2,871	-8,188
Total cost	**-19,463**	**-35,932**	**-58,642**

Table 15 and Table 16 provides the cost comparison for the ID-DD population. Results are similar to the results for the NDD population.

Table 15 Base case results (ID-DD)

	Roxadustat	Darbepoetin Alfa	MPG epoetin alfa	Epoetin beta
Drug acquisition costs	161,019	166,112	189,280	211,499
Administration costs	0	2,038	2,038	2,038
IV iron costs	14,513	19,023	19,023	19,023
Total regional cost	**175,532**	**187,173**	**210,341**	**232,560**
Patient cost	1,509	6,146	4,494	9,811
Total cost	**177,041**	**193,319**	**214,835**	**242,371**
Incremental cost		-16,278	-37,794	-65,330

Table 16 Incremental cost (roxadustat compared to comparator) by cost element (ID-DD)

	Darbepoetin Alfa	MPG epoetin alfa	Epoetin beta
Drug acquisition costs	-5,093	-28,260	-50,480
Administration costs	-2,038	-2,038	-2,038
IV iron costs	-4,511	-4,511	-4,511
Regional cost	**-11,641**	**-34,809**	**-57,028**
Patient cost	-4,637	-2,985	-8,302
Total cost	**-16,278**	**-37,794**	**-65,330**

8.7 Sensitivity analyses

8.7.1 Deterministic sensitivity analyses

Univariate sensitivity analyses were performed by varying the key input parameters one by one. Where applicable the 95% confidence interval limits for the parameter were applied as low/high input value. Otherwise a 15% change from base case input value were used.

Table 17 presents the results for the NDD patients. The comparison is made to darbepoetin alfa since the base case savings relative to the other comparators were larger in the base case analysis. None of the input parameters tested would change the conclusion that roxadustat is a cost-saving alternative to darbepoetin alfa in patients who are NDD at the time of initiating treatment.

Table 17 One-way sensitivity analyses results (NDD)

Parameter	Base case value	Alternative value		Incremental cost. Darbepoetin alfa
Base case	-	-	-	**-19,463**
Horizon (years)	5	4	±1 year	-15,400
		6		-23,388
Roxadustat correction dose (mg/week)	210.00	178.50	±15%	-20,439
		241.50		-18,486

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Parameter	Base case value	Alternative value		Incremental cost. Darbepoetin alfa
Roxadustat maintenance dose (mg/week)	205.00	184.00	95% CI	-24,135
		225.00		-15,013
Roxadustat long-term maintenance dose (mg/week)	199.00	177.00	95% CI	-27,140
		221.00		-11,785
ESA correction dose (mcg/week)	29.10	24.74	±15%	-18,654
		33.47		-20,272
ESA Maintenance dose (mcg/week)	36.00	31.90	95% CI	-14,008
		40.20		-25,051
ESA long-term maintenance dose (mcg/week)	37.26	32.90	95% CI	-10,364
		41.60		-28,519
Darbepoetin administration (correction; injections/month)	2.00	1.70	±15%	-19,408
		2.30		-19,517
Darbepoetin administration (maintenance; injections/month)	2.00	1.70	±15%	-18,967
		2.30		-19,958
Roxadustat iron administration (number/ year)	0.22	0.12	95% CI	-21,946
		0.32		-16,981
ESA iron administration (number/ year)	0.38	0.23	95% CI	-15,899
		0.52		-23,017
Cost iron administration (DKK/infusion)	2038.00	1732.30	±15%	-19,246
		2343.70		-19,679

Table 18 presents the results for the ID-DD patients. The comparison is made to epoetin beta and darbepoetin alfa. Epoetin beta was included because the dosing input for ESA was based on EPO (epoetin alfa) dosing in ALPINE, and darbepoetin alfa was included because the base case savings of roxadustat relative to the other comparators were larger in the base case analysis. None of the input parameters tested would change the conclusion that roxadustat is a cost-saving alternative to darbepoetin alfa in patients who are ID-DD at the time of initiating treatment. The parameter with the highest impact on the comparison to darbepoetin is not surprisingly the conversion factor used to recalculate the EPO dosing observed in the trial to darbepoetin alfa. The lower value was the base case input (based on the Aranesp SmPC) minus 15%. In a recent assessment by the TLV, a conversion rate of 200 IU:mcg was applied in the TLV base case but the assessment report mentions that in previous assessments input from the Swedish National Kidney Registry had suggested that 200 IU/mcg is more likely to be above what is used in Swedish clinical practice.[34] In the sensitivity analysis we therefore applied a 15% lower conversion factor in the sensitivity analysis. The upper value is based on the ratio of WHO defined daily dosages (1000 UI : 4.5mcg=222 IU/mcg).

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table 18 One-way sensitivity analyses results (ID-DD)

Parameter	Base case value	Alternative value		Incremental cost	
				Epoetin beta	Darbepoetin alfa
Base case	-	-	-	**-65,330**	**-16,278**
Horizon (years)	5	4	±1 year	-51,169	-12,416
		6		-79,013	-20,009
Roxadustat correction dose (mg/week)	210	179	±15%	-66,307	-17,254
		242		-64,354	-15,302
Roxadustat maintenance dose (mg/week)	257	238	95% CI	-69,608	-20,556
		277		-60,931	-11,879
Roxadustat stable dialysis dose (mg/week)	274	263	95% CI	-67,442	-18,390
		286		-63,131	-14,079
Roxadustat long-term maintenance dose (mg/week)	284	271	95% CI	-67,429	-18,377
		297		-63,229	-14,177
EPO correction dose (IU epoetin/week)	4,657	3,958	±15%	-64,501	-16,278
		5,355		-66,160	-16,278
EPO Maintenance dose (IU/week)	8,887	8,178	95% CI	-59,287	-11,562
		9,596		-71,376	-20,996
EPO stable dialysis dose (IU/week)	9,366	8,854	95% CI	-61,653	-13,408
		9,878		-69,007	-19,147
EPO long-term maintenance (IU/week)	10,168	9,581	95% CI	-61,699	-13,444
		10,755		-68,966	-19,115
EPO administration (correction; injections/month)	4.00	3.40	±15%	-65,222	-16,278
		4.60		-65,439	-16,278
EPO administration (maintenance; injections/month)	4.00	3.40	±15%	-64,339	-16,278
		4.60		-66,321	-16,278
DA administration (correction; injections/month)	2.00	1.70	±15%	-65,330	-16,224
		2.30		-65,330	-16,332
DA administration (maintenance; injections/month)	2.00	1.70	±15%	-65,330	-15,782
		2.30		-65,330	-16,773
Roxadustat iron administration (number/ year)	0.64	0.57	95% CI	-67,056	-18,004
		0.71		-63,617	-14,564
ESA iron administration (number/ year)	0.84	0.77	95% CI	-63,590	-14,537
		0.91		-67,059	-18,007
Cost iron administration (DKK/infusion)	2,038.00	1,732.30	±15%	-65,045	-15,992
		2,343.70		-65,616	-16,563

Parameter	Base case value	Alternative value		Incremental cost	
				Epoetin beta	Darbepoetin alfa
Conversion factor (IU EPO/mcg darbepoetin alfa)	200	170	See text	-65,330	-44,640
		222		-65,330	-351

8.7.2 Probabilistic sensitivity analyses

Probabilistic sensitivity analysis not performed.

9 Budget impact analysis

Roxadustat gives the possibility of a new approach to treating anaemia in patients with CKD; in alignment with available evidence and the prescribing information (Evrenzo Summary of Product Characteristics, SmPC) roxadustat is most likely to be introduced in new patients previously untreated with ESA who are not yet on dialysis or who are initiating dialysis. As described in section 5, Astellas expect the incident number of patients eligible for treatment to be approximately 430 patients each year. Based on the Danish market conditions and the current treatment recommendation, Astellas assumes that roxadustat will be used for 20% of the eligible NDD patients in year 5 and 10% of the eligible IDD patients in year 5.

Budget impact was estimated separately for NDD (section 9.1) and ID-DD (section 9.2). Total impact on regional budgets is reported in Table 27, section 9.3.

9.1 ESA-naïve patients who are NDD

Number of patients

The number of incident (new) ND patients developing anaemia each year to the degree warranting treatment with roxadustat (symptomatic with Hb < 10g/dL as for ESA initiation) is estimated based on prior studies of incidence to be in the region of 10% of the prevalent population – i.e., 240 ND-CKD patients in need of Hb correction will initiate treatment annually. [redacted]

Table 19 Number of ESA-naïve NDD patients expected over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Roxadustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Darbepoetin alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPG epoetin beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Epoetin beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	240	480	720	960	1,200

Table 20 Number of ESA-naïve NDD patients expected over the next five-year period - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Roxadustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Darbepoetin alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPG epoetin beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Epoetin beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	240	480	720	960	1,200

Expenditure per patient

Table 21 presents the annual cost per patient and product. The costs were estimated using the cost analysis presented above using the base case assumption for the NDD population, but excluding patient time and travel cost and without applying discounting.

Table 21 Costs per patient per year (ESA-naïve NDD patients)

	Year 1	Year 2	Year 3	Year 4	Year 5
Roxadustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Darbepoetin alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPG epoetin beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Epoetin beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Budget impact

The budget impact at public prices is presented in Table 22. Introduction of roxadustat is associated with savings on regional budget of 734,403 DKK in year 5 after achieving a positive DMC recommendation.

Table 22 Expected budget impact of recommending the pharmaceutical for ESA-naïve NDD patients

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Drug acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: IV iron costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minus: The pharmaceutical under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Drug acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: IV iron costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.2 ESA-naïve patients starting dialysis (ID-DD)

Number of patients

According to the Danish Renal Registry approximately 610 patients initiate dialysis per year. It is estimated that there will be a minor share of patients entering dialysis who are not previously treated with ESA. By combining information from the Swedish Renal Registry and the Danish Renal Registry, Astellas assume that 190 IDD patients not previously treated with ESA are in need of Hb correction each year. [redacted]

Table 23 and Table 24 presents the cumulative patient numbers by year and treatment with and without introduction of roxadustat as a treatment for symptomatic anaemia in ESA-naïve patients starting dialysis.

Table 23 Number of ESA-naïve ID-DD patients expected over the next five-year period - if the pharmaceutical is introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Roxadustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Darbepoetin alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPG epoetin beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Epoetin beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	190	380	570	760	950

Table 24 Number of ESA-naïve ID-DD patients expected over the next five-year period - if the pharmaceutical is NOT introduced

	Year 1	Year 2	Year 3	Year 4	Year 5
Roxadustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Darbepoetin alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPG epoetin beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Epoetin beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Total number of patients	190	380	570	760	950

Expenditure per patient

Table 25 presents the regional expenditure per patients. The cost was estimated using the base case assumptions for ID-DD in the cost-analysis but excluding patient cost and discounting.

Table 25 Costs per patient per year (ESA-naïve ID-DD patients)

	Year 1	Year 2	Year 3	Year 4	Year 5
Roxadustat	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Darbepoetin alfa	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
MPG epoetin beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Epoetin beta	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Budget impact

Introduction of roxadustat as a treatment of symptomatic anemia in ESA-naïve patients starting dialysis (ID-DD) and in need of Hb-correction results in a saving on regional budget of 435,325 DKK in year 5.

Table 26 Expected budget impact of recommending the pharmaceutical for the ESA-naïve ID-DD patients

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Drug acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: IV iron costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minus: The pharmaceutical under consideration is NOT recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Drug acquisition costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: Administration costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Of which: IV iron costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

9.3 Total budget impact

The total budget impact of introduction of roxadustat for but NDD and ID-DD patient population are shown in Table 27. The year-5 savings on regional budgets amount **1,2 million** DKK when estimated at current list prices.

Table 27 Expected budget impact of recommending the pharmaceutical for NDD and ID-DD

	Year 1	Year 2	Year 3	Year 4	Year 5
The pharmaceutical under consideration is recommended	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Minus: **The pharmaceutical under consideration is NOT recommended**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Budget impact of the recommendation	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

10 Discussion on the submitted documentation

The aetiology of anaemia of CKD is multifactorial involving not only a relative lack of EPO but also disruption in oxygen-sensing and iron metabolism, often exacerbated by chronic inflammation. Roxadustat is a first-in-class oral HIF-PHI offering a new approach to the management of anaemia of CKD compared to current standard of care. Treatment with roxadustat leverages the body's natural capacity (oxygen sensing or HIF pathway) to promote a coordinated erythropoietic response, activating a number of genes that stimulate erythropoietin production and improve iron regulation, as well as overcoming the negative impact of inflammation by downregulating hepcidin. This results in improved iron bioavailability, increased Hb production and increased red cell mass. Roxadustat has been studied in ALPINE - a robust clinical trial programme including more than 9,000 patients worldwide.

The results from the clinical trial programme establish that roxadustat provides a viable oral alternative to injectable ESAs for the treatment of anaemia of CKD: roxadustat was non-inferior to ESA in achieving and maintaining haemoglobin within the target range of 10-12g/dL. Oral treatment may be of particular benefit to patients who require correction of Hb in non-dialysis and home dialysis settings.

Hb response with roxadustat was observed within 4 weeks in the correction setting, and mean Hb levels were maintained in the target range over the duration of the respective studies with a stable mean dose. In contrast with ESA treatment, there was a tendency for dose requirements to increase over time on dialysis, possibly linked to chronic inflammation associated with CKD. It is also noteworthy that the sustained increase in haemoglobin with roxadustat is achieved with a lower EPO levels (within the physiological range) than with ESA. It has been suggested that off-target effects of supraphysiological levels of EPO with ESA treatment, contribute to CV morbidity especially at higher ESA doses [35]. Having a new treatment option may give the possibility of avoiding supraphysiological levels of EPO and the scenario where ESA dose needs to be escalated over time with potential consequences for elevated CV risk [36].

Importantly, comparable Hb target levels for roxadustat versus ESA were achieved with less use of IV iron. In the incident and stable dialysis settings the mean monthly iron use was 25% and 30% lower respectively with roxadustat versus ESA. Avoiding or reducing the need for IV iron administration simplifies anaemia treatment for non-dialysis and home dialysis patients (who would otherwise need a hospital visit). The overall medication burden and potential risk of adverse outcomes from this intervention is also less.

The fact that fewer patients require IV iron may also simplify treatment for the nephrologist; even after 25 years of experience of treating anaemia with iron and ESA, the optimal balance of these agents is not known [37, 38]. Since IV iron can be used to increase Hb and enhance ESA response, target Hb can be achieved via different strategies for balancing iron and ESA with either more or less of one agent than the other (i.e. low dose ESA and high dose iron or vice versa). By upregulating the body's own physiological process to make RBCs and making use of endogenous sources of iron and EPO, roxadustat better addresses the multi-faceted nature of anaemia and may thereby help simplify treatment.

In the dialysis setting, fewer patients required RBC transfusions on roxadustat compared with those treated with ESA. RBC transfusions carry a risk of complications, and the alloantibodies generated by transfusion can it make it difficult to transplant patients. RBC transfusions are therefore considered a last resort option in the guidelines and any intervention which reduces their need, can be viewed as a valuable additional benefit.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Overall, in terms of its clinical use, roxadustat presents a viable alternative to ESA for the treatment of anaemia of CKD, showing non-inferiority to ESA in correcting and maintaining Hb levels within the target range and with a similar safety profile. The oral route of administration for roxadustat and the lower number of injected therapies needed may represent an advantage for distinct patient groups.

The economic analysis consist of a cost comparison of roxadustat to ESA in ESA-naïve CKD patients in need of anaemia treatment. The analysis is mainly driven by the cost of roxadustat/ ESA and is supported by directly observed dosing during the maintenance phase comparing roxadustat and darbepoetin alfa (NDD) and EPO (in DD patients). One weakness in the economic analysis is that the recommended weight-based starting dose in the SmPC for ESA-naïve patients is lower than was used in the ALPINE clinical program, which adds uncertainty to the estimation of dose in the initial treatment phase (start of treatment to start of maintenance, when dose has been appropriately adjusted to attain Hb in the target range). The economic analysis show that the per patient cost of roxadustat is within range of the cost of the long-acting ESAs and short-acting epoetin beta when assessed at pharmacy purchase prices.

11 List of experts

Not applicable

12 References

1. Dmitrieva O, de Lusignan S, Macdougall IC, Gallagher H, Tomson C, Harris K, et al. Association of anaemia in primary care patients with chronic kidney disease: cross sectional study of quality improvement in chronic kidney disease (QICKD) trial data. BMC Nephrol. 2013;14:24.
2. Evans M, Bower H, Cockburn E, Jacobson SH, Barany P, Carrero J-J. Contemporary management of anaemia, erythropoietin resistance and cardiovascular risk in patients with advanced chronic kidney disease: a nationwide analysis. Clinical Kidney Journal. 2020.
3. Fishbane S, Spinowitz B. Update on Anemia in ESRD and Earlier Stages of CKD: Core Curriculum 2018. Am J Kidney Dis. 2018.
4. Nangaku M, Eckardt K-U. Pathogenesis of Renal Anemia. Seminars in Nephrology. 2006;26(4):261-8.
5. Peyssonnaux C, Nizet V, Johnson RS. Role of the hypoxia inducible factors HIF in iron metabolism. Cell Cycle. 2008;7(1):28-32.
6. Babitt JL, Lin HY. Mechanisms of anemia in CKD. Journal of the American Society of Nephrology : JASN. 2012;23(10):1631-4.
7. Solak Y, Cetiner M, Siriopol D, Tarim K, Afsar B, Covic A, et al. Novel Masters of Erythropoiesis: Hypoxia Inducible Factors and Recent Advances in Anemia of Renal Disease. Blood Purif. 2016;42(2):160-7.
8. Akchurin OM, Kaskel F. Update on inflammation in chronic kidney disease. Blood Purif. 2015;39(1-3):84-92.
9. Mohanram A, Zhang Z, Shahinfar S, Keane WF, Brenner BM, Toto RD. Anemia and end-stage renal disease in patients with type 2 diabetes and nephropathy. Kidney Int. 2004;66(3):1131-8.
10. Astor BC, Coresh J, Heiss G, Pettitt D, Sarnak MJ. Kidney function and anemia as risk factors for coronary heart disease and mortality: the Atherosclerosis Risk in Communities (ARIC) Study. American heart journal. 2006;151(2):492-500.
11. Weiner DE, Tighiouart H, Vlagopoulos PT, Griffith JL, Salem DN, Levey AS, et al. Effects of anemia and left ventricular hypertrophy on cardiovascular disease in patients with chronic kidney disease. Journal of the American Society of Nephrology. 2005;16(6):1803-10.
12. Thorp ML, Johnson ES, Yang X, Petrik AF, Platt R, Smith DH. Effect of anaemia on mortality, cardiovascular hospitalizations and end-stage renal disease among patients with chronic kidney disease. Nephrology (Carlton, Vic). 2009;14(2):240-6.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

13. DNSL. Landsdækkende database for patienter med kronisk nyresvigt. Årsrapport for 2020. Aarhus: Regionernes Kliniske Kvalitetsudviklingsprogram; 2021.
14. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney International Supplements. 2012;2(4):279-335.
15. RADS. Baggrundsnotat for medicinsk parenteral behandling af anæmi hos nyreinsufficiente patienter Version 1.0. . RADS; 2015 Jan 19.
16. Medicinrådet. Behandlingsvejledning inklusiv lægemiddelrekommandation for medicinsk parenteral behandling af anæmi hos nyreinsufficiente patienter - version 1.3.: Medicinrådet; 2022 April 1.
17. Locatelli F, Hannedouche T, Fishbane S, Morgan Z, Oguey D, White WB. Cardiovascular Safety and All-Cause Mortality of Methoxy Polyethylene Glycol-Epoetin Beta and Other Erythropoiesis-Stimulating Agents in Anemia of CKD: A Randomized Noninferiority Trial. Clin J Am Soc Nephrol. 2019;14(12):1701-10.
18. Haase VH. Hypoxia-inducible factor-prolyl hydroxylase inhibitors in the treatment of anemia of chronic kidney disease. Kidney Int Suppl (2011). 2021;11(1):8-25.
19. Neild GH. Life expectancy with chronic kidney disease: an educational review. Pediatr Nephrol. 2017;32(2):243-8.
20. Barratt J, Andric B, Tataradze A, Schomig M, Reusch M, Valluri U, et al. Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, open-label, active-controlled study (DOLOMITES). Nephrol Dial Transplant. 2021;36(9):1616-28.
21. Charytan C, Manllo-Karim R, Martin ER, Steer D, Bernardo M, Dua SL, et al. A Randomized Trial of Roxadustat in Anemia of Kidney Failure: SIERRAS Study. Kidney Int Rep. 2021;6(7):1829-39.
22. Csiky B, Schomig M, Esposito C, Barratt J, Reusch M, Valluri U, et al. Roxadustat for the Maintenance Treatment of Anemia in Patients with End-Stage Kidney Disease on Stable Dialysis: A European Phase 3, Randomized, Open-Label, Active-Controlled Study (PYRENEES). Adv Ther. 2021;38(10):5361-80.
23. Fishbane S, Pollock CA, El-Shahawy M, Escudero ET, Rastogi A, Van BP, et al. Roxadustat Versus Epoetin Alfa for Treating Anemia in Patients with Chronic Kidney Disease on Dialysis: Results from the Randomized Phase 3 ROCKIES Study. Journal of the American Society of Nephrology : JASN. 2022;33(4):850-66.
24. Provenzano R, Shutov E, Eremeeva L, Korneyeva S, Poole L, Saha G, et al. Roxadustat for anemia in patients with end-stage renal disease incident to dialysis. Nephrol Dial Transplant. 2021;36(9):1717-30.
25. Barratt J, Sulowicz W, Schomig M, Esposito C, Reusch M, Young J, et al. Efficacy and Cardiovascular Safety of Roxadustat in Dialysis-Dependent Chronic Kidney Disease: Pooled Analysis of Four Phase 3 Studies. Adv Ther. 2021;38(10):5345-60.
26. Astellas. Data on File document 01. Confidentail. Additional efficacy and safety results from ALPINE. 2022.
27. ClinicalTrials.gov. Roxadustat in the Treatment of Anemia in Chronic Kidney Disease (CKD) Patients, Not on Dialysis, in Comparison to Darbepoetin Alfa (Dolomites): NIH; 2022 [Available from: https://clinicaltrials.gov/ct2/show/results/NCT02021318.
28. European Medicines Agency. Assessment report. Evrenzo. EMEA/H/C/004871/0000. Committee for Medicinal Products for Human Use; 2021 June 24.
29. European Medicines Agency. Summary of product characteristics. Evrenzo. 2021 August 18.
30. Chow A, Roger S, Pollock CA, Gervasi D, Szczech L, Walkenshaw G, editors. Enhanced degradation of 3-hydroxy-3-methylglutaryl coenzyme a reductase (hmgcr) may contribute to the lowering of LDL cholesterol seen with roxadustat in chronic kidney disease patients with anemia. 58th ERA-EDTA Congress; 2021 June 5-8; Virtual. Nephrology Dialysis Transplantation 36 (Supplement 1): i1–i2, 2021.
31. European Medicines Agency. Summary of product characteristics. Aranesp. 2022.
32. Donck J, Gonzalez-Tabares L, Chanliau J, Martin H, Stamatelou K, Manamley N, et al. Preservation of anemia control and weekly ESA dosage after conversion from PEG-Epoetin beta to darbepoetin alfa in adult hemodialysis patients: the TRANSFORM study. Adv Ther. 2014;31(11):1155-68.
33. Astellas. Data on File document 02. Confidential. ALPINE dosing analysis. . 2022.
34. TLV. Underlag för beslut om subvention. Evrenzo (roxadustat). DNR: 3698/2021. TLV; 2022 May 27. Contract No.: May 27.
35. McCullough PA, Barnhart HX, Inrig JK, Reddan D, Sapp S, Patel UD, et al. Cardiovascular toxicity of epoetin-alfa in patients with chronic kidney disease. Am J Nephrol. 2013;37(6):549-58.
36. Streja E, Park J, Chan TY, Lee J, Soohoo M, Rhee CM, et al. Erythropoietin Dose and Mortality in Hemodialysis Patients: Marginal Structural Model to Examine Causality. Int J Nephrol. 2016;2016:6087134.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

37. Hung SC, Tarng DC. ESA and iron therapy in chronic kidney disease: a balance between patient safety and hemoglobin target. Kidney Int. 2014;86(4):676-8.
38. Drozdz M, Weigert A, Silva F, Frazao J, Alsuwaida A, Krishnan M, et al. Achievement of renal anemia KDIGO targets by two different clinical strategies - a European hemodialysis multicenter analysis. BMC Nephrol. 2019;20(1):5.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix A Literature search for efficacy and safety of intervention and comparator(s)

Not applicable. Comparative data sources from head-to-head studies in the ALPINE program.

Unpublished data

- Unpublished efficacy and safety parameters from the integrated analysis of patients on dialysis in ALPINE. Data on file document 01.
- Unpublished data on dosing in DOLOMITES and the integrated analysis of patients on dialysis in ALPINE. Data on file documents 02.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix B Main characteristics of included studies

DOLOMITES	NCT02021318
Objective	To compare the efficacy, safety, and tolerability of roxadustat with darbepoetin alfa (DA) for treatment of anaemia in NDD CKD patients
Publications – title, author, journal, year	Roxadustat for the treatment of anaemia in chronic kidney disease patients not on dialysis: a Phase 3, randomized, open-label, active-controlled study (DOLOMITES). **Barratt et al**. *Nephrol Dial Transplant. 2021;36(9):1616-28.*
Study type and design	A phase 3, multicentre, randomised, open-label, active-controlled study. Eligible patients were randomised (1:1) to receive roxadustat or DA for up to 104 weeks during the treatment period. An initial correction period to achieve Hb ≥11.0 g/dL and Hb change from baseline (CFB) ≥1.0 g/dL (measured at two consecutive visits separated by ≥5 days) occurred in both groups. This was followed by a maintenance period with dosing aimed at achieving Hb levels between 10.0–12.0 g/dL. During a 4-week follow-up period, anaemia treatment was at the discretion of study investigators. Randomization (1:1) were conducted according to stratification factors (region; Hb values at screening; history of cardiovascular, cerebrovascular, or thromboembolic diseases; and eGFR values at screening).
Sample size (n)	616
Main inclusion and exclusion criteria	**Key inclusion criteria** 1. At least 18 years of age 2. Diagnosis of CKD, with KDOQI Stage 3, 4 or 5 who were not receiving dialysis 3. An eGFR <60 mL/min/1.73 m2 estimated using the abbreviated 4-variable MDRD equation 4. Mean of the patient's two most recent (prior to randomisation) Hb values during the screening period, obtained at least 4 days apart, was to be ≤10.5 g/dL, with a difference of ≤ 1.0 g/dL* **Key exclusion criteria** i. ESA treatment within 12 weeks prior to randomisation ii. Treatment with IV iron within 6 weeks prior to randomisation iii. Subject has received a RBC transfusion within 8 weeks prior to randomisation iv. Known hereditary haematological diseases such as thalassemia or sickle cell anaemia, pure red cell aplasia, or other known causes for anaemia other than CKD v. Known chronic inflammatory disease that could impact erythropoiesis
Intervention	Roxadustat (three times per week) (N: 323): Initial dose according to weight. Dose adjustment was allowed every 4 weeks to maintain Hb between 10-12 g/dl according to prespecified rules. During treatment period dose was reduced if Hb rise exceeded 2g/dl and interrupted if Hb was ≥13 mg/dl.
Comparator(s)	Darbepoetin alfa (N: 293) as single subcutaneous or IV injection (0.45 µg/kg weekly or 0.75 µg/kg every other week). Initial dose was weight-based according to product SmPC. Dose adjustments were conducted in accordance with the SmPC. If the Hb rise exceeded 2.0 g/dL in 4 weeks, the dose was reduced by approximately 25%.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

DOLOMITES	NCT02021318
Follow-up time	Median treatment duration was 104 weeks (roxadustat) and 100 weeks (darbepoetin alfa)
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	**Primary endpoint**
	Hb maintenance: Hb (g/dL) response defined as: 1. Hb ≥11.0 g/dL and a Hb increase from baseline Hb by ≥1.0 g/dL in any patient with baseline Hb >8.0 g/dL or a) An increase from baseline Hb by ≥2.0 g/dL in any patient with baseline Hb ≤8.0 g/dL b) As measured at 2 consecutive visits separated by at least 5 days during the first 24 weeks of treatment without administration of rescue therapy prior to Hb response)
	Secondary endpoint(s)
	Hb maintenance: Hb (g/dL) change from baseline to the average Hb in weeks 28 to 36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period
	LDL Cholesterol: Change from baseline in LDL cholesterol (mmol/L) to the average LDL cholesterol of weeks 12 to 28
	Rescue medication: Time to first use of IV iron in weeks 1–36 (per 100 patient years at risk)
	HRQoL: Change from baseline in SF-36 PF subscore (points) in weeks 12–28
	HRQoL: Change from baseline in SF-36 VT subscore (points) in weeks 12–28
	CV profile: Change from baseline in MAP (mmHg) to the average MAP value in weeks 20 to 28
	CV profile: Occurrence and time to first occurrence of hypertension (defined as [SBP ≥170 mmHg and SBP increase from BL ≥20 mmHg] or [DBP ≥110 mmHg AND DBP increase from BL ≥15 mmHg]) during weeks 1 to 36
	Abbreviations: BL: baseline; CI: confidence intervals; CV: cardiovascular; DBP: diastolic blood pressure; FAS: full analysis set; Hb: haemoglobin; HRQoL: health-related quality of life; ITT: intention-to-treat; IV: intravenous; LDL: low density lipoprotein; LSM: least squares mean; MAP: mean arterial pressure; PF: physical functioning; PPS: per-protocol set; SBP: systolic blood pressure; SF-36: short form 36 health survey questionnaire; US: United States; VT: vitality
Method of analysis	Non-inferiority (primary endpoint)

DOLOMITES	NCT02021318
Subgroup analyses	Analyses of the primary endpoint were performed by subgroups predefined based on the key baseline demographics and disease characteristics (including factors used in stratification for randomisation).
Other relevant information	Not applicable

Integrated analyses of DD studies in ALPINE	NCT number: not applicable
Objective	To study the efficacy and safety in pooled data-sets from the ALPINE clinical programme
Publications – title, author, journal, year	Efficacy and Cardiovascular Safety of Roxadustat in Dialysis-Dependent Chronic Kidney Disease: Pooled Analysis of Four Phase 3 Studies. **Barratt et al.** *Adv Ther. 2021;38(10):5345-60.*
Study type and design	Analysis of efficacy and safety including cardiovascular outcomes and all-cause mortality across the roxadustat phase III studies. The individual studies contributing data was designed and prepared for integrated analyses as per study protocols.
Sample size (n)	4,714 (ID-DD sub-pool 1,526)
Main inclusion and exclusion criteria	Patients included in HIMALAYAS, SIERRAS, ROCKIES, PYRENEES
Intervention	Roxadustat
Comparator(s)	ESA
Follow-up time	104 weeks
Is the study used in the health economic model?	Yes
Primary, secondary and exploratory endpoints	○ Proportion of patients who achieved Hb response ○ Change from baseline in Hb ○ IV iron use ○ RBC transfusion ○ CV-Safety (MACE+, MACE, ACM)
Method of analysis	Pooled analysis

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Integrated analyses of DD studies in ALPINE	NCT number: not applicable
Subgroup analyses	○ **DD pool:** Pooled data from ESA-controlled DD studies (HIMALAYAS, SIERRAS, PYRENEES and ROCKIES) (Roxadustat N=2,354 ; ESA N=2,360 (safety population)). The DD pool was analysed for safety only. ○ **ID-DD pool:** Hb correction setting: Patients in the DD population who were on dialysis for more than 2 weeks and less than 4 months were termed incident DD patients (Roxadustat N= 756; ESA N= 759 (Full Analysis Set)). ○ **Stable DD: pool** ESA conversion setting: The DD patients who were on dialysis after this threshold of four months were termed stable DD patients reflective of the ESA conversion setting.(Roxadustat N= 1,379; ESA N= 1,417 (Per-protocol set))
Other relevant information	For CV-safety additional integrated analyses were performed • A pooled ESA-controlled Hb correction dataset in NDD and ID-DD patients [includes patients from studies DOLOMITES, HIMALAYAS, and the ID DD patients of studies SIERRAS and ROCKIES. • A pooled ESA-controlled ESA conversion dataset in Stable DD patients [includes patients from study PYRENEES) and Stable DD patients from studies ROCKIES and SIERRAS

HIMALAYAS	NCT02052310
Objective	To evaluate the efficacy and safety of roxadustat vs. epoetin alfa for the treatment of chronic kidney disease (CKD) related anaemia in patients new to dialysis
Publications – title, author, journal, year	Roxadustat for anemia in patients with end-stage renal disease incident to dialysis. **Provenzano et al.** *Nephrol Dial Transplant. 2021;36(9):1717-30.*
Study type and design	A phase 3, open-label, epoetin alfa-controlled trial in adults on haemodialysis/peritoneal dialysis for ≥2 weeks and ≤4 months before randomization and a mean haemoglobin ≤10.0 g/dL. The trial consisted of three periods: a screening period of up to 6 weeks, a treatment period of a minimum of 52 weeks and a maximum of approximately up to 3 years after last patient is randomized, and a post-treatment follow-up period of 4 weeks. Patients were randomized (1:1) to open-label, oral roxadustat or parenteral epoetin alfa thrice weekly.
Sample size (n)	1043

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

HIMALAYAS		NCT02052310
Main inclusion and exclusion criteria	**Key inclusion criteria**	**Key exclusion criteria**
	⌑ At least 18 years of age ⌑ Patient received HD or PD for ESRD for a minimum of 2 weeks and a maximum of 4 months, prior to randomisation ⌑ For patients receiving HD or HDF, the vascular access must be via native AV fistula or graft, or permanent, tunnelled catheter ⌑ Mean of the patients two most recent Hb values, as measured by central laboratory, during the screening period, obtained at least 2 days apart, must been ≤10.0 g/dL, with a difference of ≤1.3 g/dL between the highest and the lowest values. The last Hb value must have been drawn within 10 days prior to randomisation. ⌑ Ferritin level ≥100 ng/mL (≥220 pmol/L) at screening ⌑ TSAT level ≥20% at screening	⌑ Total duration of prior ESA use was ≤3 weeks within the 12 weeks before informed consent was obtained ⌑ Patient has received a RBC transfusion within 4 weeks prior to randomisation ⌑ Active, clinically significant infection that was manifested by WBC count >ULN, and/or fever with clinical signs or symptoms of infection at the time of randomisation
Intervention	Roxadustat TIW (N:522) *The starting dose of roxadustat was 70 mg (patients weighing ≤70kg) or 100 mg (patients weighing >70–160kg). A roxadustat-specific dosing algorithm was used to correct and maintain haemoglobin level.*	
Comparator(s)	Epoetin alfa (N: 521). EPO was dosed according to the country-specific product labelling. Patients on haemodialysis were required to use IV epoetin alfa; patients on peritoneal dialysis were allowed to use subcutaneous epoetin alfa, at the discretion of the Investigator.	
Follow-up time	52	
Is the study used in the health economic model?	Yes (via integrated analysis of ID-DD).	

HIMALAYAS		NCT02052310
Primary, secondary and exploratory endpoints	**Primary endpoint**	
	Hb maintenance (US definition)	Hb (g/dL) change from baseline to the average Hb in weeks 28 to 52, regardless of recue therapy
	Hb response (Ex-US definition)	The proportion of patients who achieved an Hb response at 2 consecutive visits during the first 24 weeks of treatment, without rescue therapy
	Secondary endpoints	
	Hb response	The proportion of patients who achieved an Hb response at during the first 24 weeks of treatment, without rescue therapy
	Hb maintenance	Mean Hb change from baseline to the average level from weeks 28-36 within 6 weeks prior to and during the evaluation period
	Hb response	The time to achieve the first Hb response at 2 consecutive visits during the first 24 weeks of treatment, without rescue therapy
	Hb maintenance	Proportion of patients with Hb ≥10 g/dL during weeks 28–52
	LDL Cholesterol	Mean change from baseline in LDL cholesterol averaged over weeks 12–24
	Hb maintenance	Mean change from baseline in Hb levels between week 18 to 24 in patients whose baseline hs-CRP >ULN
	Rescue medication	Average monthly IV iron use per subject from weeks 28–52
	Rescue medication	Time to first RBC transfusion during treatment
	CV profile	Mean change in mean MAP from weeks 8–12
	CV profile	Time to first exacerbation of hypertension from weeks 28–52
Method of analysis	Non-inferioity (primary endpoint)	
Subgroup analyses	Sensitivity analyses included subgroups categorized by important baseline demographic and clinical characteristics.	
Other relevant information		

SIERRAS	NCT number:
Objective	To evaluate safety and efficacy of roxadustat compared to epoetin-alfa in newly initiated (incident) dialysis subjects who have been on ESA (≥ 4 weeks) for treatment of anaemia prior to screening
Publications – title, author, journal, year	A Randomized Trial of Roxadustat in Anemia of Kidney Failure: SIERRAS Study. **Charytan et al.** *Kidney International Reports 2021*
Study type and design	A phase III, randomised, open-label, active-controlled study to assess the efficacy and safety of roxadustat treatment in adult patients with ESRD who were on HD or PD and were on ESA for treatment of anaemia. The study consisted of three periods: screening period (up to 6 weeks or 8 weeks for subjects who were taking Mircera®), treatment period (maximum up to 3 years after the last patient as randomised) and a post-treatment follow-up period (4 weeks). Patients were randomized 1:1 to roxadustat or epoetin-alpha treatment.
Sample size (n)	742

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

SIERRAS		NCT number:
Main inclusion and exclusion criteria	**Key inclusion criteria**	**Key exclusion criteria**
	• At least 18 years of age • Receiving adequate dialysis using the same modality of dialysis for native kidney ESRD for ≥3 months prior to screening and during screening. Under Protocol Amendment 2, incident-dialysis subjects receiving dialysis for ESRD for ≥2 weeks but ≤4 months at the time of randomisation. • For patients receiving HD, the vascular access must be via native AV fistula or graft, or permanent, tunnelled catheter • Patient is on IV or SC epoetin (i.e. epoetin alfa, beta, theta, zeta, delta or omega) or IV or SC darbepoetin alfa treatment for ≥8 weeks prior to randomisation with stable weekly doses (≤ 30% change from the maximum prescribed average weekly dose, i.e. ([max-min]/max≤ 0.3) during 4 weeks prior to randomisation • Mean of the patients three most recent Hb values, as measured by central laboratory, during the screening period, obtained at least 4 days apart, must be ≥9.0 g/dL and ≤12.0 g/dL with an absolute difference ≤1.3 g/dL between the highest and the lowest value. The last Hb value must be within 10 days prior to the randomisation visit • Ferritin level ≥100 ng/mL (≥220 pmol/L) at screening • TSAT level ≥20% at screening	• Patient has received a RBC transfusion within 8 weeks prior to randomisation • Known hereditary haematologic disease such as thalassemia or sickle cell anaemia, pure red cell aplasia, or other known causes for anaemia other than CKD • Known chronic inflammatory disease that could impact erythropoiesis • Patient had uncontrolled hypertension within 2 weeks prior to randomisation.
Intervention	Roxadustat TIW (N: 370). Initial dose defined by pre-specified conversion table.	
Comparator(s)	Epoetin alfa (i.v./ s.c.) TIW (N: 371). Patients that were receiving non-epoetin alfa treatment were switched to epoetin alfa treatment based on pre-specified dose conversion table. Selection of initial epoetin alfa doses was administered IV or subcutaneous TIW starting from Day 1.	
Follow-up time	52 weeks	
Is the study used in the health economic model?	Yes (via integrated ID-DD analysis)	

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

SIERRAS		NCT number:
Primary, secondary and exploratory endpoints	**Primary endpoint**	
	Hb maintenance (US definition)	Hb (g/dL) change from baseline to the average Hb in weeks 28 to 52 regardless of rescue therapy
	Hb maintenance (Ex-US definition)	Hb (g/dL) change from baseline to the average Hb in weeks 28 to 36, without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period
	Secondary endpoints	
	Hb response	Proportion of responders with Hb level ≥10.0 g/dL from weeks 28 to 52 regardless of rescue therapy
	Hb response	Proportion of responders within the target Hb range of 10.0 to 12.0 g/dL from weeks 28 to 36 without having received rescue therapy within 6 weeks prior to and during this 8-week evaluation period.
	LDL Cholesterol	LDL cholesterol change (mmol/L) from baseline to the average of Weeks 12 to 28
	Hb maintenance	Hb change from baseline to the average level during the Weeks 18 to 24 for patients with baseline hs-CRP > ULN
	Rescue medication	Average monthly IV iron use during the treatment period from weeks 28 to 52
	Rescue medication	Time to first RBC transfusion during the treatment period.
	CV profile	MAP (mmHg) change from BL to the average MAP of weeks 20 to 28
	CV profile	Time to first exacerbation of hypertension during Weeks 28 to 52
Method of analysis	Non-inferiority (primary endpoint)	
Subgroup analyses	*Subgroup analyses included* gender, age cohort, duration of dialysis, iron status, hs-CRP, hemoglobin, CV history and epoetin alfa dose.	
Other relevant information		

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Trial name: ROCKIES	NCT02174731
Objective	To evaluate the safety and efficacy of roxadustat compared to epoetin alfa for the treatment of anemia in subjects receiving dialysis
Publications – title, author, journal, year	Roxadustat Versus Epoetin Alfa for Treating Anemia in Patients with Chronic Kidney Disease on Dialysis: Results from the Randomized Phase 3 ROCKIES Study. **Fishbane et al.** *Journal of the American Society of Nephrology : JASN. 2022;33(4):850-66.*
Study type and design	**A** phase III, multicentre, randomised, open label, active-controlled study designed to provide key efficacy and safety data for roxadustat compared with epoetin alfa in the treatment of anaemia associated with DD-CKD. The study consisted of three study periods: screening period (up to 6 weeks), treatment period (treatment end date was defined based on when the target number of CV events was reached) and a post-treatment follow-up period (4 weeks) Subjects on hemodialysis (HD) or peritoneal dialysis (PD) who have been treated with an erythropoietin analogue or have an indication for treatment with an erythropoietin analogue were randomized (1:1) to treatment with roxadustat (with discontinuation of prior erythropoietin analogue therapy) or to an active-control group treated with epoetin alfa. Randomization was stratified according to Baseline Hb; previous cardiovascular/cerebrovascular/thromboembolic event; geographical region, and incident vs. stable dialysis (dialysis duration ≤4 months vs >4 months from the randomization date).
Sample size (n)	2133
Main inclusion and exclusion criteria	**Key inclusion criteria** ▪ At least 18 years of age ▪ Receiving or initiating hemodialysis or peritoneal dialysis for treatment of native kidney ESRD for a minimum of 2 weeks and a maximum of 4 months prior to randomisation ▪ Two central laboratory Hb values during the screening period, obtained at least 7 days apart, were to be <12 g/dL in subjects treated with an erythropoietin analogue at the time of enrolment or <10 g/dL in subjects not treated with an erythropoietin analogue at the time of enrolment. ▪ Ferritin ≥100 ng/mL at randomisation ▪ Transferrin saturation (TSAT) ≥20% at randomisation **Key exclusion criteria** ▪ Patient has received RBC transfusion during the screening period. ▪ Uncontrolled hypertension at the time of randomisation ▪ Known chronic inflammatory disease that could impact erythropoiesis
Intervention	Roxadustat TIW (N: 1,003) Subjects treated with an erythropoietin analogue at start of study who are randomized to the roxadustat group discontinue prior erythropoietin analogue therapy and initiated treatment with roxadustat at a starting dose according to a pre-specified conversion table. Patients indicated for ESA but not treated at enrolment was initially dose according to a weight-based scheme. Dose were subsequently adjusted to achieve and maintain Hb levels between 10 and 12 g/dL.

Trial name: ROCKIES		NCT02174731
Comparator(s)	Epoetin alfa (N: 1,016). Initial dose selection of epoetin alfa for subjects treated with an erythropoietin analogue were determined using a conversion table based on the subject's average prescribed erythropoietin analogue dose during the preceding 4-8 weeks prior to enrolment in the study. Patients indicated for ESA but not treated at enrolment was initially dose according to a weight-based scheme Dose were subsequently adjusted to achieve and maintain Hb levels between 10 and 12 g/dL.	
Follow-up time	Results from the primary analysis were based on 52 weeks follow-up (treatment period).	
Is the study used in the health economic model?	Yes (via integrated analysis of ID-DD)	
Primary, secondary and exploratory endpoints	**Primary endpoint**	
	Hb maintenance (US definition)	Hb (g/dL) change from baseline to the average Hb from weeks 28 to 52
	Hb maintenance (EU definition)	Hb (g/dl) change from baseline to the average level from week 28 to 36
	Secondary endpoint(s)	
	CV profile	Mean change from LDL cholesterol (mmol/L) from baseline to week 24
	Hb maintenance	Change in Hb from baseline to the average Hb from weeks 28-52 for patients with baseline hsCRP greater than the ULN
	Hb response	Proportion of total time of interpolated Hb values greater than or equal to 10 g/dL over Week 28-52
	Hb response	Proportion of total time of interpolated Hb values within the interval 10 to 12 g/dL over Week 28-52
	Rescue medication	Mean monthly IV iron use from Week 36 to EOS
	Rescue medication	Time to first administration of RBC transfusion
Method of analysis	Non-inferiority (primary endpoint)	
Subgroup analyses	Subgroup analysis was performed for both the primary efficacy endpoints of Hb based on stratification factors and the following groups: Age: (<65 and ≥65; <75 and ≥75 years); Gender; Race; Weight (<70 kg vs ≥70 kg; and <100 kg vs ≥ 100 kg); Weight by gender-specific median (4 groups); BMI (<30 and ≥30 kg/m^2); Geographical region (US vs Ex-US and by regions: North America; South America; Asia and Australia; Europe) Peritoneal dialysis vs. Haemodialysis; Diabetes history; Epoetin alfa dose prior to randomization: (≤ 12,500 IU/week vs >12,500 IU/week); Baseline hsCRP (≤ULN vs >ULN).	
Other relevant information		

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix C Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

Table C1. Demographics and baseline characteristics in DOLOMITES study (NDD)

Category		ROXA, n=323	DA, n=293
Sex, n (%)	Female	178 (55.1)	164 (56.0)
Age (years)	Mean (SD)	66.8 (13.6)	65.7 (14.4)
Weight (kg)	Mean (SD)	76.90 (16.33)	78.39 (17.68)
Race, n (%)	White	306 (94.7 %)	281 (95.9 %)
	Black or African American	8 (2.5%)	2 (0.7%)
	Asian	9 (2.8%)	10 (3.4%)
	Other	0	0
CKD stage, n (%)	Stage 3	72 (22.3%)	62 (21.2%)
	Stage 4	155 (48.0)	143 (48.8)
	Stage 5	96 (29.7)	88 (30.0)
eGFR (mL/min/1.73 m2)	Mean (SD)	20.31 (11.49)	20.34 (10.73)
Haemoglobin (g/dL)	Mean (SD)	9.55 (0.75)	9.55 (0.69)
Iron repletion at baseline, n (%)	Ferritin ≥100 ng/mL, and TSAT ≥20%	182 (56.3)	152 (51.9)
hs-CRP, n (%)	> ULN	111 (34.7)	116 (39.6)
Most likely CKD aetiology, n (%)	Diabetic nephropathy		
	Diabetes	141 (43.7%)	124 (42.3%)

CKD, chronic kidney disease; DA, darbepoetin alfa; eGFR, estimated glomerular filtration rate; ESA, erythropoiesis-stimulating agent; LDL, low-density lipoprotein; NDD, non-dialysis-dependent; PBO, placebo; ROXA, roxadustat; SD, standard deviation; TSAT, transferrin saturation, hs-CRP, high-sensitivity C-reactive protein.; SAF, Safety analysis set

Table C2. Baseline demographics and disease characteristics of patients included in the DD pool (SAF)

		Overall DD pool		ID pool		SD pool	
Parameter	Category/ statistic	Roxadustat (N=2354)	ESA (N=2360)	Roxadustat (N=760)	ESA (N=766)	Roxadustat (N=1594)	-ESA (N=1594)
Baseline demographics							
Sex, n (%)	Male	1365 (58.0)	1379 (58.4)	461 (60.7)	463 (60.4)	904 (56.7)	916 (57.5)
	Female	989 (42.0)	981 (41.6)	299 (39.3)	303 (39.6)	690 (43.3)	678 (42.5)
Age (years)	Mean	55.5	56.3	53.6	54.0	56.4	57.5
	SD	14.94	14.64	14.81	14.55	14.92	14.56
	<65	1652 (70.2)	1645 (69.7)	570 (75.0)	581 (75.8)	1082 (67.9)	1064 (66.8)

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

		Overall DD pool		ID pool		SD pool	
Age range (years)	65-74	468 (19.9)	462 (19.6)	132 (17.4)	129 (16.8)	336 (21.1)	333 (20.9)
	≥75	234 (9.9)	253 (10.7)	58 (7.6)	56 (7.3)	176 (11.0)	197 (12.4)
Race, n (%)	White	1581 (67.2)	1584 (67.1)	508 (66.8)	501 (65.4)	1073 (67.3)	1083 (67.9)
	Black or African American	356 (15.1)	370 (15.7)	67 (8.8)	67 (8.7)	289 (18.1)	303 (19.0)
	Asian	271 (11.5)	266 (11.3)	116 (15.3)	127 (16.6)	155 (9.7)	139 (8.7)
	Other	146 (6.2)	140 (5.9)	69 (9.1)	71 (9.3)	77 (4.9)	69 (4.3)
BMI (kg/m²)	Mean	27.43	27.51	26.43	26.63	27.90	27.94
	SD	6.48	6.49	5.87	5.92	6.70	6.71
Baseline disease characteristics							
Baseline dialysis type,n (%)	Hemodialysis	2137 (90.8)	2156 (91.4)	680 (89.5)	674 (88.0)	1457 (91.4)	1482 (93.0)
	Peritoneal dialysis	215 (9.1)	204 (8.6)	80 (10.5)	92 (12.0)	135 (8.5)	112 (7.0)
	Missing	2	0	0	0	2	0
Hb (g/dL)	Mean	9.83	9.86	8.82	8.86	10.31	10.34
	SD	1.28	1.28	1.22	1.20	1.00	1.02
Iron repletion at baseline, n (%)	Ferritin <100 ng/mL or TSAT <20%	305 (13.0)	304 (12.9)	155 (20.4)	161 (21.0)	150 (9.4)	143 (9.0)
	Ferritin ≥100 ng/mL and TSAT ≥20%	2042 (86.7)	2052 (86.9)	603 (79.3)	605 (79.0)	1439 (90.3)	1447 (90.8)
CRP, n (%)	>ULN	927 (39.4)	913 (38.7)	285 (37.5)	299 (39.0)	642 (40.3)	614 (38.5)
	≤ULN	1095 (46.5)	1133 (48.0)	406 (53.4)	400 (52.2)	689 (43.2)	733 (46.0)
	Missing	332 (14.1)	314 (13.3)	69 (9.1)	67 (8.7)	263 (16.5)	247 (15.5)
Likely CKD etiology, n (%)	Diabetic nephropathy	799 (33.9)	813 (34.4)	275 (36.2)	268 (35.0)	524 (32.9)	545 (34.2)

Abbreviations: BMI: body mass index; DD: dialysis dependent; CRP: C-reactive protein; ESA: erythropoiesis stimulating agent; ID: incident dialysis; NDD: non-dialysis-dependent; SAF: safety analysis set; SD: standard deviation; SDD: stable dialysis dependent; TSAT: transferrin saturation; ULN: upper limit of normal

Source

Comparability of patients across studies

For the consideration of efficacy and safety in non-dialysis patients, only one study – DOLOMITES – is considered in the submission, and hence the issue of comparability across studies is not relevant.

The evaluation of efficacy and safety in incident dialysis patients was based on patients pooled from different studies and hence the question of comparability of results across studies is not relevant. The inclusion criteria across studies defining incident dialysis and other patient characteristics were consistent across studies allowing for pooling. Pooling and subsequent analyses were pre-defined in the statistical analysis plan.

Comparability of the study populations with Danish patients eligible for treatment

The Danish Nephrological Society register is the main source of data on patients with CKD in Denmark. However the registry has collected data historically only on dialysis patients; to the extent to which the presented epidemiological information in the report overlap with measured baseline characteristics in the trials, we can say that the populations are broadly similar. The 2 most common underlying causes of CKD in Denmark are diabetes and hypertension, and this was also true of patients in trials. The prevalence of dialysis increases after 50 years and this is broadly in keeping with a mean age of dialysis patients in the trials. As in the trials, haemodialysis rather than peritoneal dialysis is the more common dialysis form in Denmark.

The Swedish renal registry reports more granular epidemiological data on both the non-dialysis and dialysis patient populations, and in-depth evaluation of both populations was published recently (Evans et al, 2020). Given that nephrology care and the CKD patient population are broadly similar in Denmark and Sweden, these results can also help inform the question of comparability of patients in clinical practice in Denmark with the trial population. There are no noteworthy differences in the trial population and the Swedish epidemiological data that would lead one to conclude that the trial results are not applicable in a Nordic or Danish patient population. There are minor differences in age and gender and racial differences, but sub-group analysis of trial data in relation to primary endpoint did not indicate an influence of these characteristics on primary efficacy or safety outcomes.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Appendix D Efficacy and safety results per study

Definition, validity and clinical relevance of included outcome measures

Table D1 Definition of outcomes

Outcome measure	Definition
Hb response during the first 24 weeks	Response was defined as Hb≥11.0 g/dL and Hb change ≥1.0 g/dL if BL Hb>8.0 g/dL; or change ≥2.0 g/dL if BL Hb ≤8.0 g/dL at two consecutive visits separated by ≥5 days, without having received rescue therapy. Rescue therapy was defined as RBC transfusion for all patients or DA for roxadustat-treated patients.
HB change from base line	Change in Hb from baseline to average of weeks 28–36 without use of rescue therapy within the 6 weeks prior to and during the 8-week evaluation Rescue therapy was defined as RBC transfusion for all patients or DA for roxadustat-treated patients.
Incidence of MACE+ events	Incidence rate (events per patient year) of major adverse cardiovascular event including hospitalisations for either unstable angina and/or congestive heart failure (MACE+)
Incidence of MACE+ events	Incidence rate (events per patient year) of death, non-fatal myocardial infarction, and/or stroke (MACE)
Incidence of all cause mortality	Incidence rate (event per patient year) of all-cause mortality (ACM)
SF-36 change from base line	Change in SF-36 PF and PV sub-scores from BL to the average of Weeks 12–28. US-normalized values were used for the analysis where the scores normed to the US population have a mean of 50 and SD of 10
Incidence of ESRD	Occurrence of end stage renal disease during the study (i.e from day 1 up to the end of study) was defined as at least one of the following: underwent >30 days dialysis therapy, received kidney transplant, planned kidney transplant, physician recommended renal replacement therapy and participant refused therapy, began dialysis and died < 30 days later.

Outcome measure	Definition
RBC transfusions (Number of packs)	The number of RBC packs were calculated as the sum of units transfused during the efficacy emergent period. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to EOT visit or last non-missing Hb assessment (for participants who died during the treatment period). Participants with no medication records of RBC have their number of RBC packs set to 0
RBC transfusions (Number of patients)	Participants who received RBC transfusions during the efficacy emergent period were reported. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to EOT Visit or last non-missing Hb assessment (for participants who died during the treatment period).
IV Iron infusion (Time to first IV iron infusion)	Participants were analyzed during the efficacy emergent period. The efficacy emergent period was defined as the evaluation period from the analysis date of first dose intake up to end of treatment (EOT) Visit or last non-missing Hb assessment (for participants who died during the treatment period). For participants who had received more than one intravenous iron, only their first event following study treatment was used
IV Iron infusion (mean dose)	Mean Monthly Intravenous Iron Per Participant During Weeks 53 to 104 (NDD) or 28-52 (ID-DD). Participants with no or missing medication records of IV Iron had their monthly IV Iron use set to 0 mg.

Results per study

Table D2 Results of DOLOMITES

Results of DOLOMITES (NCT02021318)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Proportion of patients who achieved an Hb	Roxadustat	286	89.5% (85.4; 91.8)%	11.51 p.p.	5.66; 17.36 p.p	NA	na	na	na	*Analysis was performed in the per protocol set (PPS). A generalized linear model as an approximation for the Miettinen and Nurminen*	[20]

Results of DOLOMITES (NCT02021318)											
response at during the first 24 weeks of treatment, without rescue therapy	DA	273	78.0% (72.6; 82.8)%							*method, adjusted for stratification factors (actual), was used to estimate the difference of proportions and 95% CI.*	
Change in Hb from baseline to average of weeks 28–36 (g/dl)	Roxadustat	286	1.848 (CI: 1.747; 1.942)*	0.015	-0.131; 0.162	NA	NA	NA	NA	*Analysis was performed in the per protocol set (PPS) using mixed model of repeated measures method.*	[20, 26]
	DA	273	1.836 (CI: 1.730; 1.942)*								
Incidence rate MACE+ (events per patient year)	Roxadustat	323	16.7%**	-1.4 p.p	NA	NA	HR: 0.90	0.61; 1.32	0.58	*Analysis was performed in the safety analysis set. Hazard Ratio is calculated using stratified Cox Proportional Hazards regression stratifying on Region and History of CV, and adjusted on Age, baseline Hb, baseline log-transformed eGFR as continuous covariates.*	[20]
	DA	293	18.1%**								
Incidence rate MACE (events per patient year)	Roxadustat	323	11.8%**	-2.3p.p	NA	NA	HR: 0.81	0.52; 1.25	0.339	*Analysis was performed in the safety analysis set. Hazard Ratio is calculated using stratified Cox Proportional Hazards regression stratifying on Region and History of CV, and adjusted on Age, baseline*	[20]
	DA	293	14.1%**								

Results of DOLOMITES (NCT02021318)										
									Hb, baseline log-transformed eGFR as continuous covariates.	
Incidence rate ACM (events per patient year)	Roxadustat	323	9.0%**	-.1.6 p.p	NA	NA	HR: 0.83	0.50; 1.38	0.467	*Analysis was performed in the safety analysis set. Hazard Ratio is calculated using stratified Cox Proportional Hazards regression stratifying on Region and History of CV, and adjusted on Age, baseline Hb, baseline log-transformed eGFR as continuous covariates.*	[20]
	DA	293	10.6%**								
Change in SF-36 PF sub-score from baseline to average of week 12-28	Roxadustat	286	1.028 (CI: 0.198; 1.859)x	-1.284	-2.423;-0.145	NA	NA	NA	NA	*Analysis was performed in the per protocol set (PPS) using mixed model of repeated measures method. Non-inferiority margin of -3 applied*	[20, 26]
	DA	273	2.313 (CI: 1.457; 3.168)								
Change in SF-36 VT sub-score from baseline to average of week 12-28	Roxadustat	286	3.893 (CI: 3.021; 4.766)	-0.457	-1.656;0.742	NA	NA	NA	NA	*Analysis was performed in the per protocol set (PPS) using mixed model of repeated measures method. Non-inferiority margin of -3 applied*	[20, 26]
	DA	273	4.350 (CI: 3.452; 5.248)								

Results of DOLOMITES (NCT02021318)										
Incidence of end state renal disease	Roxadustat	322	110/ 322 (34.2, CI: 29.0; 39.3)	-2.5 p.p	-10.1; 5.1	NA	RR: 0.93	0.75; 1.15	NA	*Analysis was performed in the full analysis set (FAS). Confidence interval for absolute risk difference was estimated using normal approximation. Confidence interval for RR was estimated using normal approximation of log RR.*	[27]
	DA	292	107/ 292 (36.6, CI: 31.1; 42.2)								
RBC transfusions. Number of packs in treatment emergent period	Roxadustat	322	0.4 (CI: 0.3; 0.5)	0	-0.2; 0.2	NA	NA	NA	NA	*Analysis was performed in the full analysis set (FAS). Confidence interval for mean difference calculated using student-t distribution*	[27]
	DA	292	0.4 (CI: 0.2; 0.6)								
RBC transfusions. Number of patients	Roxadustat	322	38/ 322 (11.8%, CI: 8.3; 15.3)	2.2 p.p	-2.7; 7.1	NA	1.23	95% CI: 0.78; 1.95	NA	*Analysis was performed in the full analysis set (FAS). Confidence interval for absolute risk difference was estimated using normal*	[27]

Results of DOLOMITES (NCT02021318)											
transfused in treatment emergent period	DA	292	28/ 292 (9.6%, CI: 6.2; 13)							*approximation. Confidence interval for RR was estimated using normal approximation of log RR.*	
IV iron infusion (time to first infusion. Time frame 36 weeks)	Roxadustat	20/ 322	6.2 (3.6; 8.8)	6.5 p.p.	NA	NA	HR: 0.45	0.26; 0.78	0.004	*Hazard Ratio was calculated using stratified Cox Proportional Hazards regression stratifying on cardiovascular history and region and adjusting on Hb and eGFR at baseline as continuous covariate.*	[20]
	DA	37/ 292	12.7 (8.9; 16.5)								
IV iron infusions. Mean dose (mg) week 53-104	Roxadustat	259	18.702 (CI: 10.4; 27)	-12.613	-27; 1.8	NA	NA	NA	NA	Analysis was performed in the full analysis set (FAS). Confidence interval for mean difference calculated using student-t distribution	[27]
	DA	248	31.315 (CI: 19.4; 43.2)								

* Change from baseline by treatment arm is from Data on file document [26]

** Incidence by treatment arm is % patients with event in treatment period + 28 days

Table D3 Results of ID-DD integrated analysis

Results of ID-DD integrated analysis											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Change in Hb from baseline to average of weeks 28–36 (g/dl)	Roxadustat	673	LSM: 2.17 (CI: 2.05; 2.30)	0.28	0.11; 2.02	NA	NA	NA	NA	*Analysis was performed in the per protocol set (PPS). Mean hemoglobin change from baseline (CFB) to weeks 28–36 was evaluated by comparing least-squares (LS) mean and LS mean difference and 95% confidence intervals between roxadustat and ESA. Non-inferiority margin for the difference was defined as –0.75.*	[25]
(study primary endpoint)	ESA	669	LSM: 1.89 (CI: 1.77; 2.02)								
Proportion of patients who achieved an Hb response during the weeks 28-36 of treatment, without	Roxadustat	673	59.9% (CI: 56.3; 63.4)	0.3 p.p.	-4.5; 5.1 p.p	NA	na	na	na	*Analysis was performed in the per protocol set (PPS). Hemoglobin response was evaluated by comparing the difference in proportions and 95% CI for those who achieved the target hemoglobin during weeks 28–36*	[25]

Results of ID-DD integrated analysis											
rescue therapy											
Incidence rate MACE+ (events per patient year)	Roxadustat	760	8	-2.2	NA	NA	0.76	0.57; 1.00	NA	*Analysis was performed in the safety analysis set. Time-frame was from date of first dose up to 7 days after last dose. Pooled hazard ratios were calculated using the inverse of variance approach over the log-transformed hazard ratios.*	[25]
	DA	766	10.2								
Incidence rate MACE (events per patient year)	Roxadustat	760	6.7	-1.5	NA	NA	0.83	0.61; 1.13	NA	*Analysis was performed in the safety analysis set. Time-frame was from date of first dose up to 7 days after last dose. Pooled hazard ratios were calculated using the inverse of variance approach over the log-transformed hazard ratios.*	[25]
	DA	766	8.2								
Incidence rate ACM (events per patient year)	Roxadustat	760	4.7	-1.1	NA	NA	0.83	0.57;1.19	NA	*Analysis was performed in the safety analysis set. Time-frame was from date of first dose up to 7 days after last dose. Pooled hazard ratios were calculated using the inverse of*	[25]
	DA	766	5.9								

Results of ID-DD integrated analysis											
										variance approach over the log-transformed hazard ratios.	
RBC transfusions. Number of patients transfused in treatment emergent period. Incidence per 100 Patient-years at risk)	Roxadustat	756	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	*Time to first RBC transfusion was analysed in the FAS population. Incidence rates were calculated as the number of incidence cases (any use of RBC transfusion) divided by patient years at risk multiplied by 100. The relative treatment effect was estimated using a Cox proportional hazard model adjusting for baseline Hb and other randomization stratification factors (except mean qualifying screening Hb).*	[26]
	ESA	759	[redacted]								
IV iron infusions. Mean dose (mg) week 28-52	Roxadustat	756	53.57 (CI: 47.8; 59.3)	-16.65	-24.8; -8.5	NA	NA	NA	NA	*Analysis was performed in the safety analysis set (SAF). Confidence interval for mean difference calculated using student-t distribution*	[25]
	DA	759	70.22 (CI: 64.4; 76.0)								

Appendix E Safety data for intervention and comparator(s)

Table E1 Safety outcomes in DOLOMITES (NDD population)

Safety outcomes	Definition	Roxadustat	DA	Source
N:	The analysis population was the safety analysis set included all randomized participants who received at least one dose of study drug.	323	293	[20]
Number of patients with at least one treatment emergent adverse event	An AE was defined as any untoward medical occurrence in a participant who was given the study drug or who had undergone study procedures and did not necessarily have a causal relationship with this treatment. All AEs collected during the safety emergent period* were counted as TEAE.	91.6%	92.5%	[20]
Number of patients with at least one SAE	An TEAE that results in death, is life-threatening, requires inpatient hospitalization or extends a current hospital stay, results in an ongoing or significant incapacity or interferes substantially with normal life functions, or causes a congenital anomaly or birth defect. Medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered serious adverse events if they put the participant in danger or require medical or surgical intervention to prevent one of the results listed above.	64.7%	61.8%	[20]
Number of patients with adverse event leading to death	TEAEs occurring during the safety-emergent period* and leading to death any time.	10.5%	11.6%	[20]
Number of patients with at least one adverse reaction.	Any TEAE with at least possible relationship to study drug (or with missing assessment of the causal relationship). Causal relationship was assessed by the investigator as 'Not related', 'Possible', 'Probably'	24.1%	22.5%	EMA PAR[28]
Number of patients who discontinue treatment irrespective of the reason	Number of patients who discontinue treatment irrespective of the reason as percentage of patients randomized	33.4%	28.7%*	[25]
Number of patients who discontinue treatment due to adverse event.	TEAE leading to withdrawal of treatment	7.7%	3.8%	[25]

* The safety emergent period was defined as the evaluation period from the analysis date of first drug intake up to 28 days after the end of treatment taking into account the different dosing frequencies of the study treatments.

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table E2 Incidence of common (≥1% in any treatment group) serious TEAEs (DOLOMITES safety population)[20]

MedDRA version 20.0 preferred term	Roxadustat (n=323)	DA (n=293)
Overall	209 (64.7)	181 (61.8)
Anaemia	5 (1.5)	6 (2.0)
Acute myocardial infarction	5 (1.5)	8 (2.7)
Bradycardia	4 (1.2)	1 (0.3)
Cardiac arrest	3 (0.9)	3 (1.0)
Cardiac failure	12 (3.7)	10 (3.4)
Cardiac failure acute	3 (0.9)	6 (2.0)
Cardiac failure congestive	2 (0.6)	10 (3.4)
Coronary artery disease	1 (0.3)	3 (1.0)
Death	5 (1.5)	4 (1.4)
General physical health deterioration	1 (0.3)	4 (1.4)
Cholecystitis acute	0 3 (1.0)	
Clostridium difficile colitis	1 (0.3)	3 (1.0)
Device related infection	3 (0.9)	4 (1.4)
Gangrene	4 (1.2)	0
Gastroenteritis	3 (0.9)	3 (1.0)
Influenza	2 (0.6)	4 (1.4)
Osteomyelitis	1 (0.3)	3 (1.0)
Peritonitis	1 (0.3)	3 (1.0)
Pneumonia	21 (6.5)	14 (4.8)
Pyelonephritis acute	1 (0.3)	7 (2.4)
Sepsis	7 (2.2)	9 (3.1)
Staphylococcal sepsis	4 (1.2)	0
Urinary tract infection	7 (2.2)	3 (1.0)
Urinary tract infection bacterial	5 (1.5)	1 (0.3)
Urosepsis	2 (0.6)	3 (1.0)
Arteriovenous fistula thrombosis	9 (2.8)	5 (1.7)
eGFR decreased	26 (8.0)	25 (8.5)
Dehydration	3 (0.9)	7 (2.4)
Fluid overload	4 (1.2)	1 (0.3)
Hyperkalaemia	7 (2.2)	6 (2.0)
Basal cell carcinoma	4 (1.2)	0
Ischaemic stroke	0	0.3 (1.0)
Syncope	6 (1.9)	3 (1.0)
Transient ischaemic attack	4 (1.2)	3 (1.0)
Acute kidney injury	7 (2.2)	7 (2.4)

MedDRA version 20.0 preferred term	Roxadustat (n=323)	DA (n=293)
Azotaemia	1 (0.3)	3 (1.0)
End-stage renal disease	108 (33.4)	106 (36.2)
Dyspnoea	6 (1.9)	0
Pleural effusion	2 (0.6)	4 (1.4)
Pulmonary hypertension	1 (0.3)	3 (1.0)
Pulmonary oedema	4 (1.2)	2 (0.7)
Deep vein thrombosis	4 (1.2)	1 (0.3)
Hypertension	8 (2.5)	5 (1.7)
Hypertensive crisis	5 (1.5)	5 (1.7)
Hypotension	4 (1.2)	2 (0.7)
Peripheral arterial occlusive disease	3 (0.9)	4 (1.4)
Peripheral ischaemia	4 (1.2)	2 (0.7)

Table E3 Safety outcomes in ID-DD and SD populations

	Definition	ID-DD pool		SD pool		Source
		Roxadustat	ESA	Roxadustat	ESA	
N	The analysis population was the safety analysis set included all randomized participants who received at least one dose of study drug	760	766	1594	1594	[25]
All TEAEs, n (%) **Incidence rate**	An AE was defined as any untoward medical occurrence in a participant who was given the study drug or who had undergone study procedures and did not necessarily have a causal relationship with this treatment. All AEs collected during the safety emergent period were counted as TEAE. The safety emergent period was defined as the evaluation period from the analysis date of first drug intake up to 28 days after the end of treatment taking into account the different dosing frequencies of the study treatments.	[redacted]	[redacted]	[redacted]	[redacted]	[26]
Drug-related TEAEs, n (%) **Incidence rate**	Any TEAE with at least possible relationship to study drug (or with missing assessment of the causal relationship). Causal relationship was assessed by the investigator as 'Not related', 'Possible', 'Probably'	[redacted]	[redacted]	[redacted]	[redacted]	[26]
Fatal TEAEs, n (%) **Incidence rate**	TEAEs occurring during the safety-emergent period and leading to death any time.	[redacted]	[redacted]	[redacted]	[redacted]	[26]
Serious TEAEs, n (%) **Incidence rate**	An TEAE that results in death, is life-threatening, requires inpatient hospitalization or extends a current hospital stay, results in an ongoing or significant incapacity or interferes	[redacted]	[redacted]	[redacted]	[redacted]	[26]

	Definition	ID-DD pool		SD pool		Source
		Roxadustat	ESA	Roxadustat	ESA	
	substantially with normal life functions, or causes a congenital anomaly or birth defect. Medical events that do not result in death, are not life-threatening, or do not require hospitalization may be considered serious adverse events if they put the participant in danger or require medical or surgical intervention to prevent one of the results listed above.					
Drug-related Serious TEAEs, n (%) **Incidence rate**	SAE with at least possible relationship to study drug (or with missing assessment of the causal relationship). Causal relationship was assessed by the investigator as 'Not related', 'Possible', 'Probably'	11 (1.4) 1.0	11 (1.4) 0.9	59 (3.7) 2.1	27 (1.7) 0.8	[26]
TEAEs leading to discontinuation of study drug or study, n (%) **Incidence rate**	TEAE leading to discontinuation of study drug or discontinuation from study	83 (10.9) 7.6	74 (9.7) 6.2	170 (10.7) 6.0	101 (6.3) 3.1	[26]
Drug-related TEAEs leading to discontinuation of study drug or study, n (%) **Incidence rate**	Drug-related TEAE - with at least possible relationship to study drug (or with missing assessment of the causal relationship). Causal relationship was assessed by the investigator as 'Not related', 'Possible', 'Probably'- leading to discontinuation or discontinuation from study	10 (1.3) 0.9	2 (0.3) 0.2	36 (2.3) 1.3	7 (0.4) 0.2	[26]

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Table E4 Serious Treatment-emergent Adverse Events (≥ 1% of Patients in Either Treatment Group in the DD Pool); DD Pools (SAF)[26]

MedDRA SOC Preferred Term	ID-DD		SD	
	Roxadustat (N=760)	ESA (N=766)	Roxadustat (N=1594)	ESA † (N=1594)
Overall, n (%) **IR**	318 (41.8) 29.0	318 (41.5) 26.7	970 (60.9) 34.0	942 (59.1) 28.8
Blood and Lymphatic System Disorders, n (%) **IR**	5 (0.7) 0.5	13 (1.7) 1.1	35 (2.2) 1.2	41 (2.6) 1.3
Anaemia, n (%) **IR**	2 (0.3) 0.2	6 (0.8) 0.5	23 (1.4) 0.8	27 (1.7) 0.8
Cardiac disorders, n (%) **IR**	57 (7.5) 5.2	71 (9.3) 6.0	281 (17.6) 9.8	318 (19.9) 9.7
Acute myocardial infarction, n (%) **IR**	9 (1.2) 0.8	18 (2.3) 1.5	76 (4.8) 2.7	71 (4.5) 2.2
Atrial fibrillation, n (%) **IR**	4 (0.5) 0.4	6 (0.8) 0.5	31 (1.9) 1.1	36 (2.3) 1.1
Cardiac arrest, n (%) **IR**	4 (0.5) 0.4	9 (1.2) 0.8	26 (1.6) 0.9	34 (2.1) 1.0
Cardiac failure, n (%) **IR**	6 (0.8) 0.5	2 (0.3) 0.2	18 (1.1) 0.6	20 (1.3) 0.6
Cardiac failure congestive, n (%) **IR**	9 (1.2) 0.8	10 (1.3) 0.8	48 (3.0) 1.7	50 (3.1) 1.5
Coronary artery disease, n (%) **IR**	8 (1.1) 0.7	4 (0.5) 0.3	26 (1.6) 0.9	31 (1.9) 0.9
Myocardial infarction, n (%) **IR**	6 (0.8) 0.5	2 (0.3) 0.2	19 (1.2) 0.7	15 (0.9) 0.5
Gastrointestinal Disorders, n (%) **IR**	52 (6.8) 4.7	50 (6.5) 4.2	156 (9.8) 5.5	183 (11.5) 5.6
Gastrointestinal haemorrhage, n (%) **IR**	6 (0.8) 0.5	6 (0.8) 0.5	30 (1.9) 1.1	42 (2.6) 1.3
General Disorders and Administration Site Conditions, n (%) **IR**	34 (4.5) 3.1	29 (3.8) 2.4	126 (7.9) 4.4	108 (6.8) 3.3
Death, n (%) **IR**	6 (0.8) 0.5	10 (1.3) 0.8	24 (1.5) 0.8	27 (1.7) 0.8
Non-cardiac chest pain, n (%) **IR**	3 (0.4) 0.3	2 (0.3) 0.2	27 (1.7) 0.9	19 (1.2) 0.6
Infections and Infestations, n (%) **IR**	136 (17.9) 12.4	118 (15.4) 9.9	419 (26.3) 14.7	425 (26.7) 13.0
Cellulitis, n (%) **IR**	5 (0.7) 0.5	8 (1.0) 0.7	22 (1.4) 0.8	29 (1.8) 0.9
Device related infection, n (%) **IR**	10 (1.3) 0.9	6 (0.8) 0.5	14 (0.9) 0.5	16 (1.0) 0.5
Gangrene, n (%) **IR**	6 (0.8) 0.5	8 (1.0) 0.7	17 (1.1) 0.6	21 (1.3) 0.6
Osteomyelitis, n (%) **IR**	4 (0.5) 0.4	5 (0.7) 0.4	14 (0.9) 0 . 5	21 (1.3) 0.6

MedDRA SOC Preferred Term	ID-DD		SD	
	Roxadustat (N=760)	ESA (N=766)	Roxadustat (N=1594)	ESA† (N=1594)
Peritonitis, n (%) **IR**	20 (2.6) 1.8	16 (2.1) 1.3	28 (1.8) 1.0	26 (1.6) 0.8
Pneumonia, n (%) **IR**	36 (4.7) 3.3	38 (5.0) 3.2	109 (6.8) 3.8	126 (7.9) 3.8
Sepsis, n (%) **IR**	18 (2.4) 1.6	11 (1.4) 0.9	61 (3.8) 2.1	69 (4.3) 2.1
Septic shock, n (%) **IR**	7 (0.9) 0.6	4 (0.5) 0.3	23 (1.4) 0.8	21 (1.3) 0.6
Urinary tract infection, n (%) **IR**	10 (1.3) 0.9	6 (0.8) 0.5	16 (1.0) 0.6	17 (1.1) 0.5
Injury, Poisoning and Procedural Complications, n (%) **IR**	76 (l0.0) 6.9	60 (7.8) 5.0	246 (15.4) 8.6	227 (14.2) 6.9
Arteriovenous fistula site complication, n (%) **IR**	8 (1.1) 0.7	3 (0.4) 0.3	20 (1.3) 0.7	10 (0.6) 0.3
Arteriovenous fistula thrombosis, n (%) **IR**	44 (5.8) 4.0	26 (3.4) 2.2	72 (4.5) 2.5	52 (3.3) 1.6
Metabolism and Nutrition Disorders, n (%) **IR**	35 (4.6) 3.2	40 (5.2) 3.4	155 (9.7) 5.4	134 (8.4) 4.1
Fiuid overload, n (%) **IR**	16 (2.1) 1.5	13 (1.7) 1.1	50 (3.1) 1.8	57 (3.6) 1.7
Hyperkalaemia, n (%) **IR**	6 (0.8) 0.5	9 (1.2) 0.8	53 (3.3) 1.9	46 (2.9) 1.4
Hypoglycaemia, n (%) **IR**	6 (0.8) 0.5	6 (0.8) 0.5	24 (1.5) 0.8	16 (1.0) 0.5
Nervous System Disorders, n (%) **IR**	45 (5.9) 4.1	50 (6.5) 4.2	150 (9.4) 5.3	146 (9.2) 4.5
Syncope, n (%) **IR**	4 (0.5) 0.4	3 (0.4) 0.3	11 (0.7) 0.4	23 (1.4) 0.7
Respiratory, Thoracic, and Mediastinal Disorders, n (%) **IR**	24 (3.2) 2.2	42 (5.5) 3.5	142 (8.9) 5.0	170 (10.7) 5.2
Acute respiratory failure, n (%) **IR**	3 (0.4) 0.3	6 (0.8) 0.5	29 (1.8) 1.0	35 (2.2) 1.1
Pleural effusion, n (%) **IR**	I (0.1) 0.1	3 (0.4) 0.3	25 (1.6) 0.9	26 (1.6) 0.8
Pulmonary oedema, n (%) **IR**	5 (0.7) 0.5	7 (0.9) 0.6	19 (1.2) 0.7	35 (2.2) 1.1
Vascular Disorders, n (%) **IR**	48 (6.3) 4.4	52 (6.8) 4.4	189 (11.9) 6.6	198 (12.4) 6.0
Deep vein thrombosis, n (%) **IR**	4 (0.5) 0.4	2 (0.3) 0.2	24 (1.5) 0.8	5 (0.3) 0.2
Hypertension, n (%) **IR**	7 (0.9) 0.6	3 (0.4) 0.3	25 (1.6) 0.9	21 (1.3) 0.6
Hypertensive crisis, n (%) **IR**	11 (1.4) 1.0	17 (2.2) 1.4	28 (1.8) 1.0	37 (2.3) 1.1
Hypertensive emergency, n (%) **IR**	3 (0.4) 0.3	6 (0.8) 0.5	25 (1.6) 0.9	31 (1.9) 0.9

MedDRA SOC Preferred Term	ID-DD		SD	
	Roxadustat (N=760)	ESA (N=766)	Roxadustat (N=1594)	ESA † (N=1594)
Hypotension, n (%)	8 (1.1)	7 (0.9)	38 (2.4)	34 (2.1)
IR	0.7	0.6	1.3	1.0

Percentages were calculated based on the total number of patients in the treatment group. The IR is patients/100 patient years.

ID-DD: dialysis-dependent; ESA: erythropoiesis stimulating agent; EPO: epoetin; IR: incidence rate; SAF: safety analysis set; TEAE: treatment-emergent adverse event.

† Data presented are pooled results from both the EPO and DA groups.

Source: Data on file [26]

Appendix F Comparative analysis of efficacy and safety

Not applicable. Comparative data presented in appendix D and E based on a single study in NDD and a pre-specified pooled analysis of ID-DD patients in the four DD studies in ALPINE.

Appendix G Extrapolation

Not applicable. Extrapolation of clinical efficacy not relevant for cost-comparison.

Appendix H – Literature search for HRQoL data

Not applicable as not cost-utility analysis performed.

Appendix I Mapping of HRQoL data

Not applicable. No cost-utility analysis performed

Appendix J Probabilistic sensitivity analyses

Not applicable. No PSA performed

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk