www.bdd.rdplf.org Volume 6, n° 1, April 2023
https://doi.org/10.25796/bdd.v6i1.77073
ISSN 2607-9917

Bulletin de la Dialyse à Domicile

# Interest of HIF stabilizers in home dialysis

(Intérêts des stabilisateurs du HIF en dialyse à domicile)

Guy Rostoker [1,2]

[1]Collège de Médecine des Hôpitaux de Paris, 75005 Paris, France
[2]Service de Néphrologie et de Dialyse, Hôpital Privé Claude Galien, Ramsay Santé, 91480 Quincy-sous-Sénart, France

To cite: Rostoker G. Interest of HIF stabilizers in home dialysis. Bull Dial Domic [Internet]. ;6(1). Available from DOI : https://doi.org/10.25796/bdd.v6i1.77073

Note : ce texte est disponible en Français à la même adresse url : https://doi.org/10.25796/bdd.v6i1.77073

## Summary

Hypoxia-inducible factor (HIF) stabilizers or dustats are orally administered small molecules with very low renal elimination (without adaptation during chronic kidney disease (CKD)) analogues with antagonistic effect of 2-oxoglutarate, a naturally occurring substrate of HIF-Prolyl Hydroxylase at the origin of the inhibition of this enzyme. This results in a simulated state of hypoxia allowing the accumulation of HIF-α in the cells followed by coordinated erythropoiesis with erythropoietin synthesis, decreased hepatic hepcidin production and optimization of iron metabolism. HIF stabilizers have only been studied in non-inferiority clinical trials versus erythopoiesis stimulating agents (ESAs). The primary endpoint for the therapeutic trials of all these different molecules was the change in hemoglobin level. Dustat corrects anemia in advanced non-dialysis and dialysis CKD in a similar way to ESAs.

Six HIF stabilizers molecules are in advanced development: Roxadustat, Daprodustat, Vadadustat, Enarodustat, Desidustat and Molidustat. Only Roxadustat or Evrenzo®, currently has a marketing authorization in Europe obtained in August 2021. Only two studies have been dedicated to peritoneal dialysis, one with Roxadustat, the other with Daprodustat. Home dialysis appears to be an elective indication for HIF stabilizers because of their absence of cold chain necessity and their positive impact on iron metabolism and the difficulties and imperfections of the current treatment of anemia with ESA and intravenous iron in this patient population.

**Keywords**: Anemia treatment, ESA, HIF stabilizer, home dialysis.

## Résumé

Les dustats ou stabilisateurs du Hypoxia-inducible factor (HIF) sont des molécules de petite taille données par voie orale avec une très faible élimination rénale (sans adaptation posologique au cours de la maladie rénale chronique (MRC)), analogues avec effet antagoniste du 2-oxoglutarate, substrat naturel de la HIF-Prolyl hydroxylase à l'origine de l'inhibition de cet enzyme. Il en résulte un état de simulation d'hypoxie permettant l'accumulation de HIF-α dans les cellules puis une érythropoïèse coordonnée avec synthèse d'érythropoïétine, diminution de la production hépatique d'hepcidine et optimisation du métabolisme martial. Les stabilisateurs du HIF ont fait uniquement l'objet d'études cliniques de non-infériorité versus les agents stimulant l'érythropoïèse (ASE). Le critère principal de jugement pour les essais thérapeutiques de toutes ces différentes molécules était la variation du taux d'hémoglobine. Les dustats corrigent de façon similaire aux ASE l'anémie de la MRC avancée non dialysée et dialysée.

Six molécules de dustat sont à un stade avancé de développement : le Roxadustat, le Daprodustat, le Vadadustat, l'Enarodustat, le Desidustat et le Molidustat. Seul le Roxadustat ou Evrenzo®, possède actuellement une autorisation de mise sur le marché (AMM) en Europe obtenue en août 2021. Seulement deux études ont été dédiées à la dialyse péritonéale l'une avec le Roxadustat, l'autre avec le Daprodustat. La dialyse à domicile apparaît être une indication élective des stabilisateurs du HIF du fait de leur absence de nécessité de la chaîne du froid et de leur impact positif sur le métabolisme martial et des difficultés et imperfections du traitement actuel de l'anémie par les ASE et les dérivés du fer dans cette population de malades.

**Mots clés** : ASE, dialyse à domicile, stabilisateur du HIF, traitement de l'anémie.

**Correspondence to**: Dr Guy Rostoker, Service de Néphrologie et de Dialyse, Hôpital Privé Claude Galien, Ramsay Santé, 20 route de Boussy, 91480 Quincy-sous-Sénart, France.
Email : rostotom@orange.fr
ORCID: https://orcid.org/0000-0002-4383-3825



journal officiel du Registre de Dialyse Péritonéale de Langue Française RDPLF www.rdplf.org

www.bdd.rdplf.org Volume 6, n° 1, April 2023
https://doi.org/10.25796/bdd.v6i1.77073
ISSN 2607-9917

## 1. Reminder on erythropoiesis stimulating agents

Recombinant erythropoietin (EPO), introduced in 1987, represented a therapeutic revolution in the management of anemia in chronic kidney disease (CKD), transforming the quality of life of dialysis patients and improving the mortality and morbidity associated with this severe anemia [1]. It is a pathophysiological treatment because the anemia in CKD is mainly related to a significant decrease in erythropoietin production by the diseased kidneys, as evinced by the sharply decreased levels of circulating erythropoietin during CKD; moreover, there is a parallel between the severity of renal failure and the decrease in circulating erythropoietin levels [2]. Erythropoietin is a growth factor acting on the bone marrow, which is necessary for the early stages of erythropoiesis; EPO thus acts on burst-forming unit-erythroid cells (BFU-E cells), colony-forming unit-erythroid cells (CFU-E cells) and proerythroblasts [3] via a specific receptor. It should be noted that in addition to this early EPO-dependent phase, erythropoiesis has a later phase dependent on the incorporation of iron into the heme nucleus of hemoglobin *(Figure 1)*.

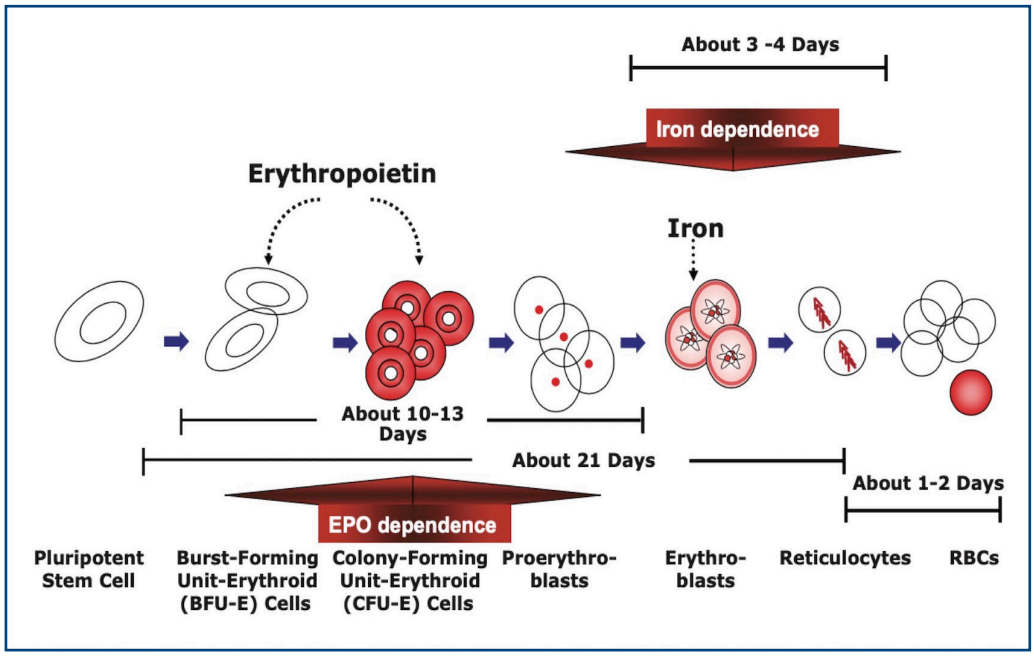



*Figure 1. EPO and iron in erythropoiesis*
Figure according to Besarab's article, [3].

In addition to its primary action on erythropoiesis, EPO is also a pleiotropic growth factor acting during fetal development, not only on erythropoiesis but also on angiogenesis, fetal brain development, and also neuronal, retinal and vascular protection, and wound healing in adulthood [4]. EPO production takes place in the liver during fetal life and in the kidneys from birth. It has recently been shown that during CKD, the liver takes over from the deficient kidneys in the synthesis of erythropoietin, especially as renal function is impaired [5].

## 2. Erythropoietin synthesis is stimulated by hypoxia and HIF

EPO production occurs in the kidney (and liver) in response to changes in tissue oxygenation or hypoxia [6]. Hypoxia leads to transcription of the erythropoietin gene in peritubular interstitial fibroblasts and in the liver [6]. EPO promotes erythropoiesis in pluripotent bone marrow cells

journal officiel du Registre de Dialyse Péritonéale de Langue Française RDPLF www.rdplf.org

www.bdd.rdplf.org Volume 6, n° 1, April 2023
https://doi.org/10.25796/bdd.v6i1.77073
ISSN 2607-9917

committed to the erythroblastic lineage (BFU-E and CFU-E) and proerythroblasts [6]. The resulting increase in circulating erythrocytes and hemoglobin leads to improved tissue oxygenation [6]. The hypoxia inducible factor (HIF) transcription factor in EPO-producing kidney cells regulates erythropoietin production in a hypoxia-inducible manner *(Figure 2)* [6].

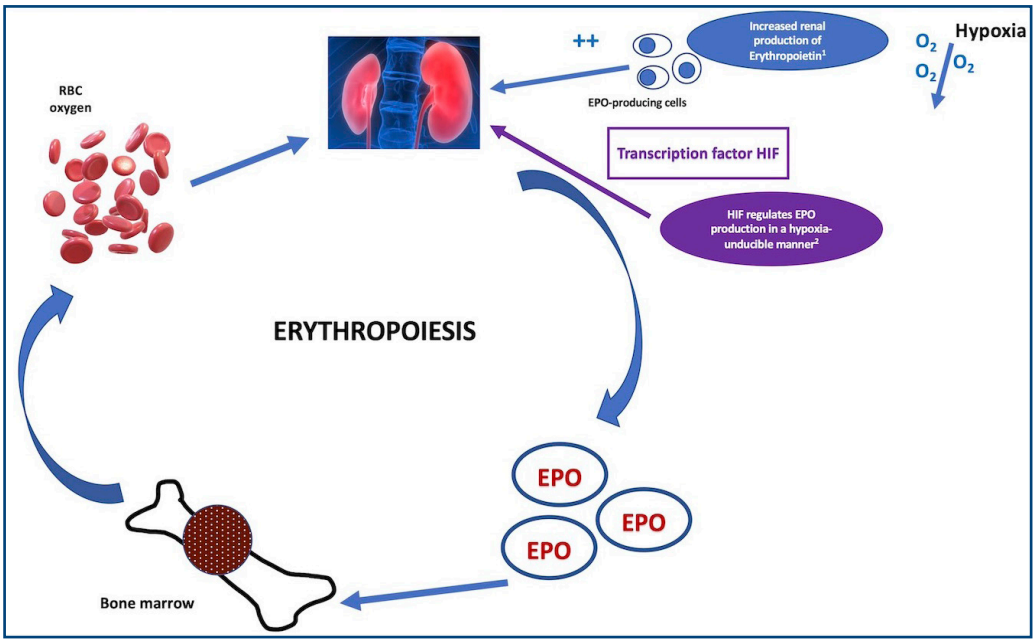



*Figure 2. Synthesis of EPO*
*EPO, erythropoietin; HIF, hypoxia-inducible factor; RBC, red blood cell.*
*Figure adapted from: 1. Koury MJ and Haase VH, [6], 2. Locatelli F, et al, [7].*

The level of HIF-α is regulated by specific enzymes called HIF-prolyl hydroxylase (HIF-PHD) that trigger its degradation at the proteasome. There are three HIF-PHD enzymes in humans that hydroxylate HIF-α and thus regulate its stability: HIF-PHD1, HIF-PHD2, and HIF-PHD3. The enzyme HIF-PHD2 is considered the primary regulator of HIF under normal oxygenation conditions [7].

The activation of HIF is a physiological response of the body in the presence of low oxygen levels (hypoxia). Indeed, at normal oxygen levels, HIF-prolyl hydroxylase remains abundant. It causes the degradation of HIF-α and thus prevents the activation of a hypoxic response. In contrast, during periods of hypoxia (low oxygen), HIF-prolyl hydroxylase is inactive, because oxygen is required for the enzymatic reaction, and HIF-α will therefore accumulate. HIF-α then dimerizes with constitutively expressed HIF-β, and the dimer moves to the nucleus, allowing transcription of key genes that manage hypoxia [7]. Several hundred genes are direct targets of HIF; these genes play a role in cell migration, cell growth and cycle, angiogenesis, vasomotor regulation, glucose metabolism and availability, and barrier functions, as well as EPO synthesis and iron availability for erythropoiesis *(Figure 3)* [8].

journal officiel du Registre de Dialyse Péritonéale de Langue Française RDPLF www.rdplf.org

www.bdd.rdplf.org Volume 6, n° 1, April 2023
https://doi.org/10.25796/bdd.v6i1.77073
ISSN 2607-9917

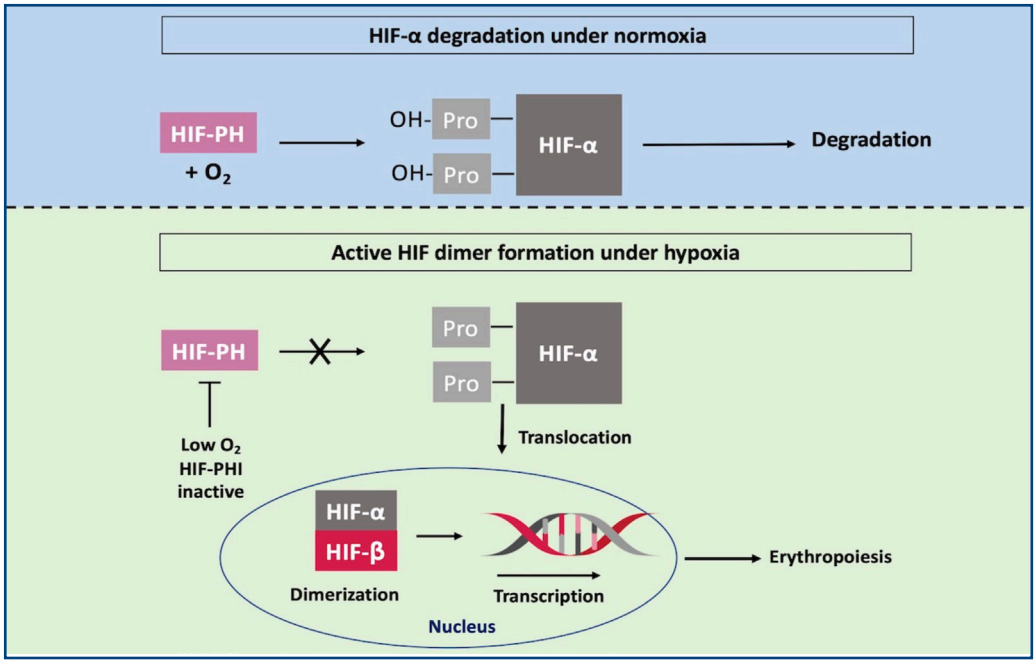



*Figure 3. HIF activation*
*HIF, Hypoxia-inducible factor, HIF-PH, HIF prolyl hydroxylase, HIF-PHI, inhibition, Pro, proline.*
*Figure adapted from Locatelli F, et al, [7].*

## 3. General information on HIF stabilizers or Dustats

### 3.1 The different molecules

While there are about a dozen molecules in development, only six are at an advanced stage.

The first molecule in this new class is Roxadustat or Evrenzo®, developed by the American biotechnology company Fibrogen (San Francisco, USA) and produced by Astellas Pharma (Tokyo, Japan) in Japan, Asia and Europe and by AstraZeneca (Cambridge, UK) in North America. Evrenzo® obtained European marketing authorization (AMM) in August 2021 [9].

The second molecule in the dustat class is Daprodustat, developed by the British laboratory GlaxoSmithKline (GSK, Brentford, UK) which just obtained AMM in the USA in February 2023 [10]. The four other molecules currently in advanced development are Vadadustat (Vafseo®) from Akebia Therapeutics (Cambridge, Massachusetts, USA) and Otsuka Pharmaceutical (Chiyoda, Tokyo, Japan)); Enarodustat (Enaroy® from Kyowa Hakko Kirin, Tokyo, Japan); Desidustat (Oxemia® from Zydus Cadila Healthcare, Ahmedabad, India); and, finally, Molidustat from Bayer (Leverkusen, Germany) [11-12].

### 3.2 Commonalities in the development and clinical trials of HIF stabilizers

These are orally administered molecules (as opposed to the intravenous and subcutaneous routes for ESAs) which have only been the subject of non-inferiority clinical studies compared with first-generation ESAs (Eprex®, Neorecormon®) and second-generation ESAs (Aranesp®) [11-12].

The primary endpoint for the therapeutic trials of all these different molecules was the change in

www.bdd.rdplf.org Volume 6, n° 1, April 2023
https://doi.org/10.25796/bdd.v6i1.77073
ISSN 2607-9917

hemoglobin level [11-12]; only the studies of Daprodustat used a primary endpoint combining hemoglobin level and major adverse cardiac events (MACE), including cardiovascular death, non-fatal myocardial infarction and non-fatal stroke [11-12]. These clinical trials were conducted in both hemodialysis patients and patients with advanced non-dialysis CKD; there were very few studies involving peritoneal dialysis (PD) patients, and none involving home hemodialysis patients, daily or otherwise [11-12]. The duration of these studies varied from 6 months to 1 year. There was no significant pharmacovigilance signal; a common point of these molecules is their important pharmaceutical potency, which is superior to that of ESAs and often produces rapid corrections of hemoglobin, which may explain the excess of cases of fistula thrombosis as well as the rare phlebitis and pulmonary embolisms observed during these studies [11-12].

## 4. Mechanisms of action of HIF stabilizers or Dustats

These are small synthetic molecules with very low renal elimination (without dosage adjustment during CKD). They are analogs with an antagonistic effect on 2-oxoglutarate, a natural substrate of HIF-prolyl hydroxylase at the origin of the inhibition of this enzyme. This results in a simulated state of hypoxia, allowing the accumulation of HIF-α in the cells [11-12].

Pharmacological inhibition of HIF-prolyl hydroxylase 2 induces transcription of EPO genes and inhibition of hepcidin synthesis, resulting in efficient and coordinated erythropoiesis. The production of erythrocytes follows the conjunction of EPO production and the synthesis of its cellular receptors associated with an increase in iron availability. This optimization of martial metabolism is due to increased intestinal iron absorption and iron release by macrophages and cells of the reticuloendothelial system following the inhibition of hepcidin synthesis and the arrest of degradation of ferroportin, the protein exporting iron from these cells [11-12]. In an ancillary study of Roxadustat, it was shown that blood erythropoietin concentrations in patients treated with this dustat were close to physiological values, whereas circulating erythropoietin concentrations on Epoetin alfa appeared to be largely supra-physiological (by a factor of 5 to 6) *(Figure 4)* [13]. In the same study, Roxadustat significantly reduced hyperhepcidemia in dialysis patients and increased iron utilization for erythropoiesis, as evinced by the increase in the hemoglobin content of reticulocytes (CHr) *(Figure 5)* [13]. It should be remembered that the inhibition of

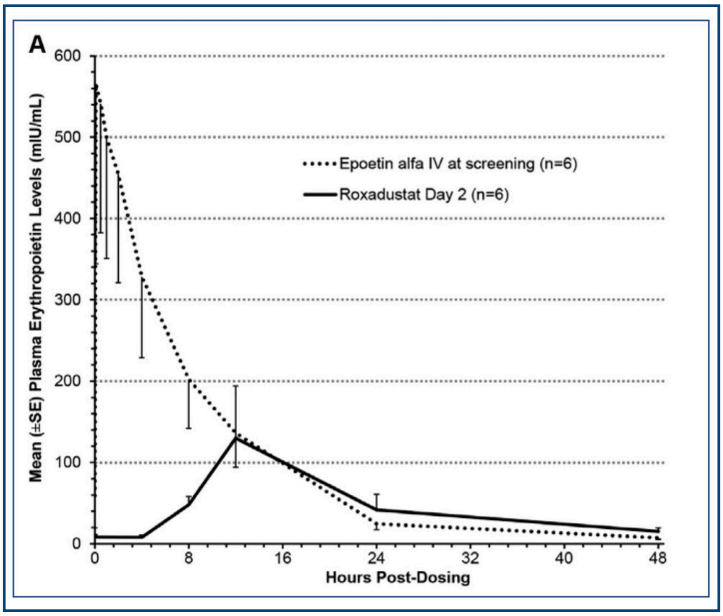



*Figure 4. Pharmacodynamic effects of roxadustat compared to epoetin alfa. Error bars signify standard error of the mean. (A) Mean plasma erythropoietin levels during treatment with roxadustat compared to prior epoetin alfa dosing in the same patients (n=6).*
*Figure according to Provenzano R, et al, [13].*

journal officiel du Registre de Dialyse Péritonéale de Langue Française RDPLF www.rdplf.org

www.bdd.rdplf.org Volume 6, n° 1, April 2023
https://doi.org/10.25796/bdd.v6i1.77073
ISSN 2607-9917

hepatic hepcidin under dustat is indirect, due to the medullary production of erythroferrone.

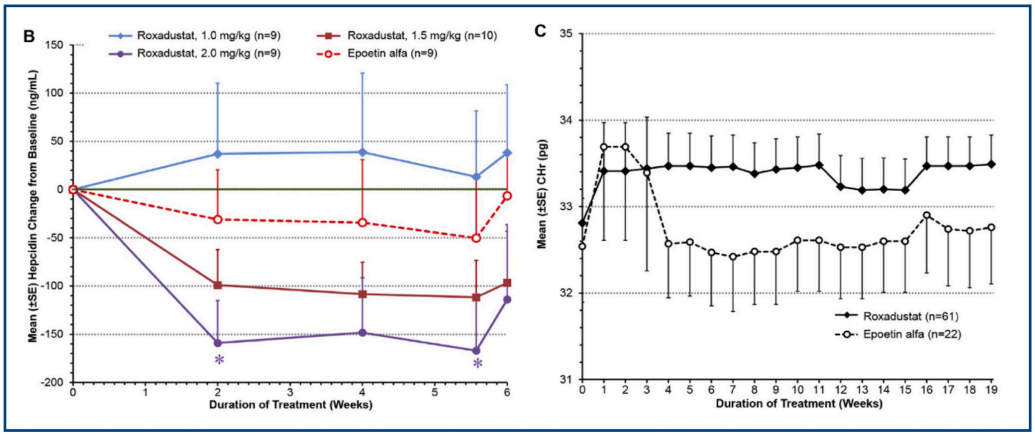



*Figure 5. Pharmacodynamic effects of roxadustat compared to epoetin alfa.*
*Error bars signify standard error of the mean.*
*(B) Change in hepcidin level (ng/mL) from baseline during 6 weeks of treatment in the 6-week cohorts with the largest sample sizes (n>5). *P <0.05 (comparing hepcidin change from baseline between the 2.0-mg/kg roxadustat group and the epoetin alfa group). (C) Mean reticulocyte hemoglobin content (CHr) over time in roxadustat- versus epoetin alfa–treated participants randomly assigned to 19 weeks of treatment (last observation carried forward, efficacy-evaluable population). Figure according to Provenzano R, et al, [13].*

## 5. Roxadustat or Evrenzo®

Evrenzo® is the first dustat marketed in Europe. Its clinical development included trials involving 9,600 patients either in advanced renal failure or on dialysis *(Figure 6)* [14]. It has similar efficacy to ESAs in treating CKD anemia *(Figure 7)* [14]. The European Medicines Agency's (EMA) summary of product characteristics states (verbatim), «What is it used for? Evrenzo is a medicine used in adults to treat the symptoms of anemia caused by chronic renal failure. How is Evrenzo used? Patients treated with an ESA and whose haemoglobin levels are stable should not be switched to Evrenzo unless there is clinical justification and expected benefits.»

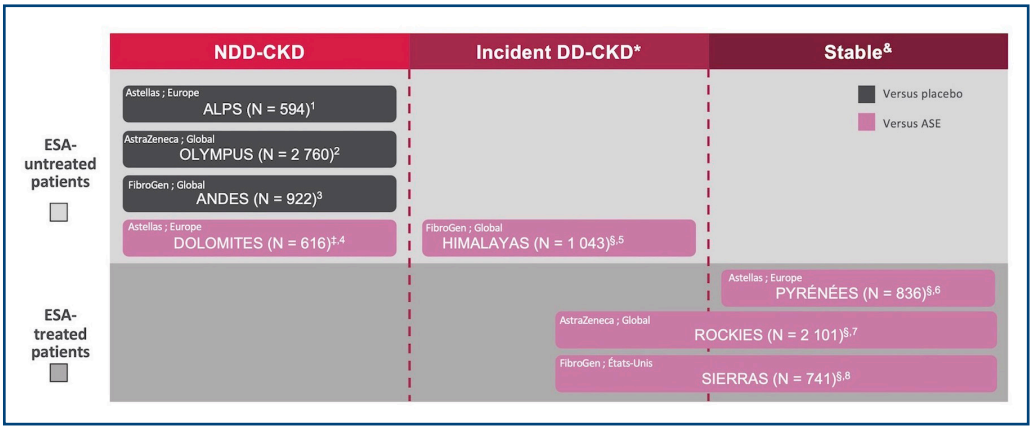
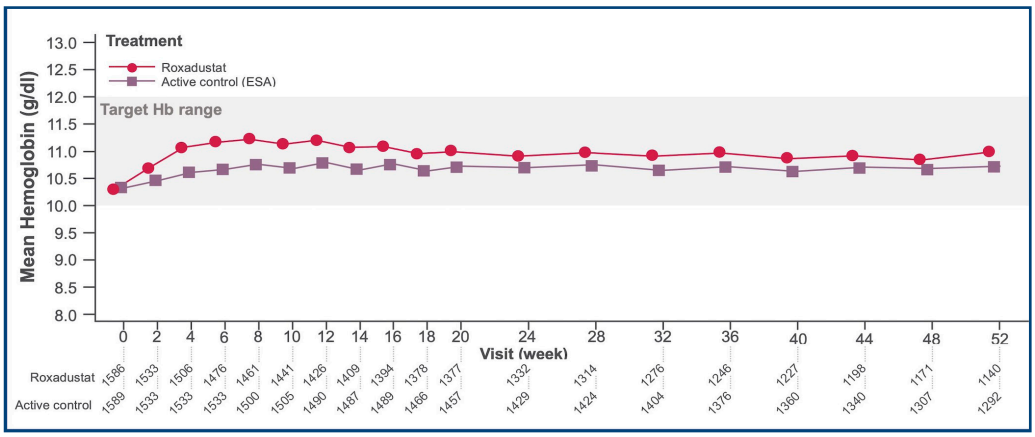



*Figure 6. Roxadustat clinical trial overview*
**Subset of patients with ≥ 2 weeks and ≤ 4 months of dialysis at the time of randomisation; &Subset of patients with > 4 months of dialysis at the time of randomisation; ‡Darbepoetin alfa active comparator; §Epoetin alfa active comparator or darbepoetin alfa. CKD, chronic kidney disease; DD, dialysis-dependent; ESA, erythropoiesis stimulating agent; NDD, non dialysis-dependent.*
*Figure adapted from: 1. Shutov E, et al. Nephrol Dial Transplant. 2021;36:1629-1639 ; 2. Fishbane S, et al. J Am Soc Nephrol. 2021;32(3):737–755; 3. Coyne DW, et al. Kidney Int Rep. 2020;6(3):624–635; 4. Barratt J, et al. Nephrol Dial Transplant. 2021; 36 : 1616-1628 ; 5. Provenzano R, et al. Nephrol Dial Transplant. 2021;36:1717-1730; 6. Csiky B, et al. Adv Ther 2021;38 : 5361-5380 ; 7. Fishbane S, et al. J Am Soc Nephrol 2022; 33: 850–866 ; 8. Charytan C, et al. Kidney Int Rep. 2021;6(7):1829–1839.*

www.bdd.rdplf.org Volume 6, n° 1, April 2023
https://doi.org/10.25796/bdd.v6i1.77073
ISSN 2607-9917



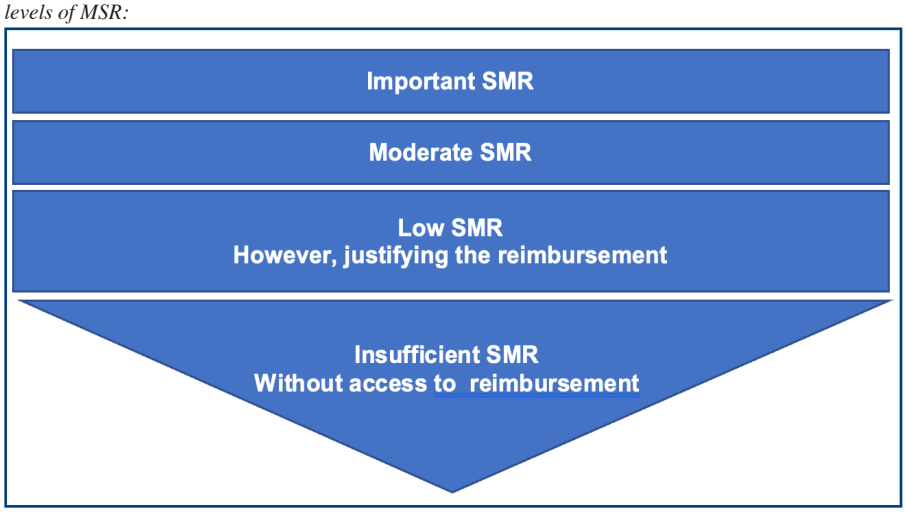

⬆ *Figure 7. Studies Pyrenees, Rockies, Sierras about Roxadustat*
*Figure from Epar-evrenzo® [15].*
*Average hemoglobin level (g/dL) over time to 52 weeks.*

In other words, according to the summary of product characteristics established by the EMA, Evrenzo® can be given in the first intention in pre-dialysis and dialysis in ESA-naive patients and in the second intention in pre-dialysis and dialysis in case of resistance or intolerance to ESAs [15].

The opinion of the Transparency Commission of the French National Authority for Health (HAS) for Evrenzo® dated March 30, 2022 specifies that its (verbatim) «medical service rendered (MSR) is important only in patients not already treated with an erythropoiesis-stimulating agent, not dialyzed or dialyzed for less than 4 months» *(Table I)* [16]. Evrenzo® has a level V medical benefit (ISMR V) *(Table II)* [16].

Currently, Roxadustat is also marketed in other European Union countries and in the United Kingdom in the European AMM indication, as well as in Japan and China in a broader indication (non-dialyzed and dialyzed CKD).

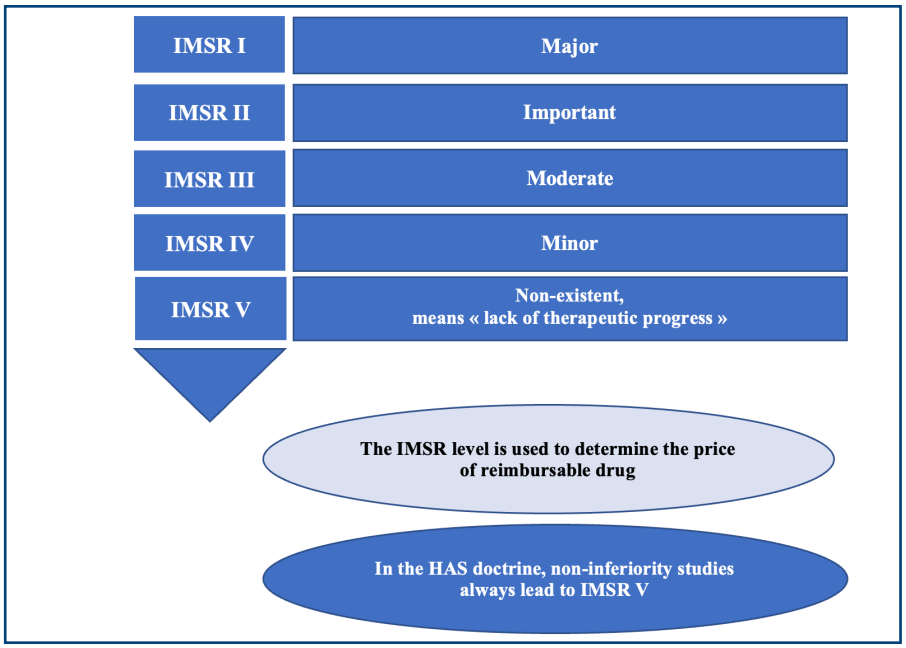
⬇ *Table I. Medical service rendered (MSR) according to the HAS*
*The medical service rendered is a criterion that takes into account both the seriousness of the pathology for which the drug is indicated and data specific to the drug itself in a given indication. There are four levels of MSR:*




journal officiel du Registre de Dialyse Péritonéale de Langue Française RDPLF www.rdplf.org

www.bdd.rdplf.org Volume 6, n° 1, April 2023
https://doi.org/10.25796/bdd.v6i1.77073
ISSN 2607-9917

*Table II. Improvement of the medical service rendered (IMSR) according to the HAS*
*The improvement in the medical service rendered corresponds to the therapeutic progress made by a drug. According to the assessment, 5 levels of IMSR have been defined.*




## 6. Daprodustat

The clinical development of Daprodustat included 8,169 patients either in advanced renal failure or on dialysis *(Figure 8)* [17]. It has similar efficacy to ESAs in treating anemia in CKD [17]. The decision of the EMA regarding the European AMM of Daprodustat is expected in April or May 2023, and should logically lead to the submission of a reimbursement application to the HAS Transparency Commission (CT) in the fall of 2023. The opinion of the CT should be known at the beginning of 2024, and the marketing of Daprodustat should occur during 2024 after the price has been fixed by the Economic Committee for Health Products.

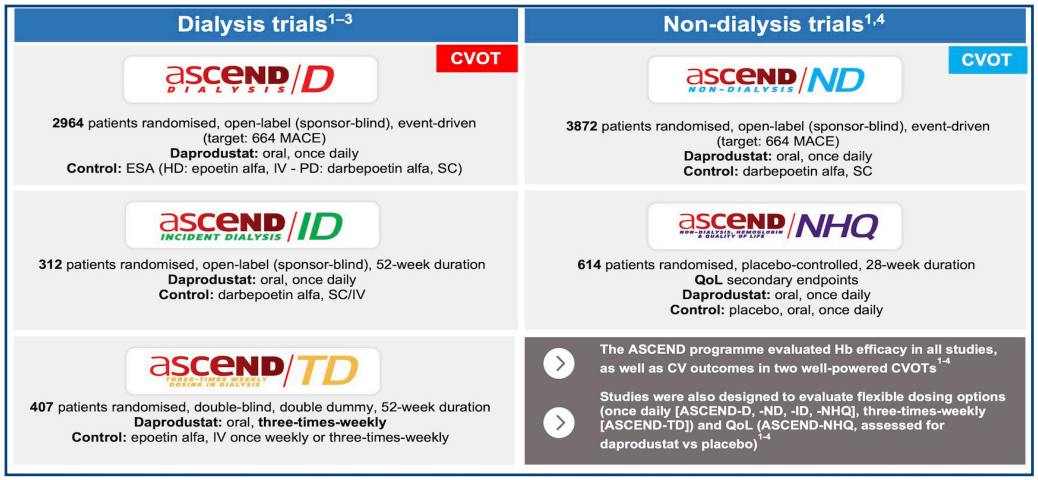



*Figure 8. ASCEND clinical programs for Daprodustat*
*CV, cardiovascular; CVOT, cardiovascular outcome trial; D, dialysis; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; HD, hemodialysis; ID, incident dialysis; IV, intravenous; MACE, major adverse cardiovascular event; ND, non-dialysis; NHQ, non-dialysis, hemoglobin, quality of life; PD, peritoneal dialysis; QoL, quality of life; SC, subcutaneous; TD, three-times-weekly and dialysis.*
*Figure adapted by GSK: 1. Singh AK, et al. Presented at American Society of Nephrology - Kidney Week 2021:FR-OR66. 2. Singh AK, et al. JAMA Intern Med. 2022;182(6):592-602. 3. Coyne DW, et al. Presented at American Society of Nephrology - Kidney Week 2021:PO0487. 4. Johansen KL, et al. Presented at American Society of Nephrology - Kidney Week 2021:FR-OR53.*



journal officiel du Registre de Dialyse Péritonéale de Langue Française RDPLF www.rdplf.org

www.bdd.rdplf.org Volume 6, n° 1, April 2023
https://doi.org/10.25796/bdd.v6i1.77073
ISSN 2607-9917

## 7. Vadadustat

Vadadustat (Vafseo® from Akebia Therapeutics (Cambridge, Massachusetts, USA) and Otsuka Pharmaceutical (Chiyoda, Tokyo, Japan)) received a positive opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) in February 2023, which is a key step in obtaining a European AMM [18]. Its clinical development has included 8,438 patients on dialysis or with advanced non-dialysis CKD, and it has similar efficacy to ESAs in treating anemia due to renal failure [19].

## 8. HIF Stabilizers and Home Dialysis

Despite the real interest in this new therapeutic class in home dialysis, linked to the absence of the cold chain, which is complex to implement in this situation, and to the positive modulation effect of dustats on martial metabolism, which is strongly disrupted in dialyzed CKD, there is a paucity of data. Studies are limited to 2 works on peritoneal dialysis (PD), one involving Roxadustat, the other involving Vadadustat [20-21].

The first study was of Roxadustat and involved 56 Japanese patients treated with PD; 13 were ESA-naive and 43 on ESA then converted to this dustat. The follow-up was 24 weeks. Both types of patients were within the 10-12 g/dl target by week 6 and remained within the target during the 24 weeks of the study *(Figure 9)* [20].

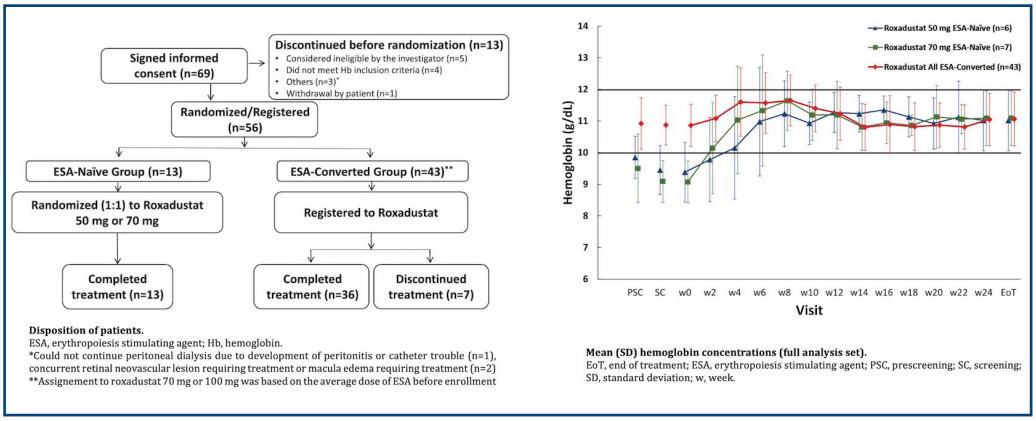



*Figure 9. Study of Roxadustat in Peritoneal Dialysis Chronic Kidney Disease Patients with anemia*
*Figure according to Akizawa T, et al, [20].*

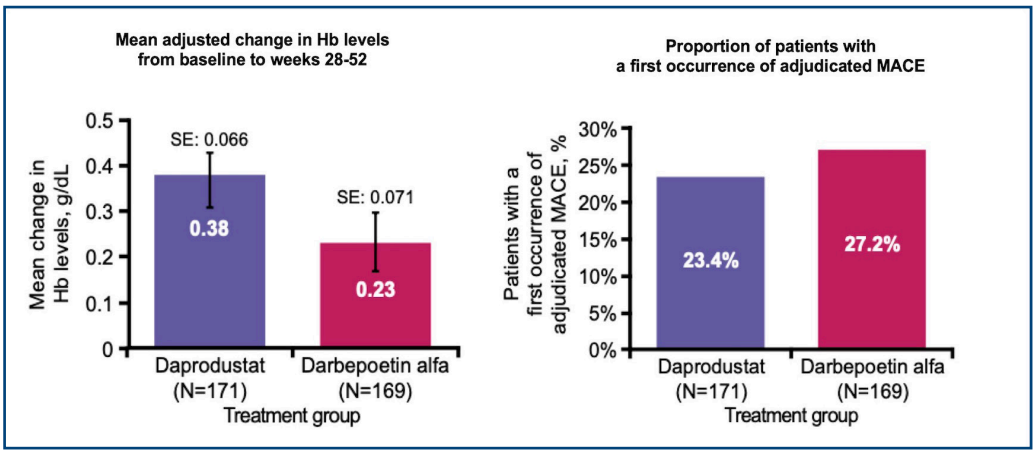



*Figure 10. Efficacy of Daprodustat in peritoneal dialysis: a pre-specified analysis of the ASCEND-D study*
*Figure according to Dasgupta I, et al, [21]*



journal officiel du Registre de Dialyse Péritonéale de Langue Française RDPLF www.rdplf.org

www.bdd.rdplf.org Volume 6, n° 1, April 2023
https://doi.org/10.25796/bdd.v6i1.77073
ISSN 2607-9917

The second work dedicated to PD was a pre-specified analysis of the ASCEND-D study (NCT02879305) of Daprodustat in dialysis, which included 340 PD patients randomized (1/1) to either Daprodustat or Darbepoetin alfa. This study, presented at the last American Society of Nephrology (ASN) congress, showed an identical cardiovascular safety and efficacy profile on anemia between Darbepoetin and Daprodustat in PD *(Figure 10)* [21].

## 9. What positioning of HIF stabilizers for nephrologists?

In recent years, the nephrological community had shown an interest and enthusiasm for the new therapeutic class of dustats [6-8]. However, this has greatly diminished in the last 3 years due to the unfinished nature of the studies on the different molecules, which have been limited to non-inferiority studies. There have not been any superiority studies or specific studies on patients who are hypo-responders or resistant to ESAs, a medical problem that is currently unresolved and is a source of great concern to the nephrologists [22]. Only home dialysis has escaped this negative judgment regarding HIF stabilizers and appeared for Locatelli and Del Veccio, in their recent narrative review published in the Journal of the American Society of Nephrology (JASN) in late 2022, as an elective indication for this new class. This has been due to the HIF stabilizers' lack of need for the cold chain, their positive impact on martial metabolism, and their oral mode of administration, which have been compared with the difficulties and imperfections of the current treatment of anemia with ESAs and iron derivatives in this patient population [12].

## 10. Conclusions

HIF stabilizers are a new and very promising therapeutic class for anemia in advanced or end-stage renal disease. They seem to be of great interest in home dialysis because of their oral form, the absence of the cold chain and their positive effect on martial metabolism.

## Links of interest

Dr. Guy Rostoker reports consulting fees from Astellas (consulting on Roxadustat, 2019-2021, 2023), GlaxoSmithKline (consulting on Daprodustat, 2022-2023), Vifor (consulting on Kapruvia, 2021-2023).
He reports research funding from Amgen, Astellas, Baxter, Hemotech, Gambro Hospal, Nipro, Physidia and Theradial. He also declares speaking fees from Amgen, Aguettant, Astellas, Roche, Sanofi and Vifor.

## References

1. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. N Engl J Med. 1987;316(2):73-78. doi: 10.1056/NEJM198701083160203.
2. Panjeta M, Tahirović I, Sofić E, Ćorić J, Dervišević A. Interpretation of erythropoietin and haemoglobin levels in patients with various stages of chronic kidney disease. J Med Biochem. 2017;36(2):145-152. doi: 10.1515/jomb-2017-0014.
3. Besarab A, Hörl WH, Silverberg D. Iron metabolism, iron deficiency, thrombocytosis, and the cardiorenal anemia syndrome. Oncologist. 2009;14(Suppl 1):22-23. doi: 10.1634/theoncologist.2009-S1-22.
4. Vaziri ND, Ateshkadi A. Effects of epoetin on vascular biology. Nephrol Dial Transplant. 1999;14 (suppl 2): 46-49. doi: 10.1093/ndt/14.suppl_2.46.

5. De Seigneux S, Meinild Lundby AK, Berchtold L, Berg AH, Saudan P, Lundby C. Increased synthesis of liver erythropoietin with CKD. J Am Soc Nephrol. 2016;27(8):2265-2269. doi: 10.1681/ASN.2015050508. Epub 2016 Jan 12.
6. Koury MJ, Haase VH. Anaemia in kidney disease: harnessing hypoxia responses for therapy. Nat Rev Nephrol. 2015;11(7):394-410. doi: 10.1038/nrneph.2015.82. Epub 2015 Jun 9.
7. Locatelli F, Fishbane S, Block GA, Macdougall IC. Targeting Hypoxia-Inducible Factors for the Treatment of Anemia in Chronic Kidney Disease Patients. Am J Nephrol. 2017;45(3):187-199. doi: 10.1159/000455166. Epub 2017 Jan 25.
8. Schödel J, Ratcliffe PJ. Mechanisms of hypoxia signalling: new implications for nephrology. Nat Rev Nephrol. 2019;15(10):641-659. doi: 10.1038/s41581-019-0182-z. Epub 2019 Sep 5.
9. European Public Assessment Report (EPAR) EMA Evrenzo. URL accessed 03/04/2023: https://www.ema.europa.eu/en/medicines/human/EPAR/evrenzo.
10. US Food and Drug Administration. FDA approval Daprodustat. URL accessed 03/04/2023: https://www.fda.gov/news-events/press-announcements/fda-approves-first-oral-treatment-anemia-caused-chronic-kidney-disease-adults-dialysis.
11. Vareesangthip K, Satirapoj B, Noppakun K, et al. The Role of Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors for anemia in chronic kidney disease: a narrative review. Int J Nephrol Renovasc Dis. 2023 in press.
12. Locatelli F, Del Vecchio L. Hypoxia-Inducible Factor–Prolyl Hydroxyl Domain Inhibitors: From Theoretical Superiority to Clinical Noninferiority Compared with Current ESAs? J Am Soc Nephrol. 2022;33(11):1966-1979. doi: 10.1681/ASN.2022040413. Epub 2022 Aug 30.
13. Provenzano R, Besarab A, Wright S, et Al. Roxadustat (FG-4592) Versus Epoetin Alfa for Anemia in Patients Receiving Maintenance Hemodialysis: A Phase 2, Randomized, 6- to 19-Week, Open-Label, Active-Comparator, Dose-Ranging, Safety and Exploratory Efficacy Study. Am J Kidney Dis. 2016;67(6):912-924. doi: 10.1053/j.ajkd.2015.12.020. Epub 2016 Feb 2.
14. Tang M, Zhu C, Yan T, Zhou Y, Lv Q, Chuan J. Safe and Effective Treatment for Anemic Patients with Chronic Kidney Disease: An Updated Systematic Review and Meta-Analysis on Roxadustat. Front. Pharmacol. 2021;12:658079. doi: 10.3389/fphar.2021.658079.
15. European Medicines Agency, Evrenzo, URL accessed on 03/04/2023: https://www.ema.europa.eu/en/medicines/human/EPAR/evrenzo#overview-section
16. Avis 30/03/2022 HAS Evrenzo. URL accessed on 03/04/2023 https://www.has-sante.fr/upload/docs/evamed/CT-19516_EVRENZO_PIC_INS_AVIS_DEF_CT19516.pdf
17. Fu Z, Geng X, Chi K, et Al. Efficacy and safety of Daprodustat versus rhEPO for anemia in patients with chronic kidney disease: a meta-Analysis and trial sequential analysis. Front Pharmacol. 2022;13:746265. doi: 10.3389/fphar.2022.746265. eCollection 2022.
18. Committee for Medicinal Products for human Use (CHMP) positive opinion for Vadadustat. URL accessed on 03/04/2023:
https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-vafseo_en.pdf
19. Xiong L, Zhang H, Guo Y, Song Y, Tao Y. Efficacy and safety of Vadadustat for anemia in patients with chronic kidney disease: a systematic review and meta-analysis. Front Pharmacol. 2022;12:795214. doi: 10.3389/fphar.2021.795214. eCollection 2021.
20. Akizawa T, Otsuka T, Reusch M, Ueno M. Intermittent oral dosing of Roxadustat in peritoneal dialysis chronic kidney disease patients with anemia: a randomized, phase 3, multicenter, open-label study. Ther Apher Dial. 2020;24(2):115-125. doi: 10.1111/1744-9987.12888. Epub 2019 Jul 31.
21. Dasgupta I, Mallett SA, Bhatt PR, et Al. Efficacy and cardiovascular safety of Daprodustat for the management of renal anemia in peritoneal dialysis patients: a pre-specified analysis of the ASCEND-D Trial. Poster n° TH-PO688. American Society of Nephrology Annual Meeting, Orlando, Nov 2022. URL

*journal officiel du Registre de Dialyse Péritonéale de Langue Française* **RDPLF** www.rdplf.org

https://doi.org/10.25796/bdd.v6i1.77073
ISSN 2607-9917

accessed on 03/04/2023: https://asn.scientificposters.com/epsAbstractASN.cfm?id=1.
22. Babitt JL, Eisenga MF, Haase VH, et Al. Controversies in optimal anemia management: conclusions from a kidney disease: Improving Global Outcomes (KDIGO) Conference. Kidney Int. 2021;99(6):1280–1295. doi: 10.1016/j.kint.2021.03.020. Epub 2021 Apr 8.

*Received 2023-04-12 accepted after revision 2023-04-21, published 2023-04-25*



*journal officiel du **R**egistre de **D**ialyse **P**éritonéale de **L**angue **F**rançaise* **RDPLF** www.rdplf.org