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Erythropoiesis-Stimulating Agents and Beyond: A Review of the Current Landscape of Renal Anemia Research

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Introduction

Anemia is a common complication that occurs in patients suffering from chronic kidney disease (CKD). Symptoms associated with anemia include fatigue, shortness of breath, dizziness, and headaches, which can impact quality of life.[1] Current treatments for this condition include erythropoiesis-stimulating agents (ESAs), iron supplements, and transfusions, either used alone or in combination. The risks versus benefits of these options should be carefully considered as each has limitations. Notably, the use of ESAs to target high hemoglobin levels in CKD patients has been associated with adverse outcomes. There are also major safety concerns surrounding the use of ESA therapy in CKD patients with active malignancy, a history of stroke, or a history of malignancy.[2]

According to Datamonitor Healthcare, there were an estimated 11.3 million prevalent cases of anemia in CKD in the US, Japan, and five major EU markets (France, Germany, Italy, Spain, and the UK) in 2015. The number of prevalent cases for this condition is forecasted to increase to approximately 14.9 million by 2035.[3] Given the current limited options and future demand for renal anemia treatment, pharmaceutical companies will have an opportunity to capitalize on this market. This analysis will examine industry-sponsored clinical trial activity and new drug development in renal anemia.

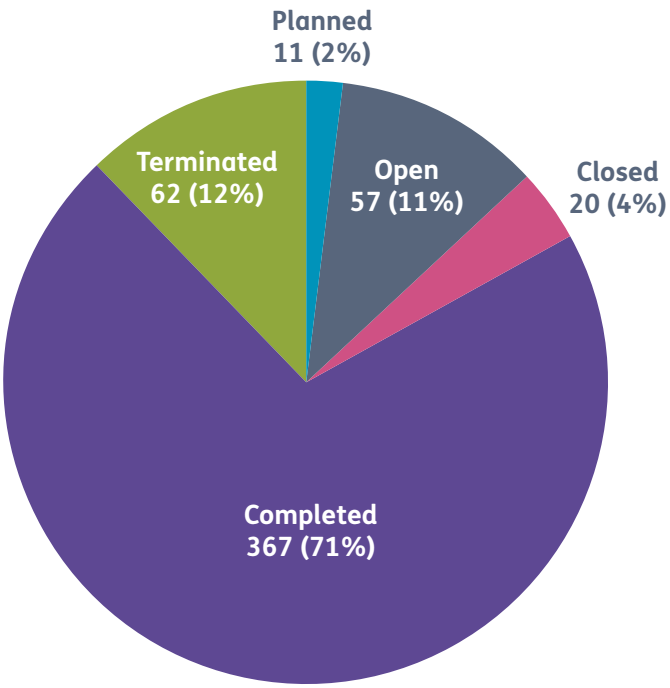
1 National Kidney Foundation (2016) A to Z Health Guide: Anemia and Chronic Kidney Disease. Available from: https://www.kidney.org/atoz/content/what_anemia_ckd [Accessed March 10, 2017].
2 Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group (2012) KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. Kidney Inter Suppl, 2, 279–335.
3 Datamonitor Healthcare's Epidemiology: Anemia in Chronic Kidney Disease, April 2016.

An Overview of Renal Anemia Activity to Date

As of March 2017, Trialtrove® captured a total of 1,051 renal anemia studies in patients with chronic kidney disease. Among these, 517 were conducted by an industry sponsor, which will be the focus of this analysis. Only 11% of industry-sponsored trials are currently ongoing, while 2% are still planned. In contrast, the majority of industry activity in this indication has either been completed (71%) or terminated (12%) (Figure 1).

Over 79% of these completed or terminated trials evaluated ESAs as primary drugs, and 57% of the ESA trials were either examining epoetin beta pegol or darbepoetin alfa (Data not shown). This is not surprising since novel and biosimilar ESAs have been a major focus of renal anemia drug development in recent years. It is also worth noting that approximately 24% of the renal anemia trials were initiated within the last five years (between March 1, 2012 and March 1, 2017), with an average of 24.2 trials beginning per year. Only three industry-sponsored trials have been initiated in 2017 thus far, and it will be interesting to see how many trials begin in 2017 compared to previous years (Data not shown).

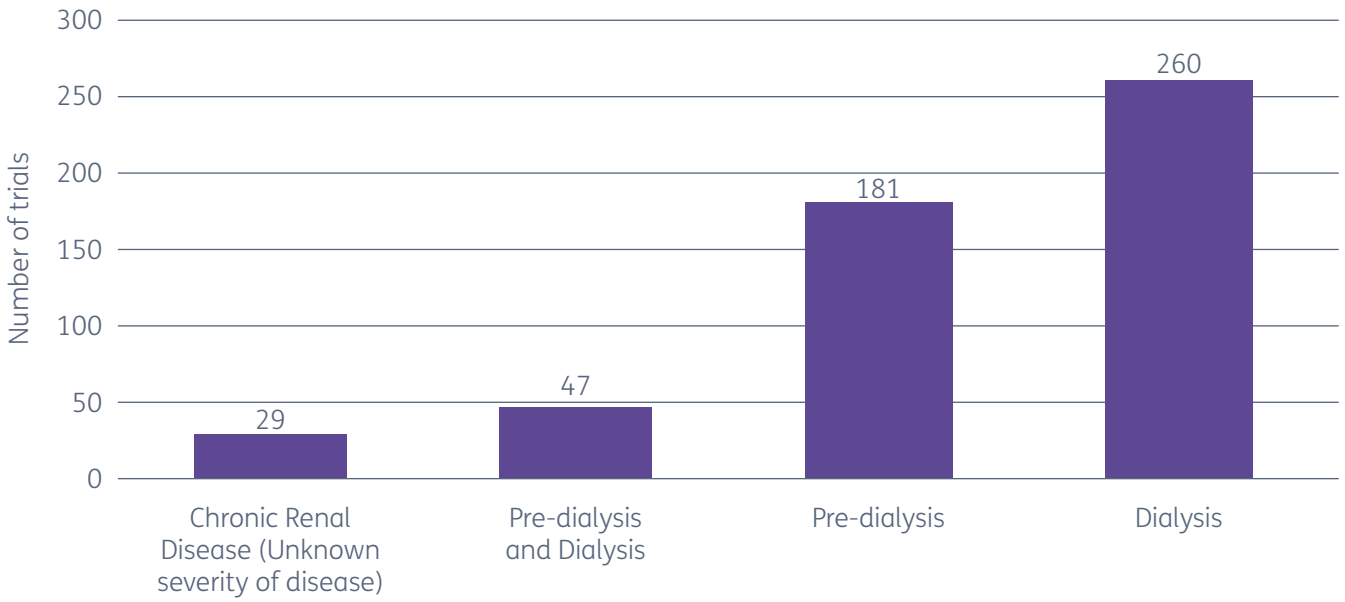
Figure 1. Clinical trial landscape: industry-sponsored renal anemia trial counts by status



Source: Trialtrove®, March 2017

Figure 2 highlights the patient segmentation of the 517 industry-sponsored renal anemia trials, and shows that a larger proportion of these trials have targeted patients receiving dialysis (59%) in comparison to pre-dialysis patients (44%), primarily in distinct trials. The majority of industry-sponsored renal anemia research has enrolled either dialysis or pre-dialysis patients alone, while only 9% of trials included both. In recent years, various companies have expressed interest in gaining approval to treat both renal anemia subpopulations with their investigational drugs, and have initiated separate pivotal Phase III trials in pre-dialysis and dialysis patients. In a small percentage of trials (6%), the severity of renal disease was not clearly defined (Figure 2).

Figure 2. Clinical trial landscape: industry-sponsored renal anemia trial counts by patient segment



Source: Trialtrove®, March 2017

Key Players in the Renal Anemia Landscape

Figure 3 and Figure 4 illustrate the top 10 sponsors of completed and terminated renal anemia trials, as well as the ongoing and planned research, respectively. Roche, Amgen, FibroGen, and GlaxoSmithKline demonstrate ongoing interest in this area as they are the only companies that appear in both figures. FibroGen is currently co-developing two hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitors, FG-2216 (Phase II) and roxadustat (Phase III), with Astellas Pharma. AstraZeneca is also involved in the co-development of roxadustat with these companies. GlaxoSmithKline is currently conducting trials with daprodustat, a HIF prolyl hydroxylase 2 and 3 inhibitor, which is in Phase III development. Roche and Amgen are sponsoring ongoing trials with their launched ESAs, epoetin beta pegol and darbepoetin alfa, respectively.

Figure 3. Top 10 sponsors of completed and terminated industry renal anemia trials

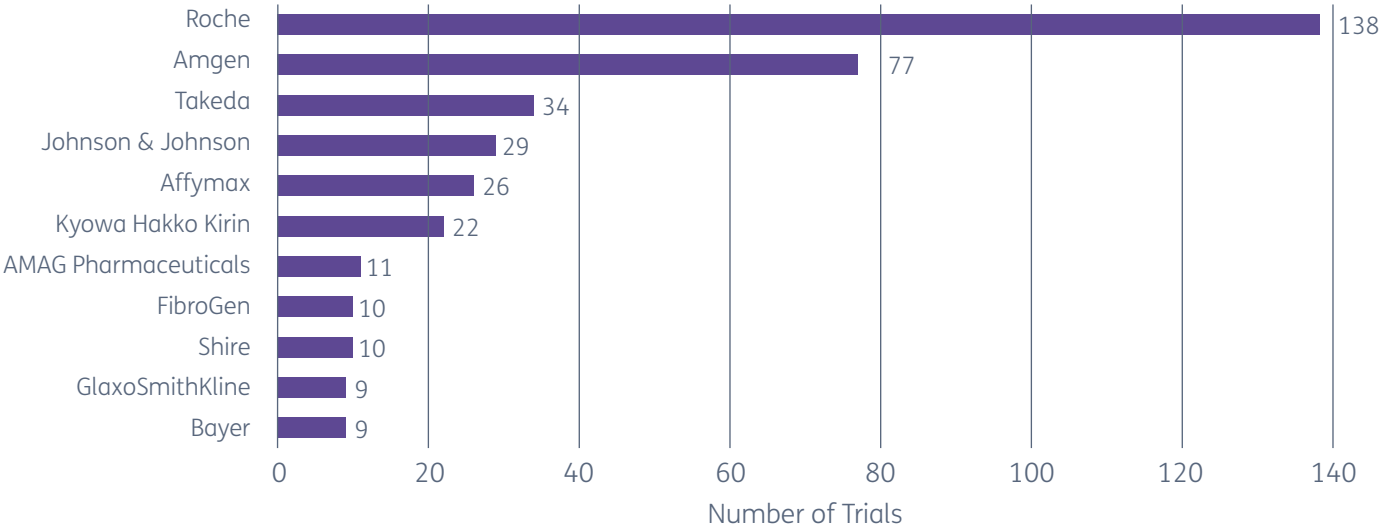
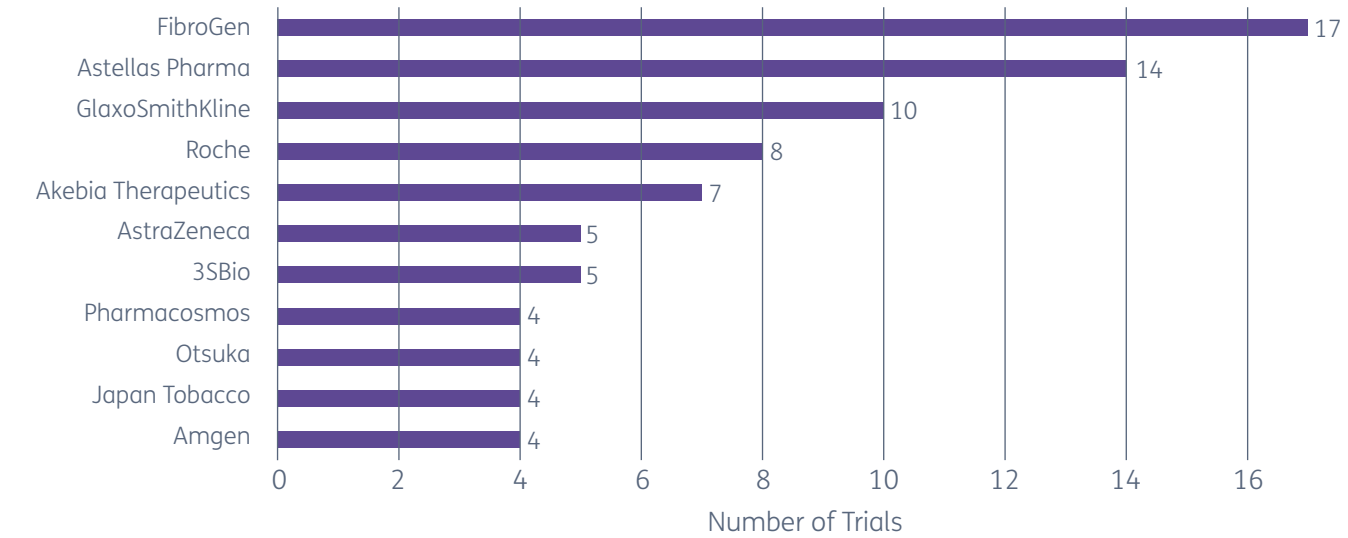


Figure 4. Top 10 sponsors of ongoing and planned industry renal anemia trials



Source: Trialtrove®, March 2017

Within Pharmaprojects®, 34 compounds are in development (preclinical through pre-registration) by industry for renal anemia, over half of which are ESAs.[4] This is not surprising due to the well-established history and standard use of ESAs to treat this condition, as well as the increasing number of ESA biosimilars on the market today. Biosimilars account for more than half of the ESAs currently in development. Two of the drugs, Panacor Bioscience's ferric citrate and Pharmacosmos' iron isomaltoside, are already launched for other indications (Data not shown).

The 13 novel drugs in development are listed in Table 1. Most of the later-stage drugs are partnered assets, specifically five of the nine drugs in Phase II and Phase III. Also, eight of the 13 novel drugs are HIF prolyl hydroxylase inhibitors, which mimic hypoxia and stimulate red blood cell production. Data from trials evaluating drugs with this mechanism have been promising; HIF prolyl hydroxylase inhibitors have successfully increased hemoglobin levels in pre-dialysis and dialysis patients. The focus on HIF prolyl hydroxylase inhibitors could imply that the pharmaceutical industry is confident that this mechanism of action will gain approval as a treatment for renal anemia.

Table 1. Novel drugs in development for renal anemia

Primary Drug Name	Companies	Mechanism of Action	Disease Status
roxadustat	FibroGen Astellas Pharma AstraZeneca	HIF prolyl hydroxylase inhibitor	Phase III
vadadustat	Akebia Therapeutics Mitsubishi Tanabe Pharma Otsuka	HIF prolyl hydroxylase inhibitor	Phase III
daprodustat	GlaxoSmithKline	HIF prolyl hydroxylase 2 inhibitor HIF prolyl hydroxylase 3 inhibitor	Phase III
FG-2216	FibroGen Astellas Pharma	HIF prolyl hydroxylase inhibitor	Phase II
sotatercept	Acceleron Pharma Celgene	Activin receptor type II ligand trap	Phase II
lexaptepid pegol	Noxxon	Hepcidin inhibitor	Phase II
molidustat	Bayer	HIF prolyl hydroxylase inhibitor	Phase II
JTZ-951	Akros Pharma Japan Tobacco	HIF prolyl hydroxylase inhibitor	Phase II
PRS-080	Pieris Pharmaceuticals	Hepcidin inhibitor	Phase II
TP-0463518	Taisho	HIF prolyl hydroxylase inhibitor	Phase I
HIF-PH inhibitors, 3SBio	3SBio	HIF prolyl hydroxylase inhibitor	Preclinical
UB-852	UBI Pharma	Unidentified pharmacological activity	Preclinical
MM-P01-01	MyungMoon Pharm	Unidentified pharmacological activity	Preclinical

Source: Pharmaprojects®, March 2017

4 The mechanism of action of pegol sihematide is currently unidentified. Analysts believe that this is likely an erythropoietin receptor agonist; awaiting primary source confirmation.

Of the 13 novel drugs, nine are included in a total of 87 industry-sponsored clinical trials evaluating the treatment of anemia in patients with renal disease (Figure 5). As of March 2017, TP-0463518, which is in Phase I development, has only been tested in healthy volunteers. The remaining three drugs – 3SBio's HIF-PH inhibitor, UB-852, and MM-P01-01 – are all in preclinical development.

The primary drugs being tested in the largest number of trials are roxadustat, daprodustat, and vadadustat – 69% of novel industry-sponsored trials include one of these three drugs (60/87 trials). All three are currently in Phase III development, with roxadustat reaching this milestone well ahead of its competitors due to the December 2012 initiation of its first Phase III trial.[5] Dosing of the first patient in the vadadustat Phase III program took place in December 2015,[6] and the start of the daprodustat program was announced on November 24, 2016.[7] It is not surprising that roxadustat will be the first HIF prolyl hydroxylase inhibitor filed, given the timing of its Phase III program. The New Drug Application (NDA) filing for the co-developed roxadustat in China is anticipated in the third quarter of 2017,[8] and the filing of the US NDA is planned for 2018.[9] In contrast, the US NDA filings for vadadustat and daprodustat are not expected until 2019 and 2021, respectively. Filings of vadadustat in Europe and daprodustat in Japan are also planned for 2019.[10,11]

Figure 5: Industry-sponsored renal anemia trials for novel drugs in development

Source: Trialtrove®, March 2017

Conclusions

The future of renal anemia treatment is currently hinging on the success or failure of the HIF prolyl hydroxylase Phase III programs that are underway. The outcomes of these programs, good or bad, will have huge implications for all of the pharmaceutical companies that are developing drugs with this mechanism of action, as well as for patients who are not responding to existing treatments. HIF prolyl hydroxylase inhibitors could revolutionize the treatment of renal anemia, but only time will tell.

5 Astellas and FibroGen (2012) FibroGen and Astellas Announce Initiation of Phase 3 Trial of FG-4592/ASP1517 for Treatment of Anemia of Chronic Kidney Disease. Available from: https://www.astellas.com/en/corporate/news/pdf/121212_1_Eg.pdf [Accessed April 17, 2017].
6 Akebia (2016) Akebia Initiates Phase 3 PRO2TECT Program. Available from: http://ir.akebia.com/releasedetail.cfm?ReleaseID=948612 [Accessed April 17, 2017].
7 GlaxoSmithKline (2016) GSK starts phase III programme with daprodustat for anaemia associated with chronic kidney disease. Available from: http://us.gsk.com/en-us/media/press-releases/2016/gsk-starts-phase-iii-programme-with-daprodustat-for-anaemia-associated-with-chronic-kidney-disease/ [Accessed March 10, 2017].
8 FibroGen (2017) Form 10-K. Available from: https://www.sec.gov/Archives/edgar/data/921299/000156459017003095/fgen-10k_20161231.htm
9 FibroGen (2017) FibroGen Reports Fiscal 2016 Financial Results. Available from: http://investor.fibrogen.com/phoenix.zhtml?c=253783&p=irol-newsArticle&ID=2250761 [Accessed March 10, 2017].
10 Akebia (2017) Form 10-K. Available from: https://www.sec.gov/Archives/edgar/data/1517022/000156459017003466/akba-10k_20161231.htm [Accessed March 10, 2017].
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