Smoke, mirrors and patient deaths: Fibrogen and AstraZeneca aren’t giving investors the full picture on roxadustat safety. We believe the FDA will not approve Roxadustat. (Price target: $14)

SMOKING GUN – there are more deaths in the Roxadustat program than were revealed at ASN

An ENTIRE STUDY is missing from the DD-CKD pooled safety data analysis

Selective data presentation masks a roxadustat death imbalance

In EVERY DD-CKD study, there are more deaths on the Roxadustat arm

The data analysis presented herein is complicated. If it were easy, we think Fibrogen shares would have already collapsed. The first part of this report provides background information essential to understanding the analysis presented in the second half. The key takeaways are: Clinical trial data reported to EudraCT shows a higher death rate in Roxadustat treated DD-CKD patients in each of the four phase 3 trials. The pooled DD-CKD safety analysis presented at the American Society of Nephrology meeting omits data from the PYRENEES study. Japanese regulators include a “red box” warning on the Roxadustat label for thromboembolic events. We believe Roxadustat failed to meet the pre-specified MACE safety endpoint and will not be approved on this data set.

What is chronic kidney disease?

The kidneys serve multiple functions but three in particular stand out. The kidneys filter the blood producing urine. The kidneys play an important role in blood pressure regulation and the kidneys make erythropoietin – the hormone that instructs the bone marrow to make red blood cells. Chronic kidney disease, which is frequently the result of long standing hypertension and/or diabetes, results in a progressive decline in the kidney’s ability to effect its essential functions. Fortunately, these functions can be recapitulated. Blood pressure can be controlled with anti-hypertensive medications, red blood cell production can be stimulated with exogenously supplied erythropoietin, and dialysis machines can recapitulate the filtration function.

What is Roxadustat?

Roxadustat is a drug that stimulates red blood cell production. AstraZeneca and Fibrogen have conducted clinical trials to show that roxadustat can replace erythropoietin as a red blood cell production stimulant. Roxadustat is administered orally thrice weekly whereas erythropoietin requires an injection. Dialysis patients are typically dialyzed thrice weekly so an injection is not too much of a burden.

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1 The interested reader is directed to Harrison’s Principles of Internal Medicine for more information on CKD.
3 Dialysis involves the insertion of a large bore catheter into the patient.
How was Roxadustat studied?

Fibrogen and partners Astellas and Astra Zeneca conducted an extensive clinical trial program that involved studies in dialysis dependent chronic kidney disease patients (DD-CKD) and non-dialysis dependent chronic kidney disease patients (NDD-CKD). The diagram below summarizes these trials and the number of patients enrolled in each.⁴

On the company’s conference call from February 27, 2018 Fibrogen’s Chief Medical Officer Peony Yu stated “MACE is being evaluated in 2 separate study pools: dialysis-dependent CKD patients and non-dialysis-dependent CKD patients.” The company’s S-1 filing says the same “The FDA has also informed us that the MACE endpoint will need to be evaluated separately for our Phase 3 trials in non-dialysis dependent-CKD patients and our Phase 3 trials in dialysis dependent-CKD patients.” As such, it is clear that the differences in the DD and NDD populations warrant separate safety analyses for each population.

Why is safety so important in this class of drugs?

In the past, nephrologists targeted hemoglobin levels of >11 - 13g/dL in CKD patients⁵ (normal is 12-16 g/dL⁶). Unfortunately, the CHOIR study revealed that treating patients to 13g/dL hemoglobin levels resulted in elevated risk of death (see figure below)⁷.

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Footnotes:

⁴ From Fibrogen’s corporate presentation April 2019.
⁵ DOI: 10.1053/j.ajkd.2006.03.010
⁶ https://labtestsonline.org/tests/hemoglobin
⁷ DOI: 10.1056/NEJMoa065485
An FDA panel was convened to discuss the issue and it recommended lower hemoglobin targets. This led to the inclusion of a black box warning on the erythropoietin prescribing information: “to limit their initiation in HD patients until the hemoglobin level is <10 g/dL and to reduce or interrupt treatment if the hemoglobin level approaches or exceeds 11 g/dL” and [using] “ESAs to target a hemoglobin level of greater than 11 g/dL increases the risk of serious adverse cardiovascular reactions and has not been shown to provide additional benefit”. It was never determined if the elevated cardiovascular risk was a direct result of higher erythropoietin doses, higher hemoglobin levels or some signaling pathway in between.

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8 DOI: 10.1038/sj.ki.5002401
Roxadustat acts on cells in such a way that it causes more erythropoietin to be secreted. Roxadustat also causes other changes in cellular metabolism. Since it was never precisely determined what caused the excess cardiovascular risk associated with higher erythropoietin doses, it is important for the companies to rule out an excess risk on cardiovascular safety.

How does one rule out elevated cardiovascular risk?

The way one can demonstrate two drugs have similar cardiovascular risks is by conducting a comparator clinical trial. These type of trials are called non-inferiority trials because one is attempting to demonstrate whether the two different drugs are the same within a certain margin of error. That margin is called the non-inferiority margin.

Cardiovascular risk is assessed using two composite endpoints MACE and MACE+. MACE stands for major adverse cardiovascular events and includes all-cause mortality, myocardial infarction (heart attack) and stroke. It is the preferred endpoint for US regulators. MACE+ includes all of the events in MACE in addition to hospitalization for unstable angina or congestive heart failure. It is the preferred endpoint for European regulators. Fibrogen has stated that the non-inferiority margin agreed to with European regulators for the MACE+ endpoint is 30%.

The FDA has historically relied on 3 point MACE analyzed in the intent to treat or ITT population as recent Jardiance documents show. These same briefing documents show that the non-inferiority margin for the MACE endpoint was 30%. In their press release on May 9, Fibrogen did not say that the MACE endpoint met the non-inferiority margin nor would they say they had even agreed to a non-inferiority margin with the FDA.

10 https://www.fda.gov/media/98879/download
Fibrogen may be inexperienced when it comes to the design and conduct of large clinical trials but it is highly unlikely AstraZeneca would embark upon a large p3 outcomes program without first having agreement with the FDA regarding the endpoint.11

**What was the population studied in the Roxadustat DD-CKD studies?**

Recall the clinical trial program for DD-CKD patients involved approximately 4,755 patients treated across four large studies. All studies were randomized 1:1 and included an erythropoietin control arm. Fibrogen and AstraZeneca make a distinction between incident dialysis patients which they define as patients who began dialysis within a minimum of 2 weeks and a maximum of 4 months, prior to study participation. Appreciate that this is a distinction without a difference because once the incident dialysis patient reaches 4 months of dialysis, they cease being an incident dialysis patient and become a “regular” dialysis patient per the definition the companies use.

**What was the primary safety endpoint of the Roxadustat DD-CKD studies?**

The primary safety endpoint of the Roxadustat clinical trials is MACE in the US and MACE+ in Europe. As seen in the screen capture from the European clinical trial register below for the ROCKIES study, the primary objective of the trial is to “Evaluate the cardiovascular (CV) safety of roxadustat based on comparison with epoetin alfa for the composite endpoint of all-cause mortality, non-fatal myocardial infarction and non-fatal stroke”12 The term “all-cause mortality” is extremely important and we therefore highlight it to remind the reader.

It is worth noting that competitor Akebia Therapeutics indicates on clinicaltrials.gov that the primary safety endpoint is for its phase three trial is also MACE and that it includes all-cause mortality: “Major adverse cardiovascular events (MACE), defined as all-cause mortality, non-fatal myocardial infarction, or non-fatal stroke.”13 Akebia may have been more transparent than FGEN when they submitted their trial design for public dissemination on clinicaltrials.gov, but the same regulatory standards will apply to both programs. As evidenced by the FDA’s treatment of Aranesp, Procrit, and Epogen, drugs with similar mechanisms of action face similar safety standards / regulatory hurdles for approval.14

**Why do we care about the ITT population?**

The ITT population is defined as any patient who is randomized into the trial. This is the broadest category of patients to be evaluated and to appreciate why this is the appropriate population, consider the

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11 FDA briefing documents often reveal that companies conducted extensive discussions with regulators prior to initiating clinical trials.
following example: Suppose a person is a heavy smoker for 20 years and finally quits only to discover 3 years after quitting that he has developed lung cancer. In an ITT analysis, this patient would be considered a smoker and the lung cancer would be plausibly attributed to smoking even though the patient quit. In a “per protocol population” aka “treatment population”, this person would be considered a non-smoker because they were a non-smoker at the time of diagnosis.

By analyzing the ITT population, we physicians are effectively stating “there are many mechanisms by which a drug could cause harm and since we cannot know what all of them are, we will follow the patients even after they discontinue the drug to make sure there is not some longer lived deleterious effect.” If there is no safety signal caused by the drug, the ITT population will show this and the result will be the strongest possible because one will have demonstrated safety while a person is on the drug and even after they discontinue.”

**AstraZeneca has confirmed the statistical analysis plan required by the FDA for approval will examine CV safety in the ITT population**

Fibrogen’s development partner, AstraZeneca, held an investor event on Sunday November 10, 2019 ostensibly to clear up investor confusion regarding data FGEN presented on Friday. AZN’s key-opinion-leader states that the data analyses are “difficult” and on prior calls, AstraZeneca called the data both “complicated” and “complex”. We think this should be a very simple matter. Does roxadustat cause more deaths than erythropoietin? Period.

At the very least AZN was clear about the regulatory standard expected by the FDA. As stated on the call “We’ve aligned with the FDA on the approach we are undertaking from the statistical point of view and the analysis sets that we will be using, ITT, both on treatment and off-treatment.” Management further clarifies later in the call “the analysis that we have agreed with the FDA, that’s the ITT analysis.”

**We are now ready to discuss how we believe Fibrogen is misleading investors:**

**What Fibrogen says about the MACE endpoints in DD-CKD:**

In their May 9, 2019 press release touting positive cardiovascular safety data, Fibrogen had this to say about the NDD-CKD population:

<table>
<thead>
<tr>
<th>Pooled MACE/MACE+ in NDD-CKD Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>In the non-dialysis pool of approximately 4,300 patients, non-inferiority was demonstrated for roxadustat compared to placebo in the time to first MACE+, based on the upper bound of the 95% CI being below the prespecified non-inferiority margin. Based on the MACE safety analyses of this population, we believe there is no clinically meaningful difference in risk of MACE between roxadustat and placebo.</td>
</tr>
</tbody>
</table>

This statement unequivocally states that Roxadustat met non-inferiority for MACE+ in the NDD-CKD population. Contrast this with the statement below regarding MACE/MACE+ in the dd-CKD population. You’ll
note it stops well short of stating that Roxadustat met the MACE primary safety analysis. It merely states what the company believes. What they believe is irrelevant. Only what the data shows matters.

Fibrogen effects a subtle bait and switch:

Slide 21 from the Fibrogen/AstraZeneca non-dialysis dependent CKD (NDD-CKD) population is reproduced below.\(^\text{15}\) Notice that the companies present pooled all-cause mortality data from the three non-dialysis dependent studies.

![Pooled MACE/MACE+ in DD-CKD Population]

The switch comes when the companies do not provide similar pooled data for the four DD-CKD studies. Investors should be immediately suspicious when the trial population in which a drug is analyzed is different. For NDD-CKD, we see the ITT population but in DD-CKD, the companies present an on-treatment analysis. The companies also only describe “on-treatment” analysis for three of the four DD-CKD studies. This raises two very

\(^{15}\) https://www.astrazeneca.com/content/dam/az/Investor_Relations/events/AZN%20Investor%20science%20conference%20call%20ASN%202019%20Presentation.pdf
important questions: “where is the ITT analysis of DD-CKD patients?” and “What happened to the PYRENEES study?” These data were not omitted by chance.

Even in the limited data reported, the number of reported deaths do not add up:

The data for all-cause mortality in the ROCKIES and HIMALAYAS studies are shown below.

ROCKIES:

<table>
<thead>
<tr>
<th>AE category</th>
<th>Roxadustat (N=1048)</th>
<th>Epoeitin alfa (N=1053)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>891</td>
<td>85.0</td>
</tr>
<tr>
<td>Any AE leading to discontinuation of drug</td>
<td>57</td>
<td>5.4</td>
</tr>
<tr>
<td>Any serious AE</td>
<td>604</td>
<td>57.6</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>167</td>
<td>15.9</td>
</tr>
</tbody>
</table>

Treatment Emergent Adverse Events

n = 167 deaths on Roxadustat

HIMALAYAS:

<table>
<thead>
<tr>
<th>AE category</th>
<th>Roxadustat (N=1053)</th>
<th>Epoeitin alfa (N=1053)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Treatment Emergent Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAAs, n (%)</td>
</tr>
<tr>
<td>Any TEAAs, n (%)</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
</tr>
</tbody>
</table>

n = 63 deaths on Roxadustat

Notice that the companies report 167 deaths in the Roxadustat arm of the ROCKIES study and 63 deaths in the Roxadustat arm in the HIMALAYAS study. These sum to a total of 230 deaths in these two studies. This data is simply not consistent with the summarized DD-CKD safety data presented below:
How is it possible that the number of all-cause mortality events in the ROCKIES and HIMALAYAS trials (230) exceeds the number of all-cause mortality events in the pooled ROCKIES, HIMALAYAS, and SIERRAS trials (207)? Note further that nowhere on this slide does it state affirmatively that this is the ITT population. See the NDD-CKD slide below for contrast.

These slides confirm that the DD-CKD population being analyzed is NOT the ITT population (see below):
Where did the Pyrenees study results disappear to?

Recall the DD-CKD clinical program included four studies yet the companies only present data from three of these studies and inconsistently at that. Why is there no data from PYRENEES included on this pooled analysis slide? Note also that there is no accompanying Kaplan-Meyer curve for DD-CKD like there was for the NDD-CKD cohort.

THE SMOKING GUN: AstraZeneca has reported ADDITIONAL roxadustat deaths that Fibrogen has not disclosed:

Fibrogen has steadfastly refused to state that the MACE endpoint was met in the DD-CKD cohort. Let’s see why that is. AstraZeneca published the results of the ROCKIES, PYRENEES, and HIMALAYAS studies on the European clinical trials web page. What do they show?

ROCKIES:
In EVERY case, there were more deaths in the Roxadustat arm. Given the death imbalance in PYRENEES (18.8% in Roxadustat vs. 14% in ESA), it is clear that including PYRENEES in the pooled MACE slide for DD-CKD would only have worsened the results.\textsuperscript{16}

Based on the data above from the European clinical trials database, the all-cause mortality rate is 19.5% in Roxadustat and 17.5% in the ESA arms with the SIERRA study still unreported. \textit{This is an 11% relative increase in all-cause mortality associated with Roxadustat.}

This imbalance in all-cause mortality likely explains why Fibrogen refused to state that they met the MACE endpoint in the DD-CKD population in the May 9 press release and during the ensuing call. It also likely explains why the companies present the all-cause mortality results for the pooled NDD-CKD data but not the DD-CKD data.

\textbf{What is the roxadustat mortality data in the ITT population?}

Since the companies will not provide this data, we have done our best to provide it to you below. As you can see below, there is a substantial imbalance in the number of deaths in each study in the Roxadustat arm.

\textsuperscript{16} Please note the column headers vary between the various EudraCT study entries. This is exactly how the data is presented on EudraCT.
Not answering the question:

On AstraZeneca’s call on Sunday, November 10 to discuss the Roxadustat data, they were asked why they did not present the DD-CKD data set in its entirety. The non-answer by the primary investigators can be read below. Why can’t they answer the question? We think the answer is that they can answer the question but that they don’t want to because of what the answer will reveal about the DD-CKD data.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of patients</th>
<th>Number of Deaths</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCKIES</td>
<td>1,053</td>
<td>231</td>
<td>EudraCT</td>
</tr>
<tr>
<td>SIERRAS</td>
<td>370</td>
<td>58</td>
<td>Fibrogen poster</td>
</tr>
<tr>
<td>HIMALAYAS</td>
<td>522</td>
<td>59</td>
<td>Fibrogen poster</td>
</tr>
<tr>
<td>PYRENEES</td>
<td>420</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>2,365</td>
<td>407</td>
<td></td>
</tr>
<tr>
<td>Rate</td>
<td>17.2%</td>
<td>19.2%</td>
<td></td>
</tr>
<tr>
<td>Relative risk</td>
<td>11.3%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Robert Provenzano:

Yes, let me just rephrase. We showed the pooled results for the dialysis dependent population and the incident dialysis population. Should there not be a slide for the dialysis dependent prevalent patients?

So I’m going to take the first cut at answering this, and then Dr. Fishbane can weigh in. As I mentioned, as kidney care progresses through the stages, it almost becomes a survival of the fittest opportunity, where highest mortalities are as you progress through CKD Stage III, IV and V, then a 200% higher mortality within the incident patients. And then almost -- well, not almost but certainly a stabilization of mortality in the dialysis patients past 4 months, the prevalent population.

So the expectations are that the greatest impact are going to be in the first 2 populations, which is why they were shown. As far as the statistical analysis, I’ll let Steve weigh in on this. But pulling out the incident patients from the pooled dialysis patients creates on underpowered analysis that would be problematic.

Steven Fishbane:

Yes, that’s exactly right. I don’t think it takes anything away from your question. It goes against convention typically to look at incident compared to prevalent patients, but there’s nothing wrong with doing it except for the issue of under powering. But thank you, because I think it because I think it is an interesting question.

Fibrogen can withhold data from investors, but not from regulators:
Roxadustat is approved in Japan. Although Japanese regulators ultimately approved roxadustat, the PMDA required a warning label in the prescribing information. The drug review includes a “red box” warning that patients may suffer thromboembolic adverse events:

### VIII. 安全性（使用上の注意等）に関する項目

1. 警告
   本剤投与中に、脳梗塞、心筋梗塞、肺塞栓症の重篤な血栓塞栓症があらわれ、死亡に至るおそれがある。本剤の投与開始前に、脳梗塞、心筋梗塞、肺塞栓症の合併症及び既往歴の有無等を含めた血栓塞栓症のリスクを評価した上で、本剤の投与の可否を慎重に判断すること。また、本剤投与中は、患者の状態を十分に観察し、血栓塞栓症が疑われる微候や症状の発現に注意すること。血栓塞栓症が疑われる症状があらわれた場合には、速やかに医療機関を受診するよう患者を指導すること。[11.1.1 参照]

Translation:
During administration of this drug, serious thromboembolism such as cerebral infarction, myocardial infarction, and pulmonary embolism may occur and death may occur. Before starting the administration of this drug, assess the risk of thromboembolism, including the presence or absence of complications such as cerebral infarction, myocardial infarction, and pulmonary embolism, and carefully determine whether or not to administer this drug. During the administration of this drug, the patient's condition should be carefully observed, and attention should be paid to the signs and symptoms of suspected thromboembolism. Instruct patients to see a medical institution promptly if they suspect thromboembolism. [Refer to 11.1.1]1

The Japanese regulators must have noted thromboembolic events in the Japanese clinical studies if they thought it prudent to specifically warn prescribing physicians about the risk.

**Duration of exposure matters:**
In the DD-CKD population, ESA patients were studied for a longer time than Roxadustat patients. See below:
There were a total of 7,059 patient years of data in the ROCKIES, SIERRAS, and HIMALAYAS pooled study results BUT 53% of those exposure years were in the EPO arms and 47% were to Roxadustat. This means any exposure adjusted difference in MACE events is likely to worsen when one considers that those events are distributed across a longer period of patient exposure in the EPO arms.

What else lurks in the European and Japanese data?

The way this data has been presented suggests an effort to minimize investor concerns about adverse events. This makes us especially vigilant for what other problems might be hidden. Recall, Roxadustat was not Fibrogen’s first HIF-2α inhibitor. That molecule was FG-2216 and it was discontinued when fatal fulminant hepatitis was observed in a patient treated with the drug.\textsuperscript{17,18}

The ROCKIES safety data reported on the European clinical trials database also includes one case of hepatotoxicity and one case of hyperbilirubinemia that were casually attributed to treatment by the investigator. We do not know if these adverse events were reported in the same patient but if they were, they would cause concern that Roxadustat too causes hepatotoxicity.

\textsuperscript{17} https://www.astellas.com/system/files/news/2018-06/080402_eg.pdf
\textsuperscript{18} https://www.sec.gov/Archives/edgar/data/921299/000119312514359619/d720189ds1.htm
Conclusions:

1) Fibrogen has stated and the European clinical trials database confirms that the primary endpoint for US approval of Roxadustat is MACE in the ITT population.

2) Fibrogen and AstraZeneca omit the PYRENEES results from their pooled analysis of DD-CKD safety.

2) We believe the MACE endpoint in the ITT DD-CKD population WAS NOT MET.

3) We do not think the FDA will approve Roxadustat for DD-CKD without additional safety trials as there is already a safe and well-studied alternative in the form of erythropoietin.

<table>
<thead>
<tr>
<th></th>
<th>Subjects affected / exposed</th>
<th>Occurrences causally related to treatment / all</th>
<th>Deaths causally related to treatment / all</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hepatotoxicity</strong></td>
<td>1 / 414 (0.24%)</td>
<td>1 / 1</td>
<td>0 / 0</td>
</tr>
<tr>
<td></td>
<td>0 / 420 (0.00%)</td>
<td>0 / 0</td>
<td>0 / 0</td>
</tr>
<tr>
<td><strong>Hyperbilirubinaemia</strong></td>
<td>1 / 414 (0.24%)</td>
<td>1 / 1</td>
<td>0 / 0</td>
</tr>
<tr>
<td></td>
<td>0 / 420 (0.00%)</td>
<td>0 / 0</td>
<td>0 / 0</td>
</tr>
</tbody>
</table>