CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213931Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 213931

APPEAL GRANTED

Ardelyx, Inc.
Attention: Robert C. Blanks, MS, RAC
Chief Regulatory Affairs and Quality Assurance Officer
34175 Ardenwood Blvd.
Fremont, CA 94555

Dear Mr. Blanks:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tenapanor hydrochloride tablets.

I also refer to your February 18, 2022, request for formal dispute resolution received on February 18, 2022. The appeal concerned the Complete Response letter issued by Aliza Thompson, MD, MS, Deputy Director, Division of Cardiology and Nephrology (DCN), on July 28, 2021.

I also refer to your December 3, 2021, request for formal dispute resolution to the Office of Cardiology, Hematology, Endocrinology and Nephrology (OCHEN), received on December 3, 2021, and the denial of the appeal by Hylton Joffe, MD, MMSc, on February 4, 2022.

I also refer to the meeting held between FDA and Ardelyx, Inc. on March 17, 2022, where the issues raised in your request for formal dispute resolution were discussed, and to my interim response, issued April 15, 2022, that conveyed my decision to convene an advisory committee (AC) meeting. This meeting was held on November 16, 2022.

My interim response provided an overview of the issues raised in the FDRR letter, background information on the tenapanor program and results, and my initial assessment; in this final response, I will reference that document where appropriate.

I have completed my review of your request for formal dispute resolution. I provided my verbal response granting your appeal via our telephone conversation on December 16, 2022. In accordance with the guidance for industry *Formal Dispute Resolution: Sponsor Appeals Above the Division Level*, this letter serves as written confirmation of our telephone conversation and my decision to grant your appeal. I describe below the basis for my decision.

To start, I think it is worth summarizing some key points made by AC members during the discussion of the questions posed to the committee.

- A number of members expressed concern about the lack of clinical trial data on outcomes associated with reducing serum phosphate (S-P) levels in CKD patients on dialysis and noted that this limited a definitive answer to the question of the clinical meaningfulness of the reductions seen with tenapanor. Some members commented that absent such information from well conducted randomized outcome trials assessing the effects of phosphate-lowering therapies, determining the actual clinical benefit of S-P lowering is not possible. Other committee members referred to observational data that suggested that even a S-P level higher by 0.7-0.8 mg/dL was associated with a worse mortality (by ~15%, it was suggested) in CKD patients on dialysis. The limitations of applying this epidemiological data to predict the outcome of interventions to lower S-P were acknowledged.

- Overall, most committee members noted the clinical need, and most considered that tenapanor offered another option to control serum phosphate levels, especially when phosphate binders are not tolerated or adequate. There were few comments directly on the clinical benefit based upon the extent of reduction, yet there was a consistent viewpoint that tenapanor had a role in managing patients in this clinical setting.

- A number of committee members commented on the more modest extent of phosphate lowering with tenapanor relative to approved agents, but noted that since phosphate binder intolerance and pill burdens were important concerns (highlighted during the open public hearing), the drug would still be useful in the therapeutic armamentarium.

- Some members noted that a sizable portion of patients do not tolerate tenapanor due to diarrhea. The issue of tenapanor safety was discussed—but a number of members noted that dialysis patients are intensively monitored and so likely would not suffer ill consequences from this adverse event.

- With regard to use in monotherapy, even committee members that agreed that tenapanor could provide a useful option, generally suggested that this would be either as add-on to phosphate binders or in patients who did not tolerate binders.

- With regard to combination therapy, several members commented on the more limited data available, noting the shorter duration of treatment (4 weeks) in the combination study of tenapanor and also that this study did not require patients to be on the maximally tolerated dose of phosphate binders before tenapanor was added. Nonetheless, there was stronger support for combination use (with a vote of 10 Yes, 2 No, 1 abstention), than for monotherapy use (with a vote of 9 Yes and 4 No).

In summary, the Advisory Committee discussion flagged the challenges of determining the clinical benefit of a drug to lower S-P given the limitations of the evidence on outcomes. However, despite acknowledging the limited data to determine the specific clinical benefit, the unmet need was highlighted, and most members supported having

tenapanor as another tool to provide phosphate lowering, especially given the challenges some patients have with phosphate binders.

Despite the lack of robust data from randomized clinical trials evaluating outcomes, as outlined in my interim response, there is a body of information from animal models of renal failure and hyperphosphatemia, and a large number of epidemiological studies, that suggest that S-P levels above the normal range are associated with poorer survival, most with an inversely proportional relationship between the extent of elevation and survival in CKD patients on dialysis (see Kalantar-Zadeh et al. Kidney International 2006; Rodriguez-Benot et al Am J Kidney Dis 26:68-77, 2005; R Dhingra et al. Arch Int Med 167: 879-885, 2007; Floege et al. NDT 26: 1948-1955, 2011; Block et al. J Am Soc Nephrol 15: 2208-2218, 2004). Such studies have notable limitations since patients with higher S-P levels may have worse metabolic disarray, or poorer compliance to treatments, and these factors (or other unmeasured factors), rather than elevations in phosphate per se, could be the basis for differences in outcome. Even if phosphate *directly* participates in the poorer outcome of patients with CKD and hyperphosphatemia, it is not necessarily the case that lowering phosphate will improve outcome—even as this would be likely.

However, with the approval of phosphate-binding agents, CDER determined that there was sufficient evidence to conclude that lowering S-P in patients with CKD on dialysis would be expected to provide clinical benefit. In other words, CDER determined that S-P is a validated surrogate endpoint in patients with CKD on dialysis and hence demonstration of S-P lowering could support a conclusion of substantial evidence of effectiveness for traditional approval. As I previously outlined in my interim response, DCN considered that the prior approvals established S-P as a validated surrogate, but also concluded that the range of S-P lowering (1.5-2.2 g/dL) provided by the approved drugs (all phosphate binders) established a certain effect size necessary to support approval—an effect size not seen with tenapanor. Specifically, DCN was concerned that tenapanor's more modest effect size might not translate to clinical benefit. That is, they considered that the effect size with tenapanor was "outside" of the range in which S-P lowering can be accepted as supporting approval.

I think it useful to first discuss two of the requirements for a drug to be approved by FDA: that there is substantial evidence of effectiveness and that the benefit risk balance is shown to be favorable. With regard to the first, for a drug to be approved, it must be shown to have the effect it is purported to have (usually demonstrated by meeting statistical significance in two or more adequate and well controlled studies) *and* the extent of the drug's effect must be clinically meaningful. For example, in a Phase 3 development program with two adequate and well controlled trials achieving formal statistical significance on the primary endpoint but where the effect size seen is clinically trivial, offering no clinically meaningful benefit to patients, CDER would conclude that the drug does not have substantial evidence of effectiveness—and would not be approvable. As I noted in my interim response, DCN concluded, as outlined in their CR

letter, that it was not clear that the effect size of S-P lowering with tenapanor was clinically relevant.

Benefit risk balance must also be favorable for a drug to be approved. As the effect size of a drug candidate on a validated surrogate diminishes, the expected outcome benefit shrinks, and at some point, the drug will no longer be considered safe since the benefit offered will likely not outweigh the drug's risks. So, even if the risks posed by tenapanor were acceptable if greater benefit was offered, we might conclude that the benefit risk balance, with the modest effect size observed, was no longer favorable, and consider the drug not to be approvable. In this scenario, we might conclude that there is substantial evidence of effectiveness, but that the benefit risk balance was not favorable.

Given the uncertainties stemming from the absence of outcome trial data, DCN's position that an effect size below the range previously approved is of unclear clinical benefit was not unreasonable. As noted already, I sought input from the AC to gain further insight on the question of clinical value of the observed reduction in S-P with tenapanor. At the AC for tenapanor, there was reasonably strong support from committee members for the clinical utility of tenapanor in filling an unmet need to help health care providers and patients manage elevated S-P, particularly in patients inadequately treated with phosphate binders. To be clear, the AC input underlined the lack of outcome data that would estimate the extent of clinical benefit from the reductions in S-P seen with tenapanor. Hence, clinical utility reflected the practical issues of managing elevated S-P, rather than a quantitative translation to a clinical outcome benefit.

Although in a smaller portion of patients (in the efficacy analysis set), larger improvements in S-P were seen (closer to the range seen with previously approved S-P lowering drugs), with a mean, placebo-corrected, reduction of 1.4 mg/dL observed in Study TEN-02-301, this same enrichment approach did not lead to a greater response in the EAS in Study TEN-02-201. Given the variability in S-P lowering with tenapanor over time, the ability to robustly identify "higher responders" was a concern raised by DCN. You did show new analyses that suggested that repeating S-P levels may better identify higher responders (relative to the single measurement used in the DCN analyses). And, AC members commented on the routine and frequent measurement of S-P, suggesting that adequacy of drug response can be assessed, and higher responders identified.

Since S-P is, based upon precedent, a validated surrogate endpoint, and considering the input from the AC, it is challenging to consider the lowering seen with tenapanor as insufficient to support approval. As I have already pointed out, this does not mean that any extent of S-P lowering is sufficient to support approval. As the extent of lowering diminishes, the benefit risk assessment of a drug may no longer be favorable; moreover, very small reductions may reasonably be concluded to not provide any discernible benefit.

It is also worth noting that currently approved phosphate-lowering drugs have a common mechanism, phosphate binding; tenapanor would be the first drug with a different mechanism of action. This, I believe, is a factor that also supports the approval of the drug—as different mechanisms may prove useful when the approved drugs with the same mechanism of action are insufficiently effective. AC members did comment on this point, noting that tenapanor provides a new "tool in the toolbox" for physicians caring for these patients in their effort to lower serum phosphate levels. The lower pill burden was also repeatedly cited—by AC members and by patients in the public comments—as an important and useful attribute of tenapanor.

As I noted in my interim response, and noted above, approvability is based upon the benefit risk balance considering the extent of S-P lowering offered; similarly, the indications in labeling are also determined by the benefit risk balance for each proposed use. Even accepting S-P lowering as a validated surrogate, the lack of robust trial data that shows us how to translate an amount of S-P lowering into a quantum of clinical benefit suggests that we should be conservative in our benefit risk balance assessments, accepting less risk given this uncertainty.

I have already discussed above my conclusion that tenapanor offers sufficient reduction of the validated surrogate of S-P lowering, with substantial evidence of effectiveness demonstrated through 3 adequate and well-controlled trials (two trials in monotherapy [Studies TEN-02-301 and TEN-02-201], and one trial in combination use [Study TEN-02-202]). With respect to benefit risk, this is best considered separately for the two potential uses of tenapanor in S-P lowering in patients with CKD on dialysis.

For drugs with a positive benefit risk balance across proposed indications, "positioning" of the drug in a disease treatment paradigm (e.g., use as initial therapy versus only after initial therapy is insufficient) is typically determined by guidelines from expert specialty societies or other standard setting organizations, and/or by a health care provider's individual decision based upon their experience and reading of the literature—and not through FDA labeling. However, different uses of a drug (e.g., first line versus second line) may have different benefit risk balances. If initial therapy is insufficiently effective or not tolerated, the potential benefit of the "next" drug in a treatment sequence (either instead of or added to) may be considered as greater, given the "harder to treat" circumstance—and therefore there may be greater acceptance of risk in this situation. Hence, a drug may not have a favorable benefit risk balance in initial use (when other more effective and/or safer drugs are available) but may have a favorable balance if initial therapy is not sufficient or tolerated.

As already noted, there are many effective approved phosphate binding drugs to treat hyperphosphatemia in patients with CKD on dialysis. These are generally reasonably tolerated (and have different adverse drug reaction profiles) and appear to provide greater S-P lowering then does tenapanor. The proportion of patients with an adequate extent of S-P lowering and who tolerate tenapanor is more limited than with phosphate

binders. For example, in Study TEN-02-301, the difference in adverse event discontinuation rate between those randomized to sevelamer and those randomized to tenapanor was notable (1.4% vs 18.2% discontinued), even acknowledging that some patients entering the study had been on sevelamer previously. As I outlined in the interim response, my assessment is that it is unlikely that the diarrhea adverse drug reactions from tenapanor will be consistently benign and without sequalae. The indicated population proposed for tenapanor is a fragile patient group with common and extensive co-morbidities; volume loss, as may be seen with diarrhea (reported as moderate to severe in 38% of patients treated with tenapanor in Study TEN-02-301), is likely to lead to at least occasional serious adverse events. Such events, although uncommon, were seen in the clinical trials. Despite careful management of these medically complex patients, these events are likely to occur in practice. I acknowledge that several AC members commented on the typically intensive monitoring of dialysis patients that would help mitigate this risk. Nonetheless, even several days of moderate or severe diarrhea can lead to an adverse event. Further, the risk is imposed on all patients receiving the drug, while only a smaller proportion (< 50%) tolerate and obtain consistent phosphate lowering with the drug (at least based upon the prespecified responder populations in the clinical trial program).

Based upon these observations, I do not believe that the benefit risk balance is favorable to support a broad use indication for tenapanor in patients with CKD on dialysis. However, for patients who do not achieve adequate S-P control on the prescribed dialytic and nutritional therapies and maximally tolerated pharmacological therapy, the addition of tenapanor to their regimen may be clinically useful; in this setting, where there are no other treatment options, I would conclude that the benefit risk balance for tenapanor is favorable.

One concern, discussed at the AC meeting, is the limitations of data on the use of tenapanor in combination with phosphate-binding drugs. Study TEN02-202 did not require patients to be on maximally tolerated doses of phosphate-binders and included a double-blind treatment period of only 4 weeks. However, the doses of the phosphate binding agents in that study appear to be consistent with (and generally in the mid-range of) the recommended daily doses in labeling; it would seem unlikely that the efficacy seen with tenapanor in Study 202 would have been different had the phosphate binder been pushed to maximally tolerated doses prior to study entry. Adequate demonstration of durability of effectiveness of tenapanor was seen in Study TEN-02-301 (over 12 weeks), and there is no reason to consider that durability of the drug would differ in combination use compared to monotherapy use. Ideally, trial data would establish both points, but the likelihood that effectiveness would have been different on top of maximal doses of phosphate binders over a longer time period is acceptably low.

In summary, I conclude that the benefit risk assessment for tenapanor is not favorable as initial therapy but is favorable when the prescribed dialytic, nutritional, and maximally tolerated pharmacological therapy does not provide adequate phosphate-lowering. I direct the Division to work with you to develop a label with this indication. To support

appropriate labeling, prior to the Complete Response submission, you should request a meeting with DCN, and provide a background package that includes a list of all new analyses that were provided as background to, presented at, discussed at, or referenced at the Advisory Committee meeting, as well as a listing of all completed trials not provided in the NDA. This information will be important so that the Division can provide guidance on what should be included in the Complete Response submission. The Complete Response submission should also include a safety update report as required under 21 CFR 314.50(d)(5)(vi)(b).

This constitutes the final decision at the Office of New Drugs level. Any questions concerning your appeal should be addressed to Melissa Sage, at (301) 796-6449.

Sincerely,

{See appended electronic signature page}

Peter Stein, MD
Director
Office of New Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PETER P STEIN
12/27/2022 11:46:27 AM

NDA 213931

APPEAL DENIED

Ardelyx, Inc.
Attention: Robert C. Blanks, MS, RAC
Chief Regulatory Affairs and Quality Assurance Officer
34175 Ardenwood Blvd.
Fremont, CA 94555

Dear Mr. Blanks:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for tenapanor hydrochloride tablets, 10 mg, 20 mg, and 30 mg.

I also refer to your December 3, 2021, request for formal dispute resolution received on December 3, 2021. The appeal concerned the Complete Response letter issued by Aliza Thompson, MD, MS, Deputy Director, Division of Cardiology and Nephrology, on July 28, 2021, for tenapanor for the control of serum phosphorus in adults with chronic kidney disease on dialysis.

I also acknowledge receipt of the requested additional clarifying information on January 7, 2022.

I have carefully reviewed the materials you submitted in support of your appeal, as well as pertinent portions of your NDA submission, FDA reviews, meeting minutes, decision memoranda, and the Complete Response letter. I have also consulted with Staff in the Division of Cardiology and Nephrology, the Division of Biometrics II in the Office of Biostatistics, and the Office of New Drug Policy.

I have completed my review of your request for formal dispute resolution and deny your appeal. I describe below the basis for my decision and provide recommendations for a possible path forward.

You are seeking approval of tenapanor, an inhibitor of sodium/hydrogen exchanger isoform 3, for the control of serum phosphorus in adults with chronic kidney disease on dialysis. You have provided pivotal efficacy data from three controlled trials: Two trials with a run-in period followed by a placebo-controlled, randomized withdrawal period (Study 301 and Study 201) and one randomized, placebo-controlled trial evaluating tenapanor as add-on to phosphate binder therapy (Study 202). As noted in the Complete Response letter issued by the Division of Cardiology and Nephrology, the Division agrees that the submitted data in these three trials show that tenapanor can reduce serum phosphorus in chronic kidney disease patients on dialysis, and I am in agreement with this conclusion.

The crux of the issue is whether the magnitude of serum phosphorus reduction seen with tenapanor is clinically meaningful and, if it is, whether that benefit outweighs the risks of the drug. It is well established that the effect shown in adequate and well-controlled clinical investigations, must be, in FDA's judgment, clinically meaningful for drug approval.[1] In addition, FDA must also determine that the expected benefits of the drug outweigh its risks to patients. Both of these longstanding and widely recognized criteria must be met for approval. Below, I discuss my assessment of these issues and provide rationale for my determination.

As you and the Division note, epidemiological studies have shown an association between elevated serum phosphorus and an increased risk of vascular, valvular, and other soft tissue calcification and cardiovascular disease in patients with chronic kidney disease. In epidemiological studies, high serum phosphorus has been associated with increased mortality in patients on dialysis. In addition, as you and the Division both note, there are no completed randomized, controlled trials that have definitively demonstrated that lowering of serum phosphorus improves clinical outcomes, such as cardiovascular events or mortality in this population. The ongoing HiLo trial (NCT04095039) is evaluating whether the current standard approach of targeting serum phosphorus below 5.5 mg/dL improves all-cause mortality and all-cause hospitalization compared to less stringent control that targets serum phosphorus above 6.5 mg/dL among patients with end-stage renal disease undergoing hemodialysis. This study has an estimated completion date of April 2023 (ClinicalTrials.gov, accessed February 4, 2022). Nonetheless, treatment guidelines recommend lowering high serum phosphorus concentrations towards the normal range or below 5.5 mg/dL in patients with end-stage renal disease on dialysis. For example, the international Kidney Disease Improving Global Outcomes (KDIGO) 2017 guideline[2] notes that lowering serum phosphorus towards the normal range in this population is a level 2C recommendation (a suggestion based on low quality evidence).

That said, in certain instances FDA has accepted serum phosphorus as a surrogate endpoint and basis for traditional approval in patients with chronic kidney disease on dialysis when the effect on serum phosphorus was sufficiently large to be considered clinically meaningful with benefit that outweighed the risks. It is important to note, however, that even for accepted surrogate endpoints, a drug effect may be so small that it does not provide any meaningful clinical benefit or alters the benefit/risk assessment. It is challenging to define a minimum drug effect on serum phosphorus given that the relationship between phosphorus lowering and clinical benefit has not been established. The Division informed you during development that the magnitude of phosphorus lowering with tenapanor needed to be sufficient to reasonably conclude there would be

[1] See preamble to FDA final rule on accelerated approval (57 FR 58942, 58944 (December 11, 1992)); Warner-Lambert Co. v. Heckler, 787 F.2d 147 (3rd Cir. 1986).
[2] KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl. 2017; 7: 1-59.

clinical benefit. For example, in an Advice letter dated November 9, 2017, the Division stated “If the size of the effect of tenapanor on serum phosphorus is significantly smaller than the size of the effect of currently approved phosphate binders, then you will need to address the clinical relevance of the effect size of your product on serum phosphorus.” As you have noted in your appeal, there are inherent limitations to cross-study comparisons with other approved phosphorus lowering therapies. Below I focus specifically on your program, which shows modest mean reductions in serum phosphorus with tenapanor.

For Study 301 and 201, your primary efficacy analyses focused on an enriched patient population defined as patients who completed the trial run-in period and had at least a 1.2 mg/dL improvement in serum phosphorus from the baseline to end of the run-in period. Your largest treatment effect was seen in Study 301 at the end of the subsequent randomized withdrawal period in this enriched population, which showed a LS mean difference for the change from baseline in serum phosphorus between tenapanor and placebo of 1.4 mg/dL, reflecting data for less than 25% of the patients who enrolled in the trial. However, your unenriched intent-to-treat analysis (reflecting data for about 45% of the patients enrolled in the trial, and which is expected to better reflect use in a general population that tolerates your drug) showed a LS mean treatment difference of 0.7 mg/dL. In Study 201, the LS mean treatment difference between tenapanor and placebo at the end of the randomized withdrawal period was 0.8 mg/dL in the enriched analysis population and 0.7 mg/dL in the unenriched intent-to-treat analysis population. In add-on-to-phosphate-binder Study 202, the LS mean treatment difference between tenapanor and placebo was 0.7 mg/dL. In summary, the preponderance of the data from these trials supports an expected overall mean treatment effect in the range of 0.7-0.8 mg/dL compared to placebo in a patient population like that enrolled in your clinical trials.

Furthermore, your efficacy results for the randomized withdrawal periods of Study 301 and 201 call into question the ability of your enrichment analysis approach to identify patients with larger responses to tenapanor. Specifically, while your enrichment analysis approach appears to have improved the treatment effect in the Study 301 placebo-controlled period (LS mean difference between tenapanor and placebo of 1.4 mg/dL for the enriched analysis population vs. 0.7 mg/dL for the unenriched analysis population), it appears not to have improved the treatment effect in the Study 201 placebo-controlled period (LS mean difference between tenapanor and placebo of 0.8 mg/dL for the enriched analysis population vs. 0.7 mg/dL for the unenriched analysis population). This finding in Study 201 illustrates that even having a greater than 1.2 mg/dL decline from baseline in serum phosphorus based on a single measurement does not necessarily translate into a larger treatment effect assessed when patients are subsequently randomized to continue tenapanor or switch to placebo. This finding raises questions about the feasibility of identifying patients who have greater responses to tenapanor in clinical practice and probably reflects to at least some degree challenges related to serum phosphorus variability in the context of the overall modest efficacy with your drug.

Taking these results in aggregate and noting that there is a considerable proportion of patients with a treatment response below these means, a substantial number of patients treated with tenapanor in clinical practice would be expected to have very small numerical reductions in serum phosphorus if they continued your drug versus comparable patients who chose to come off your drug. Whether the benefits of tenapanor in these patients is clinically meaningful and outweighs the risks (discussed below) is unclear.

What about the patients who experienced a reduction in serum phosphorus larger than the LS means? The analyses provided in your NDA do not adequately evaluate the magnitude of the serum phosphorus reductions among these patients. In Study 301, the analyses focus on the run-in period, which you note in your appeal is not appropriate for efficacy conclusions against sevelamer and, if you disregard the sevelamer data, is otherwise uncontrolled. In Study 201, the analyses also focus on the run-in period during which patients only received tenapanor. Uncontrolled analyses of serum phosphorus do not provide reliable conclusions on an endpoint that has considerable intra-patient variability.

Of more interest are responder analyses and analyses of distribution of response for tenapanor versus placebo during the randomized, placebo-controlled treatment periods of your three trials. In your appeal, you mention only one such analysis – an analysis of Study 202 responders (percentage of patients with serum phosphorus below 5.5 mg/dL) of 37% with tenapanor compared to 22% with placebo at the end of the Week 4 randomized, double-blind treatment period. However, this analysis has several limitations. First, as noted in the Interim Response to Appeal – Information Request letter, it is important to consider whether this difference in response rate is primarily driven by numerically small reductions from just above 5.5 mg/dL to just below 5.5 mg/dL. In your response, you provided a waterfall plot for the tenapanor responders but did not include the corresponding waterfall plot for the placebo responders. In addition, given the inherent intra-patient variability in serum phosphorus concentrations, additional analyses at other timepoints and across timepoints are needed to determine the extent and consistency of reductions in the tenapanor vs. placebo responders. It is possible that such analyses may show that there are patients who can have more sizeable, consistent reductions in serum phosphorus over time with tenapanor compared to placebo but without such analyses in hand this is an unanswered question. Because these analyses have not been previously submitted to the NDA prior to issuance of the Complete Response letter, I cannot request and consider these analyses as part of my decision on your Appeal.

Turning to safety, I acknowledge that tenapanor is minimally absorbed. However, that does not mean it is risk-free or has only minor risks. In Study 202, the incidence of reported diarrhea was 43% with tenapanor compared to 7% with placebo, with 22% of tenapanor-treated patients reporting moderate diarrhea and four patients (3.4%) reporting severe diarrhea. I also note that in this trial there was one tenapanor-treated patient with reported dehydration (Table 14.1.3.1) but I could not find additional details on this adverse event in the Clinical Study Report. Of note, analyses of adverse events

during the randomized, placebo-controlled period of this study may not adequately reflect longer term risks with combination therapy given the relatively short, randomized treatment duration of only four weeks.

In Study 301 and 201, the placebo-controlled periods only included patients who completed the run-in periods, reflecting a selected patient population that made it to the timepoint of randomization and who are more likely overall to tolerate tenapanor than a general population that is initially started on the drug. If we instead assess the safety data from the 26-week run-in period for Study 301, 24% of tenapanor-treated patients discontinued the drug due to adverse events (most commonly due to diarrhea) and 34% had a tenapanor dose reduction due to adverse events. During this run-in period involving more than 400 tenapanor-treated patients, 53% of the tenapanor-treated patients reported diarrhea and 6% (n=26) had diarrhea classified as severe by the investigator. In addition, there were 3 reported serious adverse events of diarrhea, including one subject (b) (6) who was hospitalized with dehydration (and hyponatremia, nodal arrhythmia, bradycardia, and acidosis) after several weeks of moderate diarrhea and another subject (b) (6) who was hospitalized with dehydration on Day 6 who had severe diarrhea that started after the first tenapanor dose. While it is challenging to determine conclusively drug relatedness for any specific adverse event, diarrhea (which could be severe) is consistent with tenapanor's mechanism of action and known safety profile. It is also important to note that patients in the target patient population can have significant comorbidities including atherosclerotic cardiovascular disease, which could make some patients particularly vulnerable to adverse effects stemming from severe diarrhea and dehydration, such as ischemia. Furthermore, the observed events described above occurred in the context of clinical trials, where a selective population of patients is managed in a tightly controlled setting. In contrast, in the real-world there is a reasonable expectation of wider use in a more diverse patient population that is not as closely monitored as in a clinical trial. The risks of severe diarrhea and its potential sequelae (e.g., dehydration, hypotension, falls, ischemia) in the context of real-world use must be weighed against any clinical benefit.

Lastly, as discussed above, it is unclear whether healthcare providers will be able to identify in clinical practice whether a patient is benefiting from tenapanor given the intra-patient variability in serum phosphorus concentrations in the context of tenapanor's modest mean effects. Although serum phosphorus is measured routinely in the patient population, the results are influenced by food intake, adherence to and timing of drug intake and dietary modifications, as well as diurnal variations.[2] Guidelines, therefore, recommend basing treatment decisions not on a single serum phosphorus result but rather on the trends of serial measurements. While a large treatment effect of a drug may be discernable beyond this variability, it is unclear whether the current treatment guideline strategy will allow reliable treatment decisions for continuing or stopping tenapanor given the overall modest mean treatment effects. This could lead to continued or indefinite treatment with tenapanor in a considerable number of patients who are not benefiting from the drug but who may still be exposed to the risks.

In summary, based on the data available to the Division at the time of the Complete Response letter, I am unable to conclude that tenapanor's overall clinical benefit is meaningful and outweighs its risks. As discussed above, given the modest mean treatment effect in the overall, unenriched patient population, there is a substantial proportion of patients who would be treated with tenapanor in clinical practice and who would have small numerical reductions in serum phosphorus if they continued your drug versus comparable patients who chose to come off your drug. Furthermore, as discussed above, the analyses included in your NDA do not adequately evaluate the distribution of response and responder analyses for tenapanor compared to placebo to understand fully the extent of the treatment effect and, importantly, whether there are patients who have a sustained, meaningful response over time. There are also potential safety concerns related to severe diarrhea and dehydration that cannot be dismissed when tenapanor is used in a wide population of patients on dialysis and must be weighed against the effectiveness of tenapanor, but this requires a better understanding of tenapanor's efficacy compared to placebo beyond the LS mean results. Lastly, there is the concern regarding the feasibility of healthcare providers being able to identify in clinical practice which patients are benefiting from tenapanor given the intra-patient variability in serum phosphorus concentrations in the context of tenapanor's modest mean effects. In a situation where the mean treatment effect of a drug is small and it is unclear if this reflects meaningful benefit that outweighs the risks, it may still be reasonable to approve a drug if one can readily identify patients with a meaningful response such that the drug can be continued in these patients and stopped in those with an inadequate or poor response. However, as discussed above, this has not been adequately demonstrated in your NDA.

As a path forward, I recommend that you submit a Complete Response to your NDA that provides the additional information and analyses described below to respond to these identified concerns.

Information and New Analyses Recommended in a Complete Response Submission:

1. Analyses that go beyond the LS mean results to assess the extent of serum phosphorus changes with tenapanor compared to placebo for Studies 301, 201, and 202, focusing on distribution of response and analyses of responders and non-responders. Given the intra-patient variability in serum phosphorus measurements in the context of the modest LS means, it is critical to conduct analyses that define responders as those who have consistently responded at more than a single timepoint and assess whether there is such an identifiable responder population.

   The analyses should be conducted on the randomized, placebo-controlled treatment periods, and include results for tenapanor and placebo. For Study 301 and 201 perform the analyses for the enriched and unenriched populations. For all analyses, baseline is the beginning of the randomized, placebo-controlled period. Clearly note the statistical population used for all analyses and how

missing data were handled. Examples of analyses include but do not need to be limited to the following:

Study 202:

- Distribution of responses (e.g., cumulative distribution plots) for tenapanor vs. placebo for change in serum phosphorus from baseline to the end of the randomized period. Include similar analyses for change in serum phosphorus from baseline to the other time points of the randomized period.

- Analyses showing the extent of change in serum phosphorus from baseline to the end of the randomized period (e.g., waterfall plots) for tenapanor and placebo responders (e.g., those who achieved serum phosphorus <5.5 mg/dL at the end of the randomized period, those who achieved serum phosphorus in the normal range at the end of the randomized period). Conduct similar analyses for the tenapanor and placebo non-responders. Conduct similar analyses from baseline to other time points of the randomized period.

- Responder analyses for tenapanor vs. placebo at each timepoint during the randomized period and at the end of the randomized period, where a responder is defined as having a certain reduction from baseline in serum phosphorus (e.g., >1 mg/dL, >1.5 mg/dL, >2 mg/dL, >2.5 mg/dL reductions). Conduct a similar analysis of the percentage of patients who have a certain increase from baseline in serum phosphorus (e.g., >1 mg/dL, >1.5 mg/dL, >2 mg/dL, >2.5 mg/dL increases).

- Analyses of the percentage of patients on tenapanor and placebo who consistently remained a responder beyond a single timepoint during the randomized period. For these persistent tenapanor and placebo responders, also assess their extent of serum phosphorus reduction. Conduct similar analyses for patients on tenapanor and placebo who consistently remained a non-responder throughout the randomized period. Examples of such analyses include:

    - Patients who consistently achieved serum phosphorus <5.5 mg/dL over 2 sequential visits, 3 sequential visits, all visits, etc. during the randomized period.

    - Patients who consistently achieved serum phosphorus <5.5 mg/dL and who had >1 mg/dL decrease from baseline in serum phosphorus over 2 sequential visits, 3 sequential visits, all visits, etc. during the randomized period. Similar analyses using other reductions instead of >1 mg/dL decrease from baseline in serum phosphorus (e.g., >1.5 mg/dL, >2 mg/dL, >2.5 mg/dL decreases)

- Proportion of responders at an early timepoint in the randomized period who remained a responder at later timepoints.

- Similar analyses as above but for patients who consistently achieved serum phosphorus in the normal range over 2 sequential visits, 3 sequential visits, all visits, etc. during the randomized period.

Study 301 and 201:

- Analyses assessing the distribution of change in serum phosphorus for tenapanor vs. placebo during the randomized, placebo-controlled withdrawal periods of Study 301 and 201.

- Analyses of the proportion of responders (e.g., those who achieved serum phosphorus <5.5 mg/dL, those who achieved serum phosphorus in the normal range) and non-responders for tenapanor and placebo at each time point of the randomized, placebo-controlled withdrawal period.

- Analyses showing the extent of change in serum phosphorus from baseline to the end of the randomized period (e.g., waterfall plots) for the tenapanor and placebo non-responders (e.g., those whose serum phosphorus was ≥5.5 mg/dL at the end of the randomized period, those whose serum phosphorus was above the upper limit of the normal range at the end of the randomized period). Conduct similar analyses for the tenapanor and placebo responders (e.g., those whose serum phosphorus was <5.5 mg/dL at the end of the randomized period, those whose serum phosphorus was within the normal range at the end of the randomized period). Also conduct similar analyses for other time points of the randomized period.

- Analyses of the percentage of patients on tenapanor and placebo at each timepoint during the randomized period and at the end of the randomized period who had a certain increase from baseline in serum phosphorus (e.g., >1 mg/dL, >1.5 mg/dL, >2 mg/dL, >2.5 mg/dL increases). Conduct a similar analysis of the percentage of patients who had a certain decrease from baseline in serum phosphorus (e.g., >1 mg/dL, >1.5 mg/dL, >2 mg/dL, >2.5 mg/dL decreases).

- Analyses of the percentage of patients on tenapanor and placebo who consistently remained a non-responder throughout the randomized, placebo-controlled periods. Conduct a similar analysis for consistent responders. For these consistent non-responders and consistent responders, also assess the extent of serum phosphorus change with

tenapanor vs. placebo. See the examples above for Study 202 and adapt them accordingly for Study 301 and 201.

2. Analyses of intra-patient variability over time in serum phosphorus concentrations in tenapanor and placebo-treated patients throughout the various treatment periods of Studies 301, 201, and 202.

3. A detailed assessment of how the benefits of tenapanor outweigh its risks based on these additional analyses in the context of the issues discussed in this Appeal Denied letter.

4. A detailed proposal for how to label your drug for prescribers for determining whether a patient is benefiting from tenapanor given the intra-patient variability in serum phosphorus concentrations in the context of the magnitude of tenapanor's treatment effects, taking into account the findings from the additional requested analyses described above as well as any other pertinent data in your NDA.

I have determined that this additional information and analyses are critical for determining whether tenapanor has clinically meaningful benefits that outweigh its risks. This new information and analyses have not been provided to the Division prior to the Complete Response action and, therefore, I am unable to consider the findings from such analyses as part of this appeal.

If you submit a Complete Response with this requested information and it still raises concerns regarding adequacy of the data to establish a meaningful effect with benefits that outweigh the risks, the Division will consider whether a public meeting of the Cardiovascular and Renal Drugs Advisory Committee would be appropriate to provide further input on this issue during the review cycle.

Questions regarding next steps as described in this letter should be directed to Sabry Soukehal, Regulatory Health Project Manager, at (240) 402-6187.

This constitutes the final decision at the Office of Cardiology, Hematology, Endocrinology and Nephrology level. If you wish to appeal this decision to the next level, your appeal should be directed to Peter Stein, MD, Director, Office of New Drugs, Center for Drug Evaluation and Research. The appeal should be sent to the NDA administrative file as an amendment, and a copy should be sent to the Center's Formal Dispute Resolution Project Manager, Melissa Sage. Any questions concerning your appeal should be addressed to Melissa Sage at (301) 796-6449.

Sincerely,

{See appended electronic signature page}

Hylton V. Joffe, MD, MMSc
Director
Office of Cardiology, Hematology, Endocrinology and Nephrology
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

HYLTON V JOFFE
02/04/2022 03:15:26 PM

IND 120566

MEETING MINUTES

Ardelyx, Inc.
Attention: Robert C. Blanks
Senior Vice President, Regulatory Affairs and Quality Assurance
34175 Ardenwood Blvd, Suite 100
Fremont, CA 94555

Dear Mr. Blanks:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tenapanor.

We also refer to the meeting between representatives of your firm and the FDA on March 03, 2020. The purpose of the meeting was to obtain the Agency's concurrence on your planned NDA submission for tenapanor 10, 20, and 30 mg BID, for the control of serum phosphorus in adult patients with chronic kidney disease on dialysis.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Sabry Soukehal, Senior Regulatory Health Project Manager, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Aliza Thompson, MD, MS
Deputy Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	March 03, 2020; 12:30 PM – 2:00 PM
Meeting Location:	White Oak Building 22, Conference Room: 1309
Application Number:	IND 120566
Product Name:	Tenapanor
Prposed indication:	Control of serum phosphorus in adult patients with chronic kidney disease on dialysis
Sponsor Name:	Ardelyx, Inc.
Meeting Chair:	Aliza Thompson, MD, MS
Meeting Recorder:	Sabry Soukehal, RAC

FDA ATTENDEES

* Division of Cardiovascular and Renal Products

Norman Stockbridge, MD, PhD	Director
Aliza Thompson, MD, MS	Deputy Director
Michael Monteleone, MS, RAC	Associate Director for Labeling
Shen Xiao, MD, PhD	Clinical Reviewer
Nhi Beasley, PharmD	Clinical Analyst
Selena Ready, PharmD, MPH	Clinical Analyst
Xuan Chi, PhD	Non-clinical Team Leader
Edward Fromm, R.Ph., RAC	Chief, Project Management Staff
Brian Cooney, PSM	Regulatory Project Manager
Christine Sadr, MS	Regulatory Health Project Manager
Sabry Soukehal, RAC	Sr. Regulatory Health Project Manager

* Office of Clinical Pharmacology

Sudharshan Hariharan, PhD	Clinical Pharmacology Team Leader
Li Wang, PhD	Clinical Pharmacology Reviewer

* Office of Pharmaceutical Quality – Division of Biopharmaceutics

Min Li, PhD	Acting Biopharmaceutics Lead
Min Sung Suh, PhD	Biopharmaceutics Reviewer

SPONSOR ATTENDEES

Robert Blanks, MS, RAC	SVP of Regulatory and Quality Assurance
David Rosenbaum, PhD	Chief Development Officer
Jeff Jacobs, PhD	SVP of Technical Operations
Vandana Nathan	Regulatory Affairs Specialist
Sanjeev Kothari, PhD	Senior Director of Pharmaceutics
[redacted] (b) (4)	

1.0 BACKGROUND

Tenapanor is a minimally absorbed locally acting inhibitor of the sodium-hydrogen antiporter 3 (NHE3), an antiporter protein found in the kidney and intestines that regulates sodium absorption and secretion by the body. Tenapanor was approved for the treatment of patients with irritable bowel syndrome with constipation (IBS-C) on September 12, 2019. Because tenapanor acts locally in the gastrointestinal tract to block intestinal phosphate absorption, the Sponsor is also developing tenapanor immediate release (IR) tablets at 10, 20, and 30 mg, equivalent to 10.6, 21.3, and 31.9 mg of the hydrochloride salt, for the control of serum phosphorus in adult patients with chronic kidney disease on dialysis.

On October 10, 2019, the Agency provided Written Responses on the Sponsor's proposed pooling strategy for the Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS) for a planned NDA for tenapanor for the control of serum phosphorus in adult patients with chronic kidney disease on dialysis. The Sponsor requested this pre-NDA meeting to ensure that the CMC, clinical and nonclinical information are adequate to support the submission of a new drug application for tenapanor IR tablets under the 505 (b)(1) regulatory pathway.

FDA sent Preliminary Comments to Ardelyx, Inc. on February 26, 2020.

2.0 DISCUSSION

Prior to the meeting, the Sponsor indicated that only Questions 6, 13, 18, and General Data and Analyses Comment C10 needed further discussion at the meeting. The meeting focused on the FDA's responses to those Questions as well as the Sponsor's follow-up comments.

2.1. Nonclinical

Question 1: Does the Agency agree that the nonclinical data package is adequate to support the NDA filing of tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis?

FDA Response: Yes, we agree.

Meeting discussion: The Sponsor accepted FDA's response; no discussion occurred.

2.2. Clinical/Clinical Pharmacology

Question 2: Does the Agency agree that the SAP for the ISS is acceptable?

FDA Response: Yes, we agree.

Meeting discussion: The Sponsor accepted FDA's response; no discussion occurred.

Question 3: Does the Agency agree the SAP for the ISE is acceptable?

FDA Response: Yes, we agree.

Meeting discussion: The Sponsor accepted FDA's response; no discussion occurred.

Question 4: Does the Agency agree with the e-Data submission plan?

FDA Response: Yes, we agree.

Meeting discussion: The Sponsor accepted FDA's response; no discussion occurred.

Question 5: Does the Agency concur with the results and conclusions of the BE study TEN-02-106, which demonstrate that the TEN-02-201 (10 mg and 30 mg) tablets are bioequivalent to the TEN-02-301 (10 mg and TBM) and 30 mg TBM tablets?

FDA Response: We agree that your topline results appear to support bioequivalence for the 10-mg and 30-mg formulations used in TEN-02-201 to the 10-mg and 30-mg TBM formulation used in TEN-02-301.

Meeting discussion: The Sponsor accepted FDA's response; no discussion occurred.

Question 6: Does the Agency concur with our request to waive the need to demonstrate BE of the TBM 20 mg and 30 mg tablets against 2 × 10 mg and 3 × 10 mg tablets that were used in the TEN-02-301 study?

FDA Response: We agree that a waiver of an *in vivo* BE study between the TBM 20- and 30 mg tablets against the 2 × 10-mg and 3 × 10-mg tablets used in the TEN-02-301 study would be acceptable if the following conditions are met:

1) The TEN-02-201 (10-mg and 30-mg) tablets are bioequivalent to the TEN-02-301 10-mg and 30-mg TBM tablets.
2) Comparative dissolution data (multi-media) demonstrate similarity of *in vitro* dissolution.

Sponsor reply for discussion at the meeting: *The Sponsor acknowledges the Agency's response and would like to have further discussion and clarification, specifically with respect to 2) as we have supplied these data in the briefing book, Pages 33-37.*

Meeting discussion: The Agency clarified that the final decision on the appropriateness of a BE waiver is a review issue. The Agency's comment was simply intended to ensure the appropriate data are provided to enable a final decision.

Question 7: The Sponsor had previously requested a waiver in performing a thorough QT/QTc study (per ICH E14 Guidance Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Arrhythmic Drugs) prior to the submission of NDA 211,801 (for the treatment of IBS-C in adults) and the waiver was granted by the reviewing Division (DGIEP). Based on the minimally systemic nature of tenapanor and the previously granted waiver, we are not planning on performing a thorough QT/QTc study. Does the Agency concur?

FDA Response: Yes, we agree.

Meeting discussion: The Sponsor accepted FDA's response; no discussion occurred.

Question 8: Does the Agency agree that the pharmacokinetic data for the M1 metabolite of tenapanor (AZ13792925) are adequate to support the NDA filing of tenapanor for the control of serum phosphorus in adult patients with CKD patients on dialysis?

FDA Response: Yes, the pharmacokinetic data for the M1 metabolite of tenapanor appear adequate to support an NDA submission.

Meeting discussion: The Sponsor accepted FDA's response; no discussion occurred.

Question 9: Does the Agency agree that the completed DDI studies are adequate for submission of the NDA for tenapanor?

FDA Response: Yes, we agree.

Meeting discussion: The Sponsor accepted FDA's response; no discussion occurred.

Question 10: Does the Agency agree that the administration of tenapanor is adequately described in the TPP?

FDA Response: What you propose seems reasonable.

Meeting discussion: The Sponsor accepted FDA's response; no discussion occurred.

Question 11: Does the Agency agree that the interim results from the ongoing open-label TEN-02-401 study as described in the TPP (b) (4) (b) (4)?

FDA Response: In brief, study TEN-02-401 is an ongoing, long-term, open-label study to evaluate the ability of tenapanor alone or in combination with sevelamer to treat to goal serum phosphorus in patients with end-stage renal disease on dialysis. We are open to considering (b) (4).

Meeting discussion: The Sponsor accepted FDA's response; no discussion occurred.

Question 12: Does the Agency agree the safety database in patients with CKD on dialysis with hyperphosphatemia is adequate to support the NDA filing of tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis?

FDA Response: Yes, we agree.

Meeting discussion: The Sponsor accepted FDA's response; no discussion occurred.

Question 13: Does the Agency agree the clinical data is adequate to support the NDA submission of tenapanor for control of serum phosphorus in adult patients with CKD on dialysis?

FDA Response: Yes, we agree. You should address in your submission why you believe the observed magnitude of the treatment effect on serum phosphorus is clinically relevant.

Sponsor reply for discussion at the meeting*: The Sponsor acknowledges the Agency's response and would like to have further discussion and clarification. Specifically, the Sponsor would approach the Agency's request above with the following:*

- *Literature showing that the tenapanor's magnitude of the treatment effect on serum phosphorus is clinically relevant, especially when one considers the chronic nature of the disease and pill burden in this patient population.*
- *In the TEN-02-301 study, the serum phosphorus lowering data of sevelamer and tenapanor during the 26-week randomized treatment period.*
- *Percent of patients with a significant serum phosphorus lowering in both the TEN-02-201 and TEN-02-301 study.*
- *The results from the TEN-02-202 study in patients with uncontrolled hyperphosphatemia (>5.5 mg/dL) receiving standard of care that shows tenapanor's ability to bring patients into control.*

Meeting discussion: The Agency indicated that it has accepted serum phosphorus as a surrogate endpoint and basis for approval for products intended to treat

hyperphosphatemia in patients with chronic kidney disease on dialysis. The evidence supporting its use as a surrogate endpoint includes biologic plausibility and epidemiologic data; but, to date, there is no evidence from outcome studies demonstrating that a treatment's effect on serum phosphorus predicts its effect on clinical outcomes. The Agency clarified, however, that while it has accepted serum phosphorus as a surrogate endpoint, a treatment effect of any size is not considered sufficient to support approval.

The Agency indicated that the Sponsor should address the clinical relevance of the size of the treatment effect observed in their development program in their NDA submission. The Agency stated that it is interested in the evidence supporting the conclusion that the size of the treatment effect is clinically relevant, as opposed to "expert opinion". The Agency also indicated that data indicating that the Sponsor's product has a marked treatment effect in patients with more marked elevations at baseline could be compelling.

Question 14: Does the Agency have any other comments on the draft TPP?

FDA Response: None at this time.

Meeting discussion: The Sponsor accepted FDA's response; no discussion occurred.

2.3. Chemistry, Manufacturing, and Controls

Question 15: Does the Agency agree that the first 3 commercial drug product batches do not have to be part of the post-stability commitment?

FDA Response: We note that the 3 registration batches were manufactured at the proposed commercial manufacturing site, using the same proposed commercial manufacturing process, in the same commercial equipment train and at the same proposed commercial scale. Based on this information, your proposal to not include the first 3 commercial drug product batches in the post-stability commitment is acceptable, provided that the proposed manufacturing process and stability protocol are deemed adequate upon review.

Meeting discussion: The Sponsor accepted FDA's response; no discussion occurred.

Question 16: Does the Agency have any additional comments on the CMC package to be submitted in the NDA for tenapanor for the control of serum phosphorus in adult patients with CKD on dialysis?

FDA Response: We agree with your plan to submit a separate Module 3 in this NDA rather than cross referencing Module 3 in NDA 211801. Overall, the aspects of the CMC development plan described in Appendix H of the meeting package and in the referenced meeting discussions appear adequate to support an NDA submission.

Meeting discussion: The Sponsor accepted FDA's response; no discussion occurred.

2.4. Regulatory

Question 17: Does the Agency agree that we could submit certain modules of NDA prior to the completion of all the modules of the NDA?

FDA Response: No. We expect the NDA dossier to be complete at the time of NDA submission.

Meeting discussion: The Sponsor accepted FDA's response; no discussion occurred.

Question 18: Does the Agency agree that we could potentially submit a clinical DDI study 30 days post the submission of the NDA in accordance with PDUFA VI?

FDA Response: No. Please refer to our response to Question 17.

Sponsor reply for discussion at the meeting*: The Sponsor acknowledges the Agency's response and would like to have further discussion. Specifically, would the Agency be amenable to including the key study data in the module sections and submit the TFLs in an initial NDA submission, while submitting the CSR within 30 days post the submission of the NDA.*

Meeting discussion: The Agency reiterated that the Sponsor should provide the complete dossier at the time of NDA submission.

Additional Requests from the Agency

For trials TEN-02-201, TEN-02-301, and TEN-02-202, please provide the following information in your NDA submission:

a. Protocol and Statistical Analysis Plan (SAP)

1) All versions of the protocol and the date when changes were implemented. Include a Summary of Changes for each version.

2) All versions of the SAP. Include a summary of changes for each version and the number of subjects enrolled in the trial at the time the change was made.

b. Clinical Trial Materials

1) Sample clinical trial kits, from all treatment arms, identical to those used during the trials. Ship them to Sabry Soukehal's desk address in the same packaging as was used for shipping to investigative sites.

2) All data management plans. Cite all amendments for each data management plan, including all manual and programmatical checks.

3) All site monitoring plans. If changes to your site monitoring plans were not documented contemporaneously by formal signed amendments, explain the amendment process.

4) A description of the responsibilities of each academic research organization (ARO) or clinical research organization (CRO).

5) All charters for committees involved in conducting your trials (e.g., Data Safety Monitoring Board [DSMB], Steering Committee, etc.).

6) All meeting minutes of all groups with any responsibility for the management of your trials, e.g., Executive Committee, Clinical Endpoint Committee, Steering Committee and DSMB. Include agendas and all data/slides presented to the Committee. Indicate whether the meeting was opened or closed. Ensure that these packages include a table of contents and are bookmarked by date.

c. General Data and Analyses

1) All code and datasets used to create your analyses found in the main sections of the ISE, ISS, and your Phase 3 trial clinical study reports.

2) Footnote the tables and figures featured in the ISE, ISS, and your Phase 3 trials with the name of the script used to create it.

3) List of datasets that you assert are of high quality for review. Explain how you assessed the quality of your datasets and what you did to ensure your datasets are suitable for an NDA review. Submit code that was used to create or clean up your analysis datasets.

4) Subject ID variable for all open label extension study datasets that links the subject to the ID used in the pivotal trial datasets.

5) Dataset that contains all subjects that were unblinded. Include the unique subject ID, the treatment received, who requested unblinding, date of unblinding, and the reason for unblinding.

6) Dataset that contains a list of all subjects for whom you submitted a CRF, or narrative. The dataset should contain three variables with an indicator for whether each item was submitted.

7) A table set up similarly to the dataset requested in #6, but with a hyperlink to the respective document. The table could be further organized by reason for narrative submission.

8) One table which includes the following information for each trial:
   - Dates of first patient and last patient visits
   - Date of data lock
   - Dates of each interim analysis
   - Dates of all versions of the SAP (with a hyperlink to each SAP)
   - Dates of the initial protocol and all revisions. (with a hyperlink to the protocol and each revision).

9) Statement of Good Clinical Practice confirming that all clinical studies were conducted under the supervision of an Institutional Review Board and with adequate informed consent procedures. If you were granted an IRB Waiver during this trial because a specific site or country operated under a Central Ethics Committee (CEC) and/or Local Ethics Committees (EC), please reference the waiver and include the date.

10) Case report forms (CRFs) and narratives for all subjects who died, dropped out, discontinued study drug for any reason, experienced a serious adverse event (SAE), or reached an efficacy endpoint. Please note that CRFs must include all clinical documents collected regardless of whether you label them as "CRFs" (Medwatch forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.).

11) Rationale for assuming the applicability of foreign data to the U.S. population and U.S. practice of medicine for any pivotal trials conducted primarily outside of the U.S.

12) An annotated version of the pre-NDA meeting minutes that include a hyperlink, when applicable, to the analysis and/or documents requested. This document is usually placed in Module 1.

Sponsor reply for discussion at the meeting*: The Sponsor acknowledges the Agency's requests and would like to have further discussion and clarification with request to C12 (General Data and Analysis, No. 12). Specifically, the request to submit all CRFs and narratives for all patients with SAEs, regardless if associated with drug, and reached an efficacy endpoint.*

Meeting discussion: The Sponsor indicated that their follow-up question was related to C10, not C12. The Agency clarified that the Sponsor should submit CRFs for SAEs that might reasonably be related to tenapanor, such as severe diarrhea, dehydration, hypovolemia, and falls, noting that the latter could result from significant dehydration or

hypovolemia. The Agency stated that the request for CRFs for patients that "reached an efficacy endpoint" was an error.

3.0 OTHER IMPORTANT MEETING INFORMATION

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[2] and Pregnancy and Lactation Labeling Final Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst

[2] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[3] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, “Product name, NDA/BLA 012345, Establishment Information for Form 356h.”

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				

(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[4]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

There were no handouts. The Sponsor's follow-up comments and questions are provided above the meeting discussion for Questions 6, 13, 18 and Additional Requests from the Agency.

[4] https://www.fda.gov/media/85061/download

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALIZA M THOMPSON
04/02/2020 09:09:58 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 120566

MEETING MINUTES

Ardelyx, Inc.
Attention: Robert C. Blanks
Vice President of Regulatory Affairs and Quality Assurance
34175 Ardenwood Blvd, Suite 100
Fremont, CA 94555

Dear Mr. Blanks:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Tenapanor.

We also refer to the meeting between representatives of your firm and the FDA on May 09, 2016. The purpose of the meeting was to discuss the Phase 3 development plans for Tenapanor Tablets.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please contact Sabry Soukehal, Regulatory Health Project Manager, at (240) 402 6187.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes and Sponsor's handout

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: End of Phase 2

Meeting Date and Time: May 09, 2016 from 2:00 to 3:00 PM
Meeting Location: White Oak Building 22, Room 1315

Application Number: 120566
Product Name: Tenapanor (also known as AZD1722 and RDX5791)
Proposed indication: Control of serum phosphorus levels in patients with chronic kidney disease on dialysis
Sponsor Name: Ardelyx, Inc.

Meeting Chair: Norman Stockbridge, MD, PhD
Meeting Recorder: Sabry Soukehal, RQAP-GLP

FDA ATTENDEES

*Division of Cardiovascular and Renal Products

Norman Stockbridge, MD, PhD	Director
Aliza Thompson, MD	Clinical Team Leader
Shen Xiao, MD	Clinical Reviewer
Thomas Papoian, PhD, DABT	Non-Clinical Team Leader
Elizabeth Hausner, DVM, DABT, DABVT	Non-Clinical Reviewer
Sabry Soukehal, RQAP-GLP	Regulatory Health Project Manager

*Office of Clinical Pharmacology

Sudharshan Hariharan, PhD	Clinical Pharmacology Team Leader
Martina Sahre, PhD	Clinical Pharmacology Reviewer

*Office of Biostatistics, Division of Biometrics I

Steven Bai, PhD	Statistician

*Office of New Drug Products, OPQ

Thomas Wong, PhD	CMC reviewer

*Division of Biopharmaceutics, OPQ

Elsbeth Chikhale, PhD	Biopharmaceutics Team Leader
Banu Zolnik, PhD	Biopharmaceutics Reviewer

SPONSOR ATTENDEES

Paul Korner, MD, MBA	Chief Medical Officer
David P. Rosenbaum, PhD	Ardelyx, Senior Vice President, Drug Development
Robert C. Blanks, MS, RAC	Ardelyx, Vice President Regulatory Affairs and Quality Assurance
Jeff W. Jacobs, PhD	SVP of Technical Operations
Sanjeev Kothari, PhD	Sr. Director of Formulations and Pharmaceutical Chemistry
[redacted] (b) (4)	

1.0 BACKGROUND

Tenapanor is a locally acting inhibitor of the sodium-hydrogen antiporter 3, also known as sodium-hydrogen exchanger 3 (NHE3).

According to the Sponsor, tenapanor inhibits the absorption of sodium and dietary phosphorus in the intestinal tract. Tenapanor is being developed for two potential indications: the control of serum phosphorus levels in patients with chronic kidney disease (CKD) on dialysis under this IND, and the treatment of irritable bowel syndrome with constipation (IBS-C) under IND 108732.

In addition to three completed clinical studies in patients with CKD (D5610C00001, D5611C00001, and D5613C00001), tenapanor is currently being evaluated in an 8-week long safety and efficacy study in End-Stage Renal Disease Patients on Hemodialysis (Study TEN-02-201).

The Sponsor requested this meeting to discuss key aspects of the proposed phase 3 clinical development plan for tenapanor for the treatment of hyperphosphatemia in CKD patients on dialysis.

FDA sent Preliminary Comments to Ardelyx, Inc. on May 05, 2016.

2. DISCUSSION

A day prior to the face-to-face meeting, the Sponsor provided responses to some of the Division's comments.

2.1. CMC

Question 8a:

Does Agency agree that, if the data are supportive, the Sponsor's plan [redacted] (b) (4) is acceptable?

FDA Response:

We do not agree with your proposal [redacted] (b) (4) Please note that the proposed formulation changes are classified as Components and Composition-Level 3 changes, which require supportive in vivo bioequivalence (BE) data; however, since you are claiming that your proposed drug product acts locally in the GI tract and it is not systemically absorbed, we believe that a bridge between formulations can be established by conducting a comparative clinical study with appropriate Pharmacodynamic (PD) endpoints.

Other potential options include collecting PD endpoint data from a subset of patients from the long-term safety clinical study and then comparing these data with the results of the TEN-02-201 study.

We suggest that you submit your proposal (with detailed information) for establishing a bridge between the clinical (TEN-02-201 study) and commercial products to your IND for FDA review and comment.

Meeting Discussion:

The Sponsor agreed to conduct a clinical study using pharmacodynamic (PD) endpoints to establish a bridge between the drug product formulation used in the clinical study (TEN-02-201) and the to-be-marketed commercial drug product.

Question 9a:

The tenapanor (b) (4) mg formulation requires a different drug load than the other drug doses, and thus the final registration/stability batches of the (b) (4) mg dose may be delayed, does the agency concur that the Sponsor could submit with less than a year of stability for the (b) (4) mg dose in the NDA and supplement at a later time during the review process?

FDA Response:

In accordance with the principles detailed in the ICH guidance QIA (R2), our expectation is that an initial NDA submission will include a minimum of 12 months of long-term stability data and 6 months accelerated data for three primary batches per strength of the same formulation as the to-be-marketed product in the proposed commercial packaging. Please note that our determination of commercially viable shelf-life will be based on the extent and quality of the available stability data per ICH guidance "Q1E Evaluation of Stability Data".

Meeting Discussion:

No additional discussion.

2.2. Non-clinical

Question 1a:

Does the Agency agree that the assessment of the exposures of the metabolites of tenapanor has been addressed adequately for registration of tenapanor for the proposed indication?

FDA Response:

No, we do not agree. A nonclinical radiolabel distribution study will be needed to address whether the metabolite crosses the blood brain barrier.

Meeting Discussion:

The Sponsor requested further clarification regarding the goal of the requested radiolabel distribution study for the active metabolite. The Division explained that because of the metabolite's binding to receptors associated with major depressive disorder and suicidal ideation, the Division wishes to see data on the distribution or lack thereof to the brain. The Sponsor stated that in their prior radiolabel study, the radiolabel placement on the parent drug would have remained with the metabolite of interest. Because the radiolabel did not appear in the brain in their prior study, the Sponsor feels confident that the metabolite does not cross the blood-brain barrier. The Division agreed that a second radiolabel study would not be necessary for adult clinical studies. The Division asked the Sponsor to send the protocol for the juvenile toxicology study to the Division prior to initiating the study (see also the discussion under Question 2a).

Question 2a:

Based on the information provided does the Agency agree that the proposed nonclinical development plan adequately supports the registration of tenapanor for the proposed indication?

FDA Response:

This will depend upon the results of the radiolabel distribution study. We also encourage you to obtain our input on the juvenile animal study protocol. We understand that the protocol has been reviewed by DGIEP; however, considerations related to the age of the population that will be studied and the condition that will be treated often factor into our recommendations.

Meeting Discussion:

The Division stated that, because the blood brain barrier is not completely developed in young children, the distribution of the active metabolite should be evaluated in juvenile animals. The Division also clarified that the design of the juvenile animal study will depend on the age of the target human pediatric population. Unless there are safety concerns, the Sponsor will likely be expected to study their product in pediatric patients of all ages. The Sponsor indicated that they plan to request a waiver of pediatric studies (b) (4) for the reasons outlined in their briefing document. The Division responded that it will evaluate the Sponsor's proposal when the pediatric study plan is submitted.

Question 2b:

Based on the information provided does the Agency agree that the nonclinical evaluation of the M1 metabolite adequately supports the registration of tenapanor for the proposed indication?

FDA Response:

See our response to question 1a.

Meeting Discussion:

No additional discussion.

2.3. Clinical Pharmacology

Question 3a:

Does the Agency agree that the completed and planned evaluation of pharmacokinetics and pharmacodynamics of tenapanor, including the metabolite M1, is sufficient to support the registration of tenapanor for the proposed indication?

FDA Response:

Yes, based on the information you have provided. We also agree with your plan to measure M1 (and possibly tenapanor) concentrations in studies in the patient population.

Meeting Discussion:

No additional discussion.

Question 3b:

Does the Agency agree that based on the minimal systemic availability of tenapanor and the drug-drug interactions studies completed to date, and the planned drug-drug interaction studies will provide sufficient drug-drug interaction data to support the registration of tenapanor for the proposed indication?

FDA Response:

Your question refers to "planned drug-drug interaction studies", but we were not able to find a listing of planned studies in your briefing package; please provide this information. We also note that there was a decrease in exposure to enalaprilat when administered with tenapanor in rats. Please comment on the mechanistic basis for this drug interaction. Since tenapanor can cause diarrhea, you should consider conducting a study to evaluate the effect of tenapanor on the potential to interact with other orally administered drugs via changes in gastric and intestinal transit times.

Meeting Discussion:

The Division voiced concern that drug-induced diarrhea could affect the absorption of orally administered drugs, and asked whether the Sponsor had studied drug-drug interactions with oral birth control drugs (a more immediate concern for patients enrolled in clinical trials). According to the Sponsor, although the drug causes softer and looser stools, for the most part, tenapanor does not cause significant diarrhea at the doses proposed for use. The Sponsor stated that many of the reports of diarrhea do not reflect "true diarrhea" and that, in clinical trials of tenapanor, the average score on the Bristol stool scale was 4.9 (according to the Sponsor, the scale uses 7 categories to grade stool with 3 to 5 being normal and 7 reflecting watery diarrhea).

The Division indicated that the Sponsor's clarification regarding tenapanor's effect on bowel habits was reassuring and that this issue (i.e., whether drug-drug interactions might occur because of drug-induced diarrhea) can be revisited as needed based on the findings in Study TEN-02-201. The Sponsor agreed to provide information on the effect of tenapanor on bowel habits in Study TEN-02-201, once the trial is completed.

With regard to the planned clinical drug interaction study between midazolam and a higher dose of tenapanor, the Division recommended using a substrate that undergoes extensive gut metabolism by CYP3A4 (e.g., simvastatin) as opposed to midazolam. The Sponsor agreed to take this recommendation into consideration.

Question 3c:

Does the Agency agree, that based on the minimal systemic availability of tenapanor and the currently available nonclinical and clinical data showing no signal of QT-prolongation, Ardelyx does not need to perform a thorough QT/QTc study (per ICH E14 Guidance Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Arrhythmic Drugs)?

FDA Response:

No, we do not agree. Although there is minimal exposure to tenapanor following doses up to 90 mg BID for 7 days, there is systemic exposure to the M1 metabolite. The ECG data collected in the Japanese MAD study (D5611C00005) might be adequate to characterize the effects of tenapanor and its M1 metabolite on QTc interval using dose- and exposure-response analysis (see ICH E14 Q&A (R3)). You should submit these data for review.

When using exposure-response as a primary analysis, it is important that the modeling methods and assumptions, criteria for model selection, rationale for model components, and potential for pooling of data across studies be specified prior to analysis to limit bias. Prospective specification of model characteristics (e.g., structural model, objective criteria, goodness of fit) based on knowledge of the pharmacology is recommended whenever possible. On occasion, the QT effect is not a direct function of plasma concentration. Testing for model assumptions, hysteresis (a plot of data by-time point and a hysteresis loop plot), and goodness of fit should be documented.

Meeting Discussion:

The Sponsor agreed with the Division's suggestion. Assuming the results of this analysis show no significant QTc effect, the Sponsor asked whether, from the Agency's perspective, the CV safety of tenapanor will have been adequately evaluated. The Division stated that if the aforementioned data and analyses adequately resolve the effect of tenapanor on the QT interval, then the Sponsor will not need to conduct a Thorough QT study.

Question 4c:

Does the Agency agree that the doses, including the down titration dosing regimen in the clinical study, TEN-02-201, are appropriate to support the registration of tenapanor for the proposed indication?

FDA Response:

Yes. We note that there were subjects in D5611C0001 who were able to tolerate doses of 45 mg BID. Have you considered using a higher starting dose in the titration arm of TEN-02-201?

Meeting Discussion:

The Sponsor indicated that they will take the Division's suggestion into consideration when planning future studies.

Question 6a:

Does the Agency agree that if the down titration is successful in study TEN-02-201 that this dosing regimen may be included in the tenapanor label for the proposed indication?

FDA Response:

From an efficacy perspective, if there is a meaningful benefit with the titration arm compared to the lower fixed dose arm then it could be included in the label; however, if there is no difference between the titration regimen and the lower fixed dose then the value of the titration should be questioned.

Meeting Discussion:

No additional discussion.

2.4. Clinical

Question 4a:

Does the Agency agree that the endpoints of the ongoing clinical study, TEN-02-201, along with the planned long term safety study, are appropriate to support the registration of tenapanor for the proposed indication?

FDA Response:

As noted below, we do not agree with your proposed primary endpoint in your ongoing clinical study, TEN-02-201.

Meeting Discussion:

See additional discussion under Question 4b.

Question 4b:

Does the Agency agree that the primary endpoint in the ongoing clinical study, TEN-02-201, is appropriate to support the registration of tenapanor for the proposed indication?

FDA Response:

No. Your proposed primary endpoint is the change in serum phosphate levels from baseline to the end of the 8-week treatment period in subjects treated with tenapanor. Since the 8-week treatment period does not include a placebo-control, these data will be difficult to interpret.

Your primary endpoint should compare the serum phosphate level from the end of the 8-week treatment period to the end of the 4-week randomized withdrawal period between treatment arms. For the purpose of your primary analysis, we recommend that you test the high dose against placebo. You may also want to consider only randomizing subjects who achieve a pre-defined level of response into the 4-week randomized withdrawal period, as this may help you detect a treatment effect.

Meeting Discussion:

The Sponsor agreed to amend their primary endpoint as recommended by the Division. The primary endpoint will be the change in serum phosphorous from the end of the 8-week treatment period to the end of the 4-week randomized-withdrawal period in patients who are responders in the 8-week treatment period. A responder in this context will be defined as a subject who achieves a 1.2 mg/dL or greater serum phosphorus reduction from baseline at the end of 8-week treatment period. According to the Sponsor, the primary efficacy endpoint will be analyzed using an analysis of covariance model with terms for pooled investigator site, treatment, and serum phosphorus value at the end of the 8-week treatment period as a covariate. The primary efficacy analysis will test the treatment difference between the pooled tenapanor group (i.e., all three tenapanor groups combined) and placebo. The statistical strategy will also include testing each tenapanor group versus placebo in a hierarchical manner.

The Division, in general, recommends comparing the highest tested dose with placebo and then evaluating lower or pooled doses, as, conceptually, there is a greater likelihood of detecting a treatment effect with the highest dose. However, given the titration scheme used in one of the dose arms, this may not be a sensible strategy here. The Division also clarified that the Sponsor does not need to test each dose formally against placebo to establish a dose-response relationship.

The Sponsor proposed to amend the Statistical Analysis Plan prior to database lock and unblinding to reflect the aforementioned changes to the primary endpoint and its analysis. The Division indicated that the Sponsor should submit the revised Statistical Analysis Plan as soon as possible to mitigate concern that knowledge of study findings influenced the analytic approach and primary endpoint findings.

Question 4e:

Does the Agency agree that the proposed long term safety study is adequate with respect to dosing, number of patients and duration for the registration of tenapanor for the proposed indication?

FDA Response:

Yes. According to your submission, the proposed long-term study will enroll ~375 hyperphosphatemic ESRD patients on dialysis and randomize them in a 2:1 ratio to tenapanor treatment or active control. You further indicate that based on estimated dropout rates, you expect to have data on ~ 220 patients treated with tenapanor for 6 months and ~150 patients treated for one year. This seems reasonable.

Meeting Discussion:

No additional discussion.

Question 5a:

Based on the information provided, does the Agency agree that the proposed clinical development plan and the proposed safety database are appropriate to adequately support the registration of tenapanor for the control of serum phosphorus levels in patients on CKD on dialysis?

FDA Response:

As noted in our response above, we do not agree with your proposed primary endpoint in Study TEN-02-201; however, we do agree with your proposed safety database, and the general design of Study TEN-02-301, a 52 week randomized, open label study with a 4-week placebo-controlled randomized withdrawal period. Please confirm that the randomized withdrawal period will be double-blinded in Study TEN-02-301 and in Study TEN-02-201.

Meeting Discussion:

See additional discussion under Question 4b.

Question 6b:

Does the Agency agree with the secondary endpoints in the clinical study, TEN-02-201 and the proposed long term safety study, (TEN-02-301), (b) (4) (b) (4)?

FDA Response:

Generally speaking, (b) (4), secondary endpoints must be tested within a plan that controls overall type 1 error. That said, we note that a number of your proposed secondary endpoints assess effects on serum phosphate levels. Although it may be reasonable to include a secondary endpoint that assesses the proportion of patients who achieve some target phosphorus level in your trials, we do not think it is sensible to specify multiple secondary endpoints related to effects on serum phosphorus levels, (b) (4) (b) (4). With regard to your other proposed endpoints:

- (b) (4) the clinical significance of treatment effects on FGF-23 levels is unclear.
- We are unable to comment on the (b) (4) treatment effects on secondary hyperparathyroidism/PTH levels, since we do not regulate products intended to treat secondary hyperparathyroidism. (b) (4) (b) (4)

Meeting Discussion:

No additional discussion.

Question 7a:

Does Agency agree that the pediatric study program may be deferred until the safety and efficacy of tenapanor has been approved for the control of serum phosphorus levels in adult CKD patients on dialysis?

FDA Response:

Please see the section below regarding PREA requirements and the process for reaching agreement on the pediatric study plan. As noted in that section, you will need to submit an Initial Pediatric Study Plan within 60 days of an End of Phase 2 meeting. Although we believe it is reasonable to request a deferral of pediatric studies until efficacy and safety have been demonstrated in adults, you need to follow the process outlined in that section.

Meeting Discussion:
No additional discussion.

2.5. Statistics

Question 4d:
Does the Agency agree that the statistical analysis plan (SAP) associated with clinical study, TEN-02-201, is appropriate to support the registration of tenapanor for the proposed indication?

FDA Response:
As noted above, we do not agree with your proposed primary endpoint; hence we are unable to comment on your statistical analysis plan at this time. Among other things, your analysis plan should specify an approach to handling missing data for key efficacy analyses and provide a clear description of how the sample size is derived.

Meeting Discussion:
The Division emphasized that the analysis plan should specify an approach to handling missing data. The Sponsor indicated that this issue will be addressed in the Statistical Analysis Plan, which will be submitted to the Agency in the coming weeks.

Question 4f:
Does the Agency agree that the statistical methods and proposed sample size for the long term safety study is appropriate for the registration of tenapanor for the proposed indication?

FDA Response:
See our responses to prior questions.

Meeting Discussion:
The Division noted that, from a safety perspective, the proposed safety database is adequate; however, based on the information provided, it is unclear whether the proposed sample size is adequate to evaluate efficacy. The Sponsor should provide additional information on the assumptions underlying their power/sample size calculation. The Sponsor agreed to submit a revised Statistical Analysis Plan addressing the Division's concerns.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized

format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information

required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

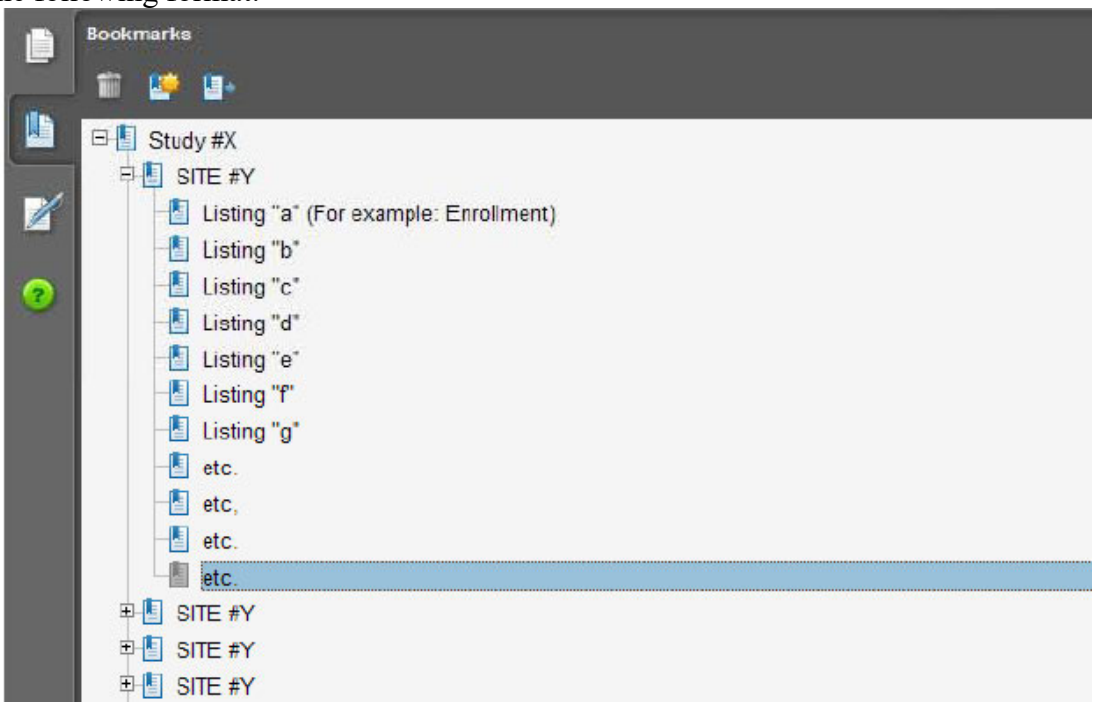
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
   j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population
5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor handed a document titled “Response to Agency’s meeting comments”.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

NORMAN L STOCKBRIDGE
06/03/2016