DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 075610

WRITTEN REQUEST

Fresenius Medical Care North America
Attention: J. Claude Miller
U.S. Agent for Vifor Fresenius Medical Care Renal Pharma
Vice President, Regulatory Affairs
920 Winter Street
Waltham, MA 02451

Dear Mr. Miller:

Reference is made to your October 31, 2014 Proposed Pediatric Study Request for PA21 (Velphoro®, Sucroferric oxyhydroxide).

Background: PA21 is a phosphate binder indicated for the control of serum phosphorus levels in adult patients with chronic kidney disease on dialysis. PA21 lowers serum phosphorus levels by binding phosphate in the gastrointestinal tract, thereby decreasing absorption. Given its mechanism of action, PA21is expected to be effective in lowering serum phosphorus levels in pediatric patients with chronic kidney disease and hyperphosphatemia; therefore, full pediatric extrapolation of efficacy is acceptable. However, safety, tolerability, and dosing data are needed to guide the use of PA21in this population. Since the number of eligible patients in the age group 0-28 days is very low, we are encouraging inclusion of patients of this age, but are not requiring a minimum number of patients less than 1 month of age.

This Written Request contains a mixture of requirements (failure to fulfill these would result in denial of exclusivity) *and* advice. We have highlighted formal requirements to make this distinction clear.

To obtain needed pediatric information on PA21, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), as amended by the Food and Drug Administration Amendments Act of 2007, that you submit information from the studies described below.

- *Nonclinical study(ies)*: Based on review of the available non-clinical toxicology, no additional animal studies are required at this time to support the clinical studies described in this written request.

- *Clinical studies:* The clinical study will be an open-label, randomized, controlled, parallel group, multicenter Phase 3 study in pediatric patients with hyperphosphatemia due to chronic kidney

disease. The objective of this study will be to provide safety and dosing data to guide the use of PA21 in pediatric patients. The study protocol must be agreed upon prior to study initiation.

The controlled study will include a washout phase (for subjects who are currently on phosphate binders), a dose titration phase, and a safety extension phase. During the dose titration phase, the dose of study drug will be increased or decreased as required to achieve an age appropriate target serum phosphorus level, or for safety or tolerability reasons. Once a subject achieves the age appropriate target serum phosphorus level and has been on a stable dose for 2 weeks, the subject will move to a safety extension phase of the trial. During this stage, subjects will continue on the dose received at the end of the dose titration phase, unless a dose change is required to maintain target serum phosphorus levels or for safety or tolerability reasons. Subjects should be treated for a minimum of 24 weeks during the safety extension phase of the trial.

- *Objective of each study:* The objective of this study is to provide safety and dosing data to guide the use of PA21 in pediatric patients with chronic kidney disease and hyperphosphatemia.

- *Patients to be studied:* Pediatric patients with hyperphosphatemia and chronic kidney disease (CKD) stages 4-5 (defined by a glomerular filtration rate <30 mL/min/1.73 m^2) or with CKD Stage 5D receiving adequate maintenance hemodialysis or peritoneal dialysis.

  - *Age group in which study(ies) will be performed*: The study must be performed in pediatric patients 0 to 17 years.

  - *Number of patients to be studied:* A minimum of 60 subjects must be treated with PA21 in the safety extension phase of the trial, with a minimum of 10 subjects in each of the following age categories: 0 to < 2 years, 2 to 6 years, 6 to 9 years and 9 to 17 years.

  Representation of ethnic and racial minorities: The studies must take into account adequate (e.g., proportionate to disease population) representation of children of ethnic and racial minorities. If you are not able to enroll an adequate number of these patients, provide a description of your efforts to do so and an explanation for why they were unsuccessful.

- *Study endpoints:*
  - Pharmacodynamic endpoints must include serum phosphorus measurements. These measurements must be made at baseline and at appropriate intervals during the titration and maintenance phase of the study. These intervals must be agreed upon prior to study initiation.
  - Safety outcomes must include: adverse events, tolerability, and laboratory assessments including serum phosphorus, calcium, intact PTH, and iron parameters.
  - The following adverse events must be actively monitored: Gastrointestinal adverse events, including diarrhea, nausea, constipation, vomiting and dyspepsia. All adverse events must be monitored until symptom resolution or until the condition stabilizes.
  - A Data Monitoring Committee (DMC) must be included because the study is being performed in children, a vulnerable population. See Guidance: Establishment and Operation of Clinical Trial Data Monitoring Committees http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126578.pdf

- *Known drug safety concerns and monitoring:*
  Potential safety concerns include hypophosphatemia, adverse gastrointestinal reactions and drug-drug interactions preventing absorption of concomitant medications. Subjects should be monitored for the development of hypophosphatemia and adverse gastrointestinal reactions and given appropriate instruction on ways to address potential drug-drug interactions. Although PK studies suggest low iron uptake from PA21, iron parameters should also be monitored.

- *Extraordinary results:* In the course of conducting these studies, you may discover evidence to indicate that there are unexpected safety concerns, unexpected findings of benefit in a smaller sample size, or other unexpected results. In the event of such findings, there may be a need to deviate from the requirements of this Written Request. If you believe this is the case, you must contact the Agency to seek an amendment. It is solely within the Agency's discretion to decide whether it is appropriate to issue an amendment.

- *Drug information:*
  - *dosage form:* An age-appropriate formulation must be used.
  - *route of administration:* Oral
  - *regimen:* The dosing regimen must be agreed upon prior to study initiation.

  Use an age-appropriate formulation in the study(ies) described above. If an age-appropriate formulation is not currently available, you must develop and test an age-appropriate formulation and, if it is found safe and effective in the studied pediatric population(s), you must seek marketing approval for that age-appropriate formulation.

  In accordance with section 505A(e)(2), if

  1) you develop an age-appropriate formulation that is found to be safe and effective in the pediatric population(s) studied (i.e., receives approval);
  2) the Agency grants pediatric exclusivity, including publishing the exclusivity determination notice required under section 505A(e)(1) of the Act; and
  3) you have not marketed the formulation within one year after the Agency publishes such notice, the Agency will publish a second notice indicating you have not marketed the new pediatric formulation.

  If you demonstrate that reasonable attempts to develop a commercially marketable formulation have failed, you must develop and test an age-appropriate formulation that can be compounded by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients. Under these circumstances, you must provide the Agency with documentation of your attempts to develop such a formulation and the reasons such attempts failed. If we agree that you have valid reasons for not developing a commercially marketable, age-appropriate formulation, then you must submit instructions for compounding an age-appropriate formulation from commercially available ingredients that are acceptable to the Agency. If you conduct the requested studies using a compounded formulation, the following information must be provided and will appear in the product labeling upon approval: active ingredients, diluents, suspending and sweetening agents;

detailed step-by-step compounding instructions; packaging and storage requirements; and formulation stability information.

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

- *Statistical information, including power of study(ies) and statistical assessments:*
  The study sample size is based on the assessment of tolerability and common adverse reactions. Provide descriptive statistics for data on dose, serum phosphorus, and common adverse event rates.

- *Labeling that may result from the study(ies)*: You must submit proposed pediatric labeling to incorporate the findings of the study(ies). Under section 505A(j) of the Act, regardless of whether the study(ies) demonstrate that polynuclear iron(III)-oxyhydroxide is safe and effective, or whether such study results are inconclusive in the studied pediatric population(s) or subpopulation(s), the labeling must include information about the results of the study(ies). Under section 505A(k)(2) of the Act, you must distribute to physicians and other health care providers at least annually (or more frequently if FDA determines that it would be beneficial to the public health), information regarding such labeling changes that are approved as a result of the study(ies).

- *Format and types of reports to be submitted*: You must submit full study reports (which have not been previously submitted to the Agency) that address the issues outlined in this request, with full analysis, assessment, and interpretation. In addition, the reports must include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(ies) should be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander or White. For ethnicity, you should use one of the following designations: Hispanic/Latino or Not Hispanic/Latino. If you choose to use other categories, you should obtain agency agreement.

Under section 505A(d)(2)(B) of the Act, when you submit the study reports, you must submit all postmarketing adverse event reports regarding this drug that are available to you at that time. All post-market reports that would be reportable under section 21 CFR 314.80 should include adverse events occurring in an adult or a pediatric patient. In general, the format of the post-market adverse event report should follow the model for a periodic safety update report described in the ICH Harmonised Tripartite Guideline Periodic Benefit-Risk Evaluation Report (PBRER) You are encouraged to contact the reviewing Division for further guidance.

Although not currently required, we request that study data be submitted electronically according to the Study Data Tabulation (SDTM) standard published by the Clinical Data Interchange Standards Consortium (CDISC) provided in the document "Study Data Specifications," which is posted on the http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf and referenced in the FDA Guidance for

Industry, *Providing Regulatory Submissions in Electronic Format - Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* at http://www.fda.gov/Cder/guidance/7087rev.htm.

- *Timeframe for submitting reports of the study(ies):* Reports of the above studies must be submitted to the Agency on or before February 28, 2020. Please keep in mind that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine (9) months or more after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, to ensure that a particular patent or exclusivity is eligible for pediatric exclusivity to attach, you are advised to submit the reports of the studies at least 15 months (9 months plus 6 months/180 days for determination) before such patent or exclusivity is otherwise due to expire.

- *Response to Written Request:* Under section 505A(d)(2)(A)(i), within 180 days of receipt of this Written Request you must notify the Agency whether or not you agree to the Written Request. If you agree to the request, you must indicate when the pediatric studies will be initiated. If you do not agree to the request, you must indicate why you are declining to conduct the study(ies). If you decline on the grounds that it is not possible to develop the appropriate pediatric formulation, you must submit to us the reasons it cannot be developed.

  Furthermore, if you agree to conduct the study(ies), but have not submitted the study reports on or before the date specified in the Written Request, the Agency may utilize the process discussed in section 505A(n) of the Act.

Submit protocols for the above study(ies) to an investigational new drug application (IND) and clearly mark your submission "**PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the study(ies) must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission to the Director, Office of Generic Drugs, HFD-600, Metro Park North IV, 7519 Standish Place, Rockville, MD 20855-2773. If you wish to fax it, the fax number is 240-276-9327.

In accordance with section 505A(k)(1) of the Act, *Dissemination of Pediatric Information*, FDA must make available to the public the medical, statistical, and clinical pharmacology reviews of the pediatric studies conducted in response to this Written Request within 210 days of submission of your study report(s). These reviews will be posted regardless of the following circumstances:

1. the type of response to the Written Request (i.e. complete or partial response);
2. the status of the application (i.e. withdrawn after the supplement has been filed or pending);
3. the action taken (i.e. approval, complete response); or

4. the exclusivity determination (i.e. granted or denied).

FDA will post the medical, statistical, and clinical pharmacology reviews on the FDA website at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM049872

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES"** in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

Please note that, if your trial is considered an "applicable clinical trial" under section 402(j)(1)(A)(i) of the Public Health Service Act (PHS Act), you are required to comply with the provisions of section 402(j) of the PHS Act with regard to registration of your trial and submission of trial results. Additional information on submission of such information can be found at www.ClinicalTrials.gov.

If you have any questions, please call Anna Park, Regulatory Project Manager, at (301)796-1129.

Sincerely,

{See appended electronic signature page}

Ellis Unger, MD
Director
Office of Drug Evaluation I, HFD-110
Center for Drug Evaluation and Research

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

/s/

ELLIS F UNGER
04/27/2015