Validus PHARMACEUTICALS

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July 25, 2018

Mitchell Mathis, MD
Division of Psychiatry Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation I
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: NDA 021710; IND (b) (4); EQUETRO (carbamazepine) Extended Release Capsules; Request to (b) (4) PMR 1487-5
e-CTD Seq. No.: 0008

Dear Dr. Mathis:

Reference is made to the e-mail Validus Pharmaceuticals LLC, received from Keith Kiedrow, FDA Team Leader Sr. Regulatory Project Manager, on July 13, 2018 regarding New Drug Application (NDA) 021710 for EQUETRO® Capsules, PMR 1487-5 associated with Equetro and our ongoing pediatric study entitled "VAL-EQP-001-A Phase IV, Unequal Randomization, Double-Blind Study to Evaluate the Dose Tolerance and Safety of Extended-Release Equetro (carbamazepine) versus Placebo Followed by an Open-Label and Long-Term Maintenance Treatment in Children and Adolescents aged 10-17 years Diagnosed with Acute Manic or Mixed Bipolar I Disorder" requesting information demonstrating the difficulties in completing this study.

Validus in good faith has executed the agreed upon protocol. Following is a synopsis of Validus' activities demonstrating our commitment to complete and comply with the PREA Regulation and the difficulties we encountered. Following is an overview included in this response:

- Timeline of Activities
- Challenges in Subject Recruitment
- Status of Subjects Recruited
- Conclusion

Timeline of Activities:

- 2012 – Validus met with the Agency regarding the study. The Agency had rejected the Validus' March 15, 2011 submission of (b) (4) Study to IND (b) (4) entitled (b) (4) (b) (4) (b) (4) The Agency informed Validus that they would only accept data from a double-blind placebo controlled study to confirm the safety and effectiveness in children and adolescents aged 10-17 yrs. for Bipolar I Disorder.
- 2012-2014 – FDA offered their assistance in developing a pediatric study protocol that would fulfill the PREA requirements for approval in this patient population (10-17 yrs). Protocol development and exchange of input delayed acceptance of the final protocol by all participants

(Validus, FDA, and Chief Investigator, Dr. Findling). Additional protocol delays can be attributed to the following:

- Requested changes of by Investigators during an Investigator meeting.
- Development of Informed Consent meeting IRB Requirements.
- IRB Approvals of proposed protocol and Informed Consent.
- FDA's request for pharmacokinetic data.

- Sept. 2014 – Validus received acknowledgement from Dr. Sharon Sagoo, Regulatory Project Manager, Div. of Psychiatry Products that the protocol to be implemented was generally acceptable. This protocol included the addition of the pharmacokinetic study requested by the Agency.
- Nov. 2014 - Beg. 2015 – Validus finalized plans to execute the pediatric protocol. This included:
  - (b) (4)
  -
  -
- Feb 2016 – Three of four Investigator sites initiated recruitment of subjects.
  1. (b) (4)
  2.
  3.
  4.
- February 2016 – *Present* – Study Enrollment and Protocol Difficulties Due to:
  - *Effects of Study Design.*
    - Arduous patient requirements: Subjects and parents are required to visit the investigator sites on a weekly basis for 2 to 4 months initially, followed by monthly visits for an additional 6 months. Each office visit requires 3-4 hr. for safety and efficacy evaluations during a period of 8 -10 months of participation.
    - Informed Consent (IC) clearly explains the commitments of the subject and their parents during the 8 to 10 month trial. Many parents decline to participate due to the time they would have to devote to these visits. Others were concerned that their children needing therapy and might be on a placebo for two months.
    - Inclusion and exclusion criteria being very restrictive in that the diagnosis of Bipolar I Disorder is governed by a series of validated scales in order to select subjects with the exact diagnosis.
    - Conflicting Diagnosis: Symptoms of Bipolar I Disorder often conflict with a diagnosis of ADHD.
  - *Patient Attrition.* Subjects were dropped due to the following:
    - (b) (4)
    -
    -
    -

Challenges in Subject Recruitment

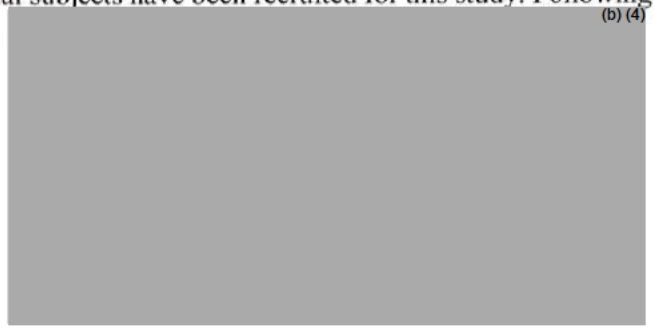
Based on prior research and published article co-written by our Chief Investigator, Dr. Robert L. Findling, M.D., et. al., the difficulty in recruitment of children diagnosed with Bipolar I Disorder has been recognized since 2007 by many pediatric psychiatrists. A published journal article confirming that this diagnosis is difficult to establish is provided for your reference. The article entitled "Evaluation and Comparison of Psychometric Instruments for Pediatric Bipolar Spectrum Disorders in Four Age Groups" has been provided.

Adding to the difficulty of subject recruitment, the protocol limits the age group to children and adolescents aged 10-17 yrs having a true diagnosis of Bipolar I Disorder. This further restricts the patient population that can be recruited for this study. Validus and its Investigators continue to attempt to recruit subjects for this study. We are aware of the difficulty in identifying subjects with a diagnosis of Bipolar I Disorder and meeting the inclusion/exclusion criteria of this protocol.

Based on the rate of subjects recruited for this study, the Investigators must screen 3-4 subjects before one meets the protocol criteria. Notwithstanding this, the subjects selected may not successfully complete the screening phase. Therefore completing this study would be highly impracticable and impossible given the allotted timeframe.

Status of Subjects Recruited

Since initiation of the study in February 2016, Validus continues to actively interact with the investigator sites to encourage subject enrollment. Investigators actively interview, screen, and qualify subjects. To date, 60 potential subjects have been recruited for this study. Following is a breakdown of these subjects:

- 

Note: 150 subjects are required to complete this trial. The trial must be long enough and adequately powered to have sufficient relapse events to demonstrate a treatment effect. Refer to Figure 1. for an Accountability of Study Subjects.

Figure 1. Accountability of Study Subjects

It should be noted that Validus routinely provided the Agency updates via IND (b) (4) Annual Reports in 2017 (Table 2) and 2018 (Table 2). For ease of review, copies of these Annual Reports are provided herein.

Conclusion

Validus and its investigators continue to make a good faith effort to recruit subjects meeting the protocol inclusion/exclusion criteria. However, recruiting the sufficient number of subjects to fulfill the protocol requirements in order to demonstrate statistical differences will require an inordinate amount of time.

Given the difficulty and challenges Validus has had in executing this study, Validus is requesting the Agency (b) (4) PMR 1487-5.

If necessary, Validus would be happy to meet with the Agency in person to further discuss the challenges in completing this study.

We request that all information in this file be treated as confidential commercial information by the Food and Drug Administration pursuant to 21 CFR §20.61, and that no information from this file be provided to any unauthorized persons without written consent from Validus.

If you have any questions regarding this submission, please do not hesitate to contact me or Richard A. Guarino, M.D., Vice President Medical Affairs at (973) 265-2777, Ext. 121, or via e-mail at rguarino@validuspharma.com.

Sincerely,

Gina Walljasper

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