MIDATECH PHARMA US INC.

8601 Six Forks Road
Suite 160 (Forum 1)
Raleigh, NC 27615

November 15, 2016

Donna Griebel, MD, Director
Division of Gastroenterology and Inborn Errors Products
Center for Drug Evaluation & Research
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: NDA 22524 ZUPLENZ (ondansetron) Oral Soluble Film
SN0060
RESPONSE TO PREA NON-COMPLIANCE LETTER dated 10/03/2016
PREA DEFERRAL EXTENSION REQUESTED

Dear Dr. Griebel:

Reference is made to NDA #22,524 approved July 2, 2010 and to submission SN0047 in which the ownership of this NDA was transferred from Galena Biopharma, Inc. to Midatech Pharma US Inc. effective January 28, 2016. Reference is also made to FDA letter dated October 3, 2016, Notification of Non-Compliance with PREA, regarding proposed study PMR 1664-2.

To the best of Midatech's understanding, there are four studies on record as PREA commitments originating with the 2010 NDA Approval, and together with the waiver/deferral requests submitted, considered, granted, or denied since 2010, the due dates for final report submissions to the NDA file are on record as follows:

Study Number	**Expected Deadline for Final Report**	**Study Title**
1664-1	January 2017	A PK and safety study to characterize the pharmacokinetics of Zuplenz (ondansetron) oral soluble film in pediatric patients ages 4 to <17 years receiving highly emetogenic chemotherapy.
1664-2	July 2016	An efficacy and safety study to characterize the pharmacokinetics of Zuplenz (ondansetron) oral soluble film in pediatric patients ages 4 to <17 years receiving highly emetogenic chemotherapy.
1664-3	September 2017	A PK and safety study to characterize the pharmacokinetics of Zuplenz (ondansetron) oral soluble film in pediatric surgical patients ages 0 to < 17 years for the prevention of postoperative nausea and vomiting in pediatric surgical patients ages 0 to <17 years.
1664-4	June 2018	An efficacy and safety study to characterize the pharmacokinetics of Zuplenz (ondansetron) oral soluble film in pediatric surgical patients ages 0 to < 17 years for the prevention of postoperative nausea and vomiting in pediatric surgical patients ages 0 to <17 years.

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As reflected in the above table for both pediatric indications, for the prevention of nausea and vomiting in patients receiving highly emetogenic chemotherapy and for prevention of postoperative nausea and vomiting, the proposed pediatric program includes an initial PK study to characterize the pharmacokinetics of Zuplenz followed by an efficacy study. It was intended that each PK study would be conducted prior to initiating each efficacy trial.

The October 3, 2016 Notification of Non-Compliance with PREA letter refers to Study 1664-2. Study 1664-2 is the study number assigned for a safety/efficacy study in pediatric patients receiving highly emetogenic chemotherapy proposed by previous NDA holders. As stated in the FDA's October 3rd letter and as shown in the above table, the final report deadline for Study 1664-2 was July 2016. However, this July 2016 efficacy report deadline is *prior* to the expected report deadline on record (January 2017) for the proposed PK study (Study 1664-1) from which the design of the 1664-2 efficacy study would be derived. Clearly, the completion date for the safety/efficacy trial should be at least several months after completion of the PK study. When Midatech assumed responsibility for NDA #22524 in January 2016, Study 1664-1 had not yet been initiated.

As the new Owner of NDA #22,524 since January 2016 and the new Sponsor of the corresponding IND # 102262 since July 2016, Midatech is thoroughly committed to investigating and considering appropriate mechanisms to address the safety and efficacy of oral ondansetron in pediatric patients. To that end, we are actively engaged in the following activities:

- Reviewing the detailed correspondence between the 4 previous NDA owners (Par/Strativa, MonoSol Rx, Vestiq Pharmaceuticals, and Galena Biopharma) and the Agency that have occurred during the past 6 years. This inherited file includes approximately 35 submissions to NDA #22,524 and IND #102,262 by the listed previous NDA owners and responses in kind by the Agency.
- Performing pharmacokinetic modeling and simulations on existing datasets in adults and pediatrics to inform a minimally-invasive and appropriate program in consideration of pediatric subjects.
    - (b) (4)
    - [redacted]
    - [redacted]
    - [redacted]
- Reviewing directly-relevant publications on the use of ondansetron in pediatrics that have recently appeared, including but not limited to:

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- For highly emetogenic chemotherapy: Kovacs et al. "Palonosetron versus ondansetron for prevention of chemotherapy-induced nausea and vomiting in paediatric patients with cancer receiving moderately or highly emetogenic chemotherapy: a randomised, phase 3, double-blind, double-dummy, non-inferiority study", Lancet Oncology,Vol. 17 (2016), pp. 332 – 344, and
- For post-operative nausea and vomiting: Shen et al., "Dexamethasone, ondansetron, and their combination and postoperative nausea and vomiting in children undergoing strabismus surgery: a meta-analysis of randomized controlled trials," Pediatric Anesthesia, Vol. 24 (2014), pp. 490 – 498.

We note that the Lancet Oncology publication appeared in the literature *after* the most recent FDA advice letter was drafted (3/10/2016) and received by the previous IND holders (MonoSol Rx, LLC); and with a phase 3, randomized, double-blind, double-dummy study design, this study carries particular weight in consideration of the plan on record.

All of these activities are highly relevant to the rationale and design of a contemporary pediatric program that will provide robust information regarding orally administered ondansetron in the pediatric population, while meeting the highest ethical standards for studies in pediatric subjects. We intend to incorporate the results of current activities into a comprehensive pediatric submission package, which will include widely accepted modeling approaches to help inform any proposed clinical investigations. As such, we will request review and input by the FDA Pharmacometrics Group at the time of the submission. An important consideration to the plan will be to minimize undue burden on pediatric subjects.

We respectfully request a deferral extension for Studies 1664-1 and 1664-2 until July 2017, by which time we will have completed the above activities and will have submitted a comprehensive package to the NDA along with a request for Pharmacometrics Group review and a Type C Meeting Request.

Midatech Pharma US Inc. is committed to working closely with the FDA to meet the highest and most ethical standards pertaining to pediatric research as owners of NDA #22,524 and we appreciate the Agency's assistance in these matters.

If you have questions or require additional information, please contact me at 919-861-0226 by telephone, 919-861-0239 by facsimile, or by e-mail at MaryKay.Delmedico@MidatechPharmaUS.com.

Sincerely,

Mary Kay Delmedico, Ph.D.
Vice President, Scientific & Regulatory Affairs

GUIDE TO FDA REVIEWERS

ELECTRONIC SUBMISSION

This application is submitted in compliance with the "*Guidance for Industry – Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*" (June 2008).

ELECTRONIC DESCRIPTION

Contents of the media: one (1) transmission through the Electronic Submissions Gateway (ESG).

VIRUS VERIFICATION

This submission is virus-free and confirmed via KasperskyAnti-Virus Support Application.

TECHNICAL POINT OF CONTACT

Irisha Johnson, Triangle Regulatory Publishing, LLC
Office(919) 415-1724
Mobile: (908) 884-3318
IJohnson@TriRegPub.com