Tralement NDA	A randomized controlled trial of Tralement versus a fixed dose manganese-free combination trace element product to evaluate manganese in patients receiving long-term parenteral nutrition.	NDA 209376 (PMR 3877-01)	06/2024 (Study Completion Date)	03/2025 (Final Report Submission to FDA)	Delayed

PMR History for Adult/Ped – PMR 3877-01:

Tralement -NDA approved on 7/2/2020 PMR 3877-01
ARI committed to conducting the following study:

- A randomized controlled trial of Tralement versus a fixed dose manganese-free combination trace element product to evaluate manganese in patients receiving long-term parenteral nutrition.
- The original timetable we submitted on June 5, 2020, to the FDA states that ARI would conduct this clinical trials according to the following schedule:
  - Draft Protocol Submission: 09/2020
  - Final Protocol Submission: 03/2021
  - Study Completion: 03/2024
  - Final Report Submission: 12/2024
- Draft protocols have been submitted to the FDA on 9/15/2020.
- General Advice letter from the FDA was received on 1/26/2021
- Based on the General advise letter a revised protocol was submitted to the FDA on 3/30/2021.
- FDA sent a second Advice information letter to ARI on 5/19/2021
- ARI submitted a revised protocol to the FDA on 9/30/2021
- FDA requested additional information on 11/29/2021
- ARI submitted a revised protocol on 12/8/2021
- FDA sent a third Advice information letter to ARI on 4/1/2022
- ARI submitted a revised protocol on 5/23/2022 and requested a revised deferral extension to the timeline for PMR 3877-01
  - Final Protocol submission: **9/2021**
  - Study Completion: **12/2026**
  - Final report Submission: **07/2027**
- FDA sent an email requesting 2 edits to the Protocols on 7/1/2022
- Final edited protocols sent to FDA on 7/8/2022
- FDA agreed to final protocols on 7/12/2022.
- Therefore, the status of the PMR is considered delayed.
- Statistical Analysis plan was submitted on 9/16/2022.
- ARI submitted a revised protocol on 03/29/2023 for TE20001 (Adult)
- ARI submitted a revised protocol on 05/03/2023 for TE20002 (Ped)
- ARI received an information request for both protocol amendments (Adult and Ped) on 05/11/23

- ARI responded to the information request for both Adult and Ped on 06/12/23
- FDA's explanation for the PMR Delay: *An Acknowledge Revised PMR/PMC Milestones (and communicate good cause) letter issued on 4/27/2021 to revise the missed Final Protocol Submission milestone. In the same letter, FDA acknowledged the applicant's anticipated delay of the Trial Completion and Final Report Submission milestones and the proposed milestones to revise the Trial Completion date to 06/2024 and Final Report Submission date to 3/2025. An Acknowledge Final Protocol letter issued 7/12/2022.*
    - Final Protocol submission: **9/2021**
    - Study Completion: **06/2024**
    - Final report Submission: **03/2025**
- ARI submitted a request to defer the original agreed upon PMR timelines on March 28, 2024. Within this request we asked FDA if it is acceptable to meet with the Agency to discuss the challenges we faced recruiting and starting the study under PMR 3877-01. ARI proposed the below timelines (note FDA has not agreed to them)
    - Our proposed revised PMR timeline is as follows:
        - Final Protocol Submission: 06/2021
        - Study Completion: **12/2026**
        - Final Report Submission: **07/2027**
- On April 12, 2024 FDA agreed that the Division Hepatology and Nutrition concurs with ARI's plan to submit a meeting request (Type C) for PMR 3877-1. The meeting background package should include a detailed discussion of the challenges encountered with enrolling the trial and the alternative approaches we are proposing for evaluating potential manganese neurotoxicity with Tralement. This information will assist the FDA Division Hepatology and Nutrition with determining whether granting the above revised milestone dates is appropriate.

Injectafer NDA	Conduct a randomized, placebo-controlled trial in pediatric patients age birth to <18 years with iron deficiency and symptomatic heart failure.	NDA 203565 (S-20) (PMR 4402-1)	June 2026 (Study Completion Date)	March 2027 (Final Report Submission to FDA)	Pending

PMR History for Injectafer (Ped) - PMR 4402-01:

Injectafer -NDA (s-020) approved on 5/31/2023 PMR 4402-1
ARI committed to conducting the following study:

- A randomized, placebo-controlled trial in pediatric patients age birth to <18 years with iron deficiency and symptomatic heart failure.
- The original timetable we submitted on August 13, 2021 in the Agreed iPSP, to the FDA states that ARI would conduct this clinical trials according to the following schedule:
    Draft Protocol Submission: 12/2022
    Final Protocol Submission: 06/2023

Study Completion: 06/2026
Final Report Submission: 03/2027

- Draft protocol was submitted on 12/06/2023
- On March 21, 2024 ARI submitted an extension of time to the PMR Regulatory Schedule. As outlined in the NDA 203565 approval letter, dated May 31, 2023, the current approved PMR timeline is provided below:
    - Final Protocol Submission: 06/2024
    - Study Completion: 06/2026
    - Final Report Submission: 03/2027
  - Our proposed revised PMR timeline is as follows:
    - Final Protocol Submission: **08/2024**
    - Study Completion: **08/2026**
    - Final Report Submission: 03/2027
- On April 1, 2024 ARI submitted a meeting request (Type C) to FDA. We requested FDA meet with ARI either via a video conference or a telephone conference to discuss the difficulties and challenges for study PMR4402-01 (Pediatric Study). We also requested the meeting to discuss our agreed upon initial Pediatric Study Plan iPSP and a submission of a full waiver in accordance with 21 CFR 201.23(c)(1)(i) for PMR4402-01 due to the impracticality of the study.