Executive Version

April 29, 2022

Adrulipase: A Reformulation (Enteric microgranule), informed by clinical trial experience, to provide optimal enteric protection and fat digestion

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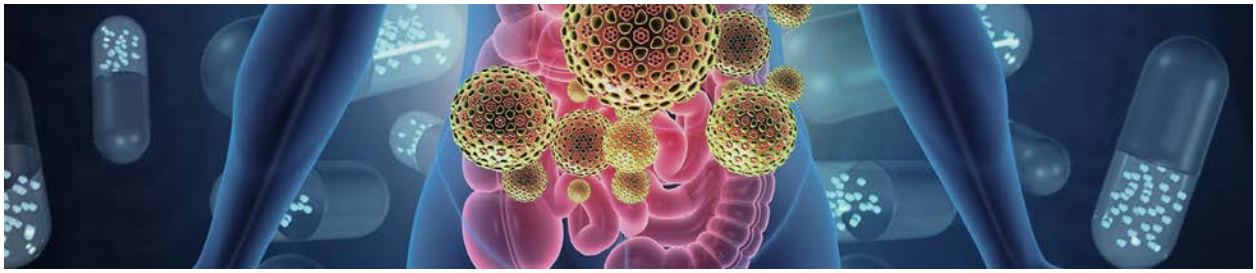


EXECUTIVE SUMMARY

First Wave BioPharma has made significant progress towards enhancing the formulation of adrulipase to overcome identified limitations of the previous formulation. The reformulation (Enteric microgranules) efforts are guided by prior clinical experience and current development efforts. The aim of the new formulation is to consistently achieve coefficient of fat absorption (CFA) values of >80% in patients with exocrine pancreatic insufficiency due to cystic fibrosis, chronic pancreatitis or other indications.

The key anticipated advantages of the new formulation are:

- Decreased daily pill burden
- Protection at low pH of stomach
- Elimination of the requirement for an enteric capsule
- Improved drug mixing with food in the stomach
- Drug exits the stomach into the duodenum[1] along with food
- Rapid release at duodenal pH to digest fats

This report outlines the status of the reformulation efforts. The development of the new formulation is progressing well and on track to initiate a proof-of-concept study in 2H-2022.

[1] First part of the small intestine, connected to stomach, largely responsible for breakdown of food by enzymes

INTRODUCTION

Adrulipase is a recombinant lipase enzyme for the treatment of exocrine pancreatic insufficiency (EPI) associated with cystic fibrosis (CF) and chronic pancreatitis (CP). Adrulipase, supplied as an oral, non-systemic, biologic capsule, is a lipase derived from *Yarrowia lipolytica* yeast that breaks up fat in the digestive tract of EPI patients so it can be absorbed.

EPI is a condition characterized by deficiency of the exocrine pancreatic enzymes (Lipase, Protease, and Amylase), resulting in a patient's inability to digest food properly, or maldigestion. The market for EPI is expected to be about $2.6 Billion by 2026. The true prevalence of EPI is unknown. However, in the U.S., there are ~30,000 patients with EPI due to CF and ~90,000 patients with EPI due to CP. The deficiency in the lipase enzyme is responsible for greasy diarrhea, fecal urge, abdominal pain, and weight loss. Ideally, a stable daily dose of pancreatic enzyme replacement therapy (PERT) will enable CF patients to eat a normal to high-fat diet and minimize unpleasant gastrointestinal symptoms while maximizing nutrient absorption.

The digestive standard of care for both CF and CP patients with EPI is commercially available PERTs that are derived from pig pancreas. Pig PERTs contain a mixture of lipase, protease, and amylase enzymes. Their supply is dependent on herd availability and thus susceptible to disruptions due to pandemic or political impacts on pig herds.

First Wave is developing adrulipase as a treatment to provide CF and CP patients with a safe and effective life-sustaining therapy to control EPI that is non-animal derived and offers the potential to dramatically reduce their daily pill burden.

COMPLETED CLINICAL TRIALS (MONOTHERAPY)

Table 1: Existing Formulation of Adrulipase Did Not Meet Expectations in Three Clinical Trials

Clinical Trial	Dose/Capsule	Adrulipase CFA
Chronic Pancreatitis	Baseline	41%
	0.3 gm IR	56%
	0.6 gm IR	52%
	1.0 gm IR	60%
	2.0 gm IR	63%
Cystic Fibrosis	2.0 gm IR	56%
	4.0 gm IR	53%
	6.0 gm IR	51%
	2.0 gm DR	66%
	4.0 gm DR	53%

The target CFA, a regulatory endpoint to estimate fat absorption, is >80%. With porcine PERTs the observed CFA in well-controlled CF patients was 83-86%. With the Immediate Release (IR) and Delayed Release enteric capsule (DR) formulations of adrulipase the average CFA was <80% across multiple clinical studies in patients with CP and CF. Based on the data, Adrulipase helped digest fat in EPI patients but not to the desired extent. The variability in responses observed (e.g., CFA range = 24% - 92% in OPTION-2) suggest a challenge with formulation and/or acid-sensitivity of adrulipase.

RATIONALE TO SUPPORT REFORMULATION

The decision to reformulate adrulipase into enteric microgranules (Compressed and ground particulates expected to be < 1mm that have an enteric polymer incorporated) was taken after a thorough review of all available clinical data, non-clinical data including in vitro and analytical experiments, with input from expert consultants.

KEY FINDINGS

Key Finding #1

The clinical data with adrulipase IR indicate that a consistent CFA>80% in all eligible patients cannot be achieved with the existing formulation (Table 1). There is a dose response observed (CP study) with doses up to 2 grams/day, however a trending loss of efficacy is observed at higher doses (Table 1).

With the DR formulation, the enteric capsules used may not have exited the stomach along with the food - i.e., the enzyme was not available at the same time as the food was emptying from the stomach into the duodenum[2].

An optimal formulation of adrulipase will be one where the drug formulation mixes with the food in the stomach. This would allow adrulipase to be present along with food in the duodenum over the entire duration of gastric emptying (Typically a 2-3 hour period) after a meal is consumed.

[2] K Ewe, A.G. Press, M Oestreicher Dtsch Med Wochenschau 117(8) pp. 287-290. (1992)

Key Finding #2

Compared to commercially available porcine PERTS, adrulipase is acid-resistant while its temperature sensitivity is comparable[3]. Adrulipase is however sensitive to prolonged exposure to acidic pH (pH<3). These data were confirmed by in vitro experiments that evaluated adrulipase activity across a range of pH and room temperature or physiological temperature (37 ℃).

Protection of adrulipase in the low pH conditions of the stomach through gastric emptying along with food is desired and a formulation that helps retain activity over a longer period at physiological temperatures is optimal to digest fats.

[3] LS- RPT-1543-Draft Report; Pace Laboratories, Woburn, MA, USA

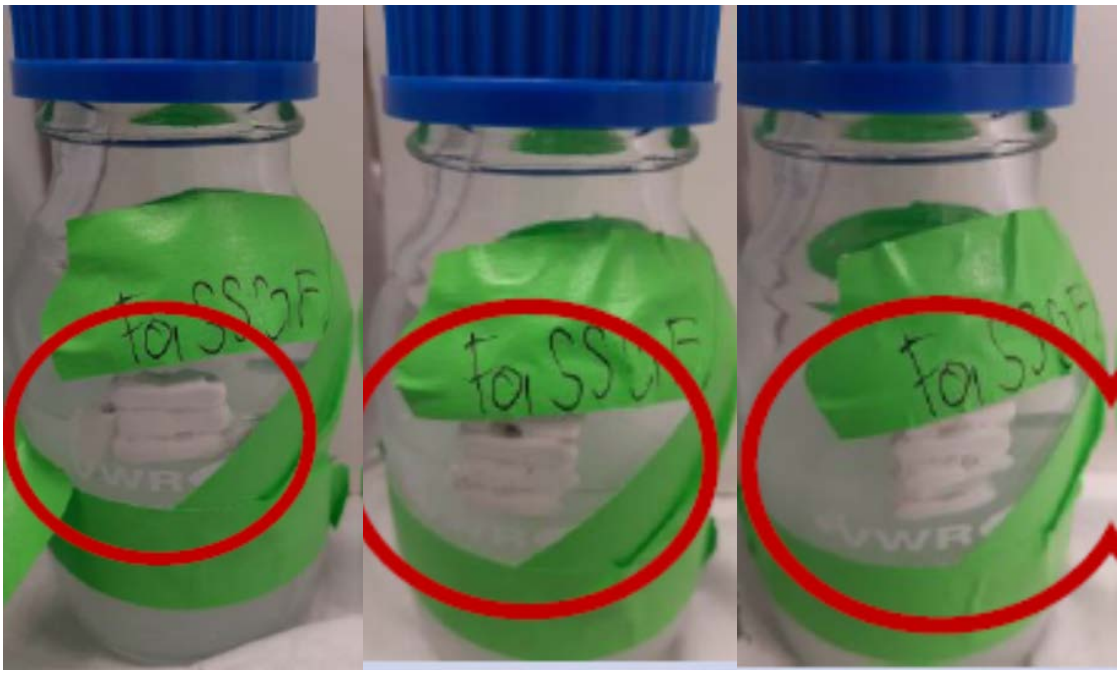
Key Finding #3

Clumping of IR capsules was observed in biorelevant simulated gastric fluid (SGF). Clumping occurs within 5 minutes and persists through the entire duration of observation of 35 minutes (Figure 1).

This may explain the potential loss of efficacy at the higher doses evaluated. In the 4 and 6 gm doses of Adrulipase IR patients took 8 and 12 capsules per meal, respectively. The clumping observed in vitro may offer a potential explanation for the lower CFA values observed; as a greater number of capsules are ingested the potential for clumping in the stomach increases, thereby inhibiting the immediate release of the lipase.

To further de-risk the next clinical study a similar experiment will be conducted on the final formulation prior to study initiation and this will inform the dosing regimen. Reformulation efforts include approaches to significantly increase drug load to potentially reduce the number of capsules required to achieve the targeted dose.

Figure 1: Clumping of IR capsules in biorelevant SGF



Seven IR capsules were placed in biorelevant SGF and observed over 35 minutes. Within 5 minutes the capsules clumped together and did not disintegrate over the entire course of observation.

CURRENT STATUS OF REFORMULATION

Efforts to Optimize Drug Load

The Drug Substance (DS) has been refined to increase the lipase load by ~2x. With this change the number of capsules required per day for all doses would reduce by at least half from the previously run clinical studies.

It is estimated that patients take approximately 18 capsules/day, on average, of the currently approved commercial PERTs. This critical change to the DS formulation has the potential both to reduce pill burden by more than 50% and to increase patient/prescriber adoption and compliance.

Protection from Acid Added to Adrulipase

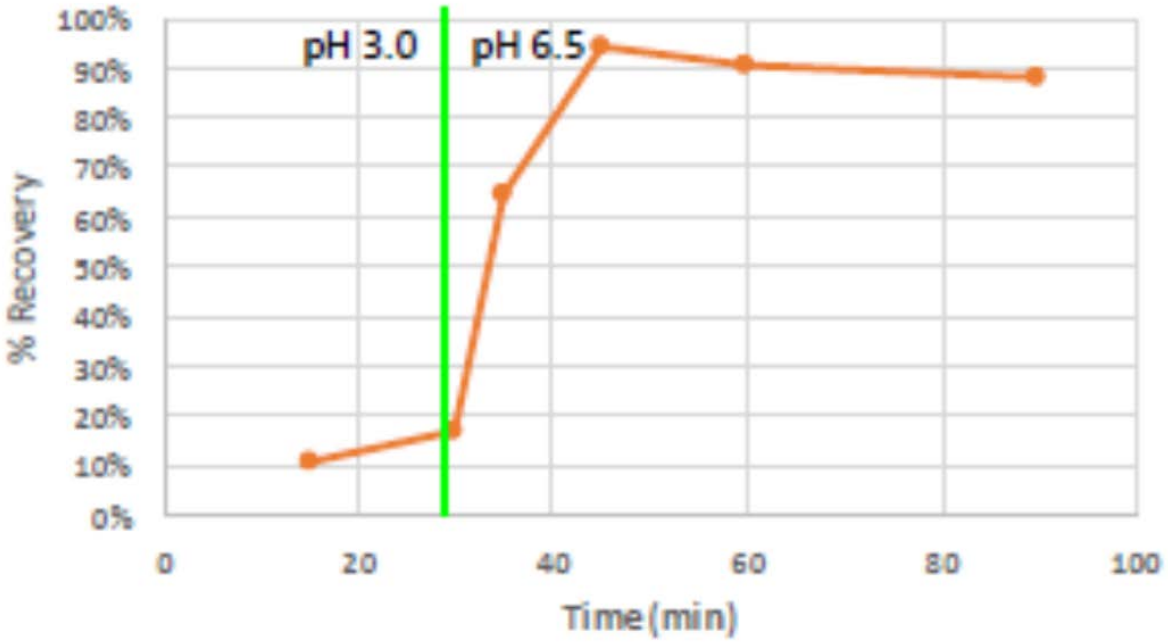
Acid protection was deemed essential to the reformulation efforts. A modification to the process has been made to incorporate an enteric polymer, which provides protection to the enzyme at low pH[3]. Several enteric polymers were evaluated and a formulation was selected with the desired properties. The selected formulation offers protection at low pH and is rapidly released at pH >5.5 (Figure 2). The size of the enteric microgranules is anticipated to be <1mm. We believe that this allows for effective drug mixing with food particles in the stomach and exiting into the duodenum for optimal digestion of fats.

The key anticipated advantages to these improvements are:

- Protection at low pH of stomach
- Elimination of the requirement for an enteric capsule
- Improved drug mixing with food in the stomach
- Formulation empties into the duodenum along with food
- Rapid release at duodenal pH to digest fats

[3] LS- RPT-1543-Draft Report; Pace Laboratories, Woburn, MA, USA

Figure 2: New Formulation Protects Adrulipase at Low Stomach pH and Rapid Release at Intestinal pH



The recovery of adrulipase in the new formulation was evaluated after sequential exposure to pH 3.0 (Mimicking gastric conditions with food) and pH 6.5 (Intestinal pH). The graph represents the % Recovery of Adrulipase over time and confirms that adrulipase was not released and therefore protected at pH<3. At pH 6.5 adrulipase is rapidly released, within 15 minutes.

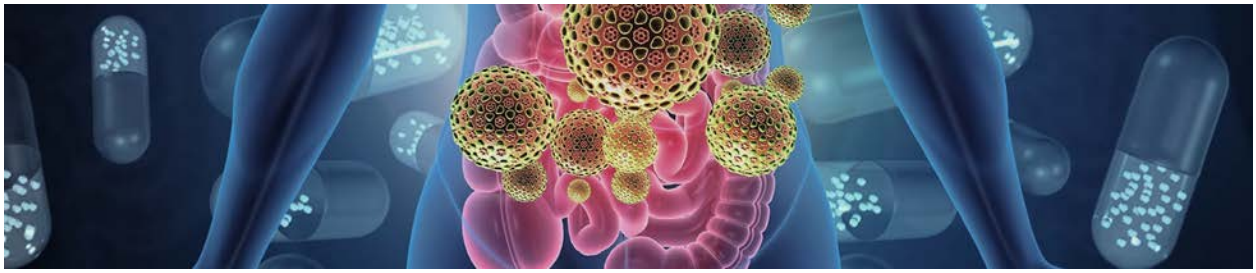
Additional Efforts

Drug Product (DP)

The ongoing efforts include optimizing the process to adequately control the final microgranulation particles to be used in a clinical study. Initial efforts confirmed that the physical characteristics of the microgranules, including particle size and hardness, play a significant role in the timing of the enteric polymer release and protection of lipase activity. Critically, initial experiments have demonstrated that lipase stability at physiological temperatures may be improved by controlling the size and hardness of the granules. Additional work will further optimize the adrulipase DP formulation that enters clinical trials.

Additional evaluations

We continue to work closely with our SAB and expert consultants to identify and evaluate additional in vitro models that may be useful.



CONCLUSION

The reformulation of adrulipase enteric microgranules continues to progress well. We are on track to have an optimal formulation that provides the anticipated advantages, has the potential to meeting the target clinical endpoint (CFA>80%), and support evaluation of this new formulation of adrulipase in a proof-of-concept clinical study in the second half of 2022.