Pooled-Analysis of Incidence and Severity of Post-Surgical Intraabdominal Adhesions following Bowel Resection Surgery and Treatment with Enteral Protease Inhibitor LB1148

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Background

Adhesion prevalence is historically reported to be >90% in patients who undergo abdominal surgery and represents a potentially significant contribution to serious complications such as small bowel obstruction, morbidity, subsequent surgery, infertility, and chronic abdominal pain. Adhesion formation has been proposed to result from an interaction of cytokines, growth factors, cell adhesion molecules, and other factors near an area of tissue perturbation during surgery. However, recent evidence suggests intestinal trauma (incisions, surgical manipulation, and hypoperfusion) can lead to a breakdown of the intestinal mucosal barrier, and subsequent translocation of digestive proteases into the intestinal tissues and visceral cavity. These digestive enzymes can cause proteolytic damage to the mesothelial surface of the viscera, which can trigger adhesion formation as part of the biological repair process to heal the damaged tissues. Currently, there are no approved oral therapeutics to prevent or reduce post-surgical adhesion formation.

LB1148 is a novel oral liquid formulation of the digestive protease inhibitor, tranexamic acid (TXA). TXA is a broad-spectrum serine protease inhibitor that exerts inhibitory activity against key digestive enzymes such as trypsin, independently from plasminogen inhibition. Inhibition of these potent digestive enzymes can reduce the damage to the mesothelial surfaces and subsequent formation of postsurgical adhesions.

Methods

This poster presents a pooled analysis of the studies LBS-IST-POI-101 and LBS-POI-201-CN which assessed the efficacy of LB1148 to reduce the formation of adhesions as an endpoint in subjects undergoing abdominal surgery who underwent a second abdominal reoperation. In both studies, adhesions were quantified at the time of surgical closure during a first surgery and at the time of opening a second surgery. LBS-IST-POI-101 (NCT04100447) is a Phase 1, single-center, open-label (single arm), study enrolling 11 subjects undergoing gastrointestinal (GI) surgery. Three patients were evaluated for adhesion formation. LBS-POI-201-CN (NCT05056935) is a Phase 2, randomized, double-blind, placebo-controlled study evaluating 120 patients to evaluate LB1148 for return of gastrointestinal function in subjects undergoing elective bowel resection (PROFILE-CN) (Figure 1). Data were pooled from the two trials and the incidence, extent and severity of adhesion for subjects treated with LB1148 or placebo were compared. Grading of the adhesions to produce an adhesion burden scale (extent and severity) was determined by the investigating surgeon using the Intra-abdominal Adhesion Extent and Severity Assessment Worksheet (Figure 2) during the second surgical procedure.

Figure 1: Study Design

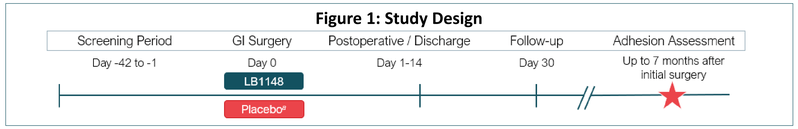


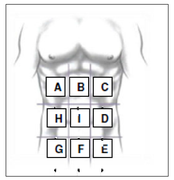
Figure 2: Intra-abdominal Adhesion Extent and Severity Assessment

Adhesion Assessment Procedure: For each abdominal region, the score of the extent and severity of adhesions are evaluated by the surgeon on Day 0 and at the time of second surgery. Intra-abdominal adhesions were graded for 9 abdominal regions A through I in Figure 2 (right upper, epigastrium, left upper, left flank, left lower, pelvis, right lower, right flank and central). (Coccolini et al., 2013)

Adhesion Severity Score
0 = no adhesions
1 = filmy thickness, avascular
2 = moderate thickness, limited vascularity
3 = dense thickness, vascularized

Adhesion Extent Score
0 = no adhesion
1 = minimal (<1/3 of the site is covered)
2 = moderate (1/3 to 2/3 of the site is covered)
3 = extensive (>2/3 of the site is covered)

Location of Abdominal Region



a = LBS-POI-201 only

Results

LB1148 Reduced Incidence of Adhesions by 72% in Patients Undergoing Bowel Resection

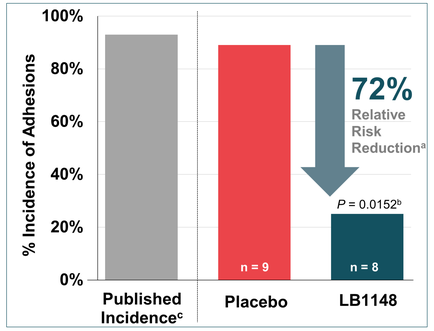


Figure 3: The results from the pooled analysis showed that 8/9 (89%) of subjects in the placebo had one or more adhesions. This incidence rate of adhesions is approximating published studies showing that up to 93% of surgery patients have post-surgical adhesions. For subjects treated with LB1148, 2/8 (25%) had adhesions observed during the second follow-up surgery, representing a relative risk reduction of 72% (*P*-value of 0.0152).

LB1148 Reduced Extent and Severity of Adhesions by 92% in Patients Undergoing Bowel Resection

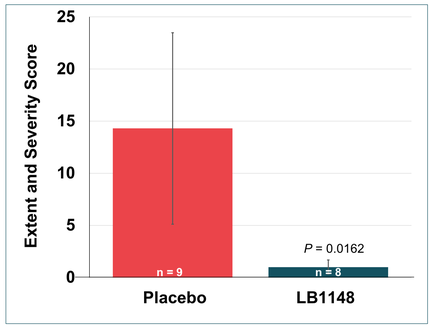


Figure 4: The mean extent and severity adhesion score in subjects who had a second surgery in the pooled analysis was 1.0 (±0.672 SEM) for LB1148 treated subjects and 14.3 1.0 (±9.19 SEM) for placebo subjects, representing reduction in the extent and severity score of 93% (*P* = 0.0162).

Demographics

	LB1148	Placebo
Patients Enrolled	8	9
Male / Female	4 / 4	7 / 2
Median Age (range)	57.5 (40-85)	59 (47-72)
Reason for Bowel Resection		
Cancer	8	9
Surgical Approach		
Laparotomy	2	0
Minimally Invasive	6	9

a = compared to placebo; *b = Fisher's exact test; c* = Ouaïssi 2011

Key Findings

- 100% of placebo-treated subjects underwent a laparoscopic procedure, and 8 of 9 had ≥ 1 adhesions
- The incidence of adhesions in the placebo group was similar to the published incidence
- 75% (6 of 8) of LB1148-treated subjects underwent a laparoscopic procedure
- LB1148 reduced the incidence of adhesions by 72%
- LB1148 reduced the extent and severity of adhesions by 92%
- No drug-related serious adverse occurred in the trials

Discussion

Although this analysis included a small number of subjects across two studies, the ability of LB1148 to reduce the incidence of adhesions provides evidence supporting further clinical advancement. The overall surgical procedural type between placebo and drug was comparable and reflects the increasing trend toward minimally invasive techniques in abdominal surgery. LB1148 treated subjects had a lower incidence of adhesion formation, a lesser extent of adhesion formation and reduced severity of adhesions that formed. These differences were improved in the LB1148 group. These data demonstrate that the differences between groups are likely due to drug treatment. Measuring the clinical sequel of adhesion formation is a prolonged process; however, measuring the extent and severity of adhesions in an abdominal adhesion burden scale may predict long term clinical outcomes.

In conclusion, the lower incidence of post-surgical intra-abdominal adhesions, and the reduction in the extent and severity of adhesions provides clear preliminary evidence of LB1148 to clinically reduce post-surgical adhesions when compared to placebo. An additional Phase 2 clinical trial is ongoing (NCT02836470).

References

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