Brilacidin for Inflammatory Bowel Disease: A Novel, Non-Corticosteroid, Non-Biologic Drug Candidate in Clinical Development

Arthur P. Bertolino, Jane A. Harness, and Leo Ehrlich
Innovation Pharmaceuticals Inc., Beverly, MA, USA

Introduction/ Background

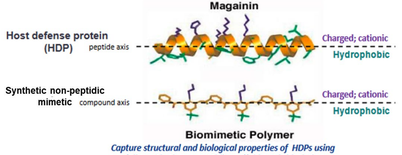
Brilacidin is being developed as a novel, non-corticosteroid, non-biologic treatment for Inflammatory Bowel Disease (IBD), with formulation development plans including oral tablets for the treatment of Ulcerative Colitis and Crohn's Disease, and foam and/or gel for the treatment of mild-to-moderate Ulcerative Proctitis/Ulcerative Proctosigmoiditis (UP/UPS), two types of IBD. Brilacidin is a fully synthetic, non-peptidic, Host Defense Protein (HDP) mimetic with a molecular weight (free base) of 936.9 g/mol.

HDPs, also referred to as defensins, isolated from organisms across the phylogenetic spectrum form part of an innate immune system and serve as the first line of defense against microbial infection in many species. HDPs are typically small (12-80 amino acids) cationic amphipathic proteins that provide protection against a wide variety of pathogenic organisms. Apart from the ability of HDPs to kill bacteria by direct action (by both membrane and non-membrane effects), they have a potential role in modulation of multiple cellular immune and inflammatory responses.

Brilacidin appears to be anti-inflammatory based largely on its inhibition of phosphodiesterases (PDE4 and PDE3) and its down regulation of pro-inflammatory cytokines. The drug candidate, which to date has been evaluated in clinical trials in three indications (serious skin infections, oral mucositis, IBD), also has antibacterial activity with a predominantly gram-positive spectrum. The current clinical study was initiated to examine efficacy, safety and PK in treatment of UP/UPS when administered locally as a retention enema.

Design Approach

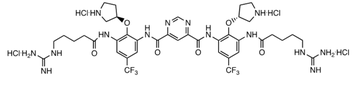
The biological activities of host defense proteins depend on an *amphiphilic helix*



Biomimetic Polymer

Capture structural and biological properties of HDPs using fully synthetic, nonpeptidic scaffolds and sidechains

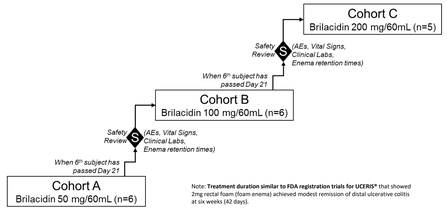
Not peptidomimetics



Molecular Wt: 1082.7 (tetrahydrochloride)
936.9 (free base)

Study Design

Study Schematic:



Note: **Treatment duration similar to FDA registration trials for UCERIS®** that showed 2mg rectal foam (foam enema) achieved modest remission of distal ulcerative colitis at six weeks (42 days).

- **Phase 2, Open Label, Dose-Escalation Trial (3 dose levels/ cohorts)**
- **Active Mild-to-Moderate Ulcerative Proctitis (UP)/Ulcerative Proctosigmoiditis (UPS)** (Treated 17 subjects)
  - Six (6) Subjects in each of Cohorts A and B (Brilacidin 50 mg and 100 mg, respectively), 5 Subjects in Cohort C (Brilacidin 200 mg)

Primary Efficacy Endpoint:

Clinical Remission at Day 42/Week 6
(defined by Modified Mayo scoring)

Endoscopy Findings [E] subscore ≤ 1

AND

Rectal Bleeding [RB] subscore = 0

AND

Stool Frequency [SF] subscore improvement or no change from baseline

Note: Brilacidin Retention Enema (60 mL; 2 oz): Once daily at bedtime for 6 weeks (42 days); with attempt to retain through the night/minimally retain for 30 (± 5) mins. Endoscopic Evaluation: Investigator assessment of rectal and sigmoid mucosa up to 40 cm from anal verge at screening and at end of treatment / Day 42 (± 3 days)

Modified Mayo Disease Activity Index (MMDAI) scoring

Score	Stool (Bowel) Frequency [SF]	Rectal Bleeding [RB]	Physician's Global Assessment [PGA]	Endoscopy Findings [E]
0	Normal number of stools per day for this subject	No blood seen	Normal	Normal or inactive disease
1	1 to 2 more stools than normal	Streaks of blood with stool less than half the time	Mild disease	Mild disease (erythema, decreased vascular pattern)
2	3 to 4 more stools than normal	Obvious blood with stool most of the time	Moderate disease	Moderate disease (marked erythema, absent vascular pattern, friability, erosions)
3	5 or more stools than normal	Blood alone passed	Severe disease	Severe disease (spontaneous bleeding, ulceration)

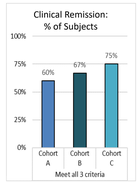
Results

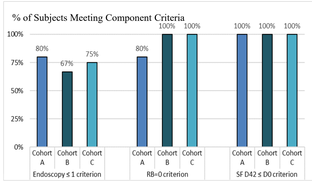
Clinical Remission in > 50% subjects (Day 42)

Similar across cohorts

- 60% Cohort A (3 of 5)
- 67% Cohort B (4 of 6)
- 75% Cohort C (3 of 4)

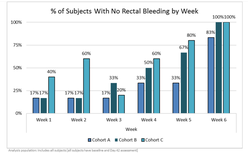
Analysis population: Includes subjects with Endoscopy, Rectal Bleeding and Stool Frequency subscores at baseline and Day 42; one subject in Cohort A and one subject in Cohort C are not included due to no Day 42 endoscopy (subjects declined)





Rectal Bleeding (RB) subscore

- Improved for all subjects, all cohorts
- No rectal bleeding (RB=0) at Day 42
  - 5 of 6 subjects Cohort A
  - All 6 subjects Cohort B
  - All 5 subjects Cohort C



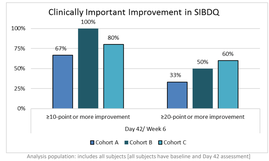
Brilacidin Concentrations (plasma) by Cohort

- Cohort A
  - All subjects <100 ng/mL
- Cohort B
  - Maximum 605 ng/mL (Average C_{max} 215 ng/mL)
- Cohort C
  - Maximum 1264 ng/mL (Average C_{max} 743 ng/mL)

Improvement in Quality-of-Life (QoL)

(reported by **16 /17 subjects** after 6 wks treatment)

- **QoL instrument**
  - Short Inflammatory Bowel Disease Questionnaire [SIBDQ]
- **10 pt change SIBDQ clinically important**
- **At Day 42**
  - **More than 60% subjects in each cohort achieved ≥10-point or more improvement**
  - At least half of subjects in cohorts B and C also showed ≥20-point or more improvement
  - >50-point improvement observed for one subject in Cohort B



Analysis population: includes all subjects [all subjects have baseline and Day 42 assessment]

Overall, good retention for a water-based enema

Most prevalent retention time category per subject highlighted in green

Incidence of Retention Times	Cohort A Brilacidin 50 mg						Cohort B Brilacidin 100 mg						Cohort C Brilacidin 200 mg					
	#990 201	#990 202	#990 204	#990 205	#990 209	#990 210	#990 103	#990 213	#990 215	#990 216	#990 217	#990 305	#990 218	#990 306	#990 308	#990 105	#990 311
< 30 min	0	6	1	1	0	0	0	0	4	3	1	0	5	7	1	0	18
≥ 30 min to < 1 h	0	5	3	0	0	16	0	33	37	30	34	0	31	3	2	3	8
≥1 h to < 4 h	10	3	11	15	13	19	5	8	1	9	7	6	6	4	16	3	1
≥4 h	32	28	27	26	29	7	37	1	0	0	0	36	0	28	23	36	14

Cohort A, majority of enemas retained by all 6 subjects for at least 1 hour or more

Cohorts B and C: 4 of 6 subjects in Cohort B, and 2 of 5 subjects in Cohort C, recorded shorter duration retention times (range 14 to 59 mins) most frequently

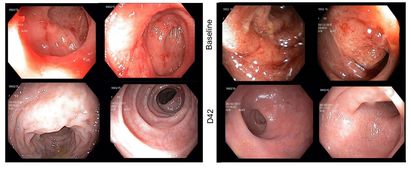
- 42 dosing enemas per subject (except Cohort C subject #990311 with 41- last enema omitted due to scheduling)
- What is recorded? Time of "Enema Evacuation or Next Stool" after enema administration. Time is recorded in patient diary for out-patient visits (from D6 to D41/42)

Safety

- **Adverse Events**
  - No Serious Adverse Events (SAEs)
  - No severe adverse events; all AEs mild or moderate severity
  - Treatment-Emergent AEs (by 8 subjects)
    - Investigator Causality: Possibly Related (1); Unlikely Related (16); Not Related (1); ∑=18
      - Possibly Related event was of abdomen pain, start/stop on Day 2, for Cohort C subject
    - None resulted in treatment withdrawal/dose change or study withdrawal
- **Clinical Laboratory Review**
  - No apparent clinically significant trends observed for blood chemistry, hematology, urinalysis
- **Vital Signs**
  - No clinically significant trends observed

Examples of Clinical Remission (Endoscopy)

Treated with Brilacidin 100 mg (Cohort B)



Subject 990216 (rectum) Subject 990215 (rectum)

Note: Baseline/ D42(After Treatment) series not necessarily identical anatomical positions

Conclusions

- **Brilacidin exhibited favorable efficacy in UP/UPS (IBD) across 3 dose-escalation cohorts (50 mg, 100 mg, 200 mg as retention enema)**
  - Proof-of-Concept achieved with current simple water formulation*
  - Clinical Remission (with endoscopic response) in at least half of subjects in each cohort
  - Improved Quality-of-Life
- **Safety data show Brilacidin well-tolerated**
- **PK demonstrates limited systemic absorption by local route of administration**

Data support Brilacidin clinical efficacy with local treatment

*Formulation development plans for Brilacidin include tablets for oral dosing of more extensive Ulcerative Colitis and Crohn's Disease and foam and/or gel for UP/UPS

Further Information

Innovation Pharmaceuticals Inc.
100 Cummings Center
Suite 151-B
Beverly, MA 01915

info@IPharmInc.com
978-921-4180

Presentation date: 13 November 2018 at IBD Innovate 2018