# CB2 Agonist, Lenabasum, for the Treatment of Pulmonary Exacerbations in Cystic Fibrosis

Chmiel, James F.;[1] Konstan, Michael;[2] Flume, Patrick;[3] VanDevanter, Donald R;[4] West, Natalie E.;[5] Scott Constantine;[6] Dgetluck, Nancy;[6] Schwartz, Brian;[6] Dinh, Quinn;[6] White, Barbara;[6] Elborn, J. Stuart[7] and the Investigators of the JBT101-CF-002 Trial. Riley Hospital for Children at IU Health, Indiana University School of Medicine, Indianapolis, IN, United States; 2. Rainbow Babies and Children's Hospital and Case Western Reserve University School of Medicine, Cleveland, OH, United States; 3. Medical University of South Carolina, Charleston, SC, United States; 4. Case Western Reserve University School of Medicine, Cleveland, OH, United States; 5. Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, Baltimore, MD, United States; 6. Corbus Pharmaceuticals Inc., Norwood, MA, United States; 7. Imperial College and Royal Brompton Hospital, London, and Queen's University, Belfast, United Kingdom

INDIANA UNIVERSITY SCHOOL OF MEDICINE

**Poster 817**

## Background

- Pulmonary exacerbations (PEx) remain a significant burden in people with CF despite current standard therapies including antibiotics (Abx) and CFTR modulators
- Lenabasum is an oral, non-immunosuppressive, cannabinoid receptor type 2 (CB2) agonist that resolves inflammation and limits fibrosis in animal and human models of disease
- Lenabasum treatment was safely administered, well-tolerated, and associated with a numerically lower rate of PEx than placebo in a prior small (N = 85), 16-week Phase 2 safety trial in adults with CF

## Objective

- Evaluate efficacy and safety of lenabasum in people with CF who are at high risk of recurrent PEx, when added to background treatment for CF

## Study Design

- 28-week double-blind parallel dose interventional trial of lenabasum 20 mg BID, lenabasum 5 mg BID, and placebo (PBO) BID with 2:1:2 randomization
- Subjects ≥ 12 years of age with documented CF
- Subjects must have 1-3 PEx in the last year treated with intravenous (IV) Abx and no Abx for PEx within 28 days of Day 1. If subjects have only 1 PEx treated with IV ABx in the last year, they must also have ≥ 1 PEx treated with oral Abx
- Randomization stratified by:
  - # PEx requiring IV Abx in last 12 months (1, 2, or 3)
  - FEV1 % predicted (< 70%, ≥ 70%)
  - Site location (US, Canada and Europe)
- 8 visits over 28 weeks, then safety follow-up 28 days later
- 447 subjects randomized at 105 sites in 21 countries

## Primary and First Secondary Endpoints

- **Primary endpoint**: PEx rate per subject per 28 weeks using primary definition of PEx, lenabasum 20 mg vs PBO
- **First secondary endpoint:** PEx rate per subject per 28 weeks using secondary definition of PEx, lenabasum 20 mg vs PBO
- **Primary definition of PEx**:
  - Physician diagnosis of PEx
  - New oral or IV Abx prescribed starting > 28 days after completion of last course of Abx for a prior PEx
  - Subject has ≥ 4/12 Fuchs criteria
- **Secondary definition of PEx:** Same except no requirement for Fuchs criteria

## Results and Summary

**Table 1. Disposition of Randomized Subjects**

| Disposition | Number (%) of Randomized Subjects: Placebo | Lenabasum 5 mg | Lenabasum 20 mg |
|---|---|---|---|
| Randomized | 181 | 91 | 175 |
| Randomized, not dosed | 10 (5.5) | 2 (2.2) | 10 (5.7) |
| Modified intent-to-treat (mITT) population | 171 (94.5) | 89 (97.8) | 165 (94.3) |
| Safety population | 171 (94.5) | 89 (97.8) | 165 (94.3) |
| Completed Study | 154 (85.1) | 85 (93.4) | 148 (84.6) |
| Discontinued study and reasons: | 27 (14.9) | 6 (6.6) | 27 (15.4) |
| Lack of efficacy - withdrawal by subject | 2 (1.1) | 2 (2.2) | 3 (1.7) |
| Physician decision - other | 1 (0.6) | 1 (1.1) | 1 (0.6) |
| Withdrawal of consent by subject | 5 (2.8) | 0 | 4 (2.3) |
| Non-compliance with study | 1 (0.6) | 0 | 2 (1.1) |
| Pregnancy | 2 (1.1) | 0 | 0 |
| Adverse event (AE) | 3 (1.7) | 1 (1.1) | 7 (4.0) |
| Other (includes subjects not dosed) | 13 (7.2) | 2 (2.2) | 10 (5.7) |

**Table 2. Baseline Characteristics, mITT population**

| Characteristic | Placebo N = 171 | Lenabasum 5 mg N = 89 | Lenabasum 20 mg N = 165 |
|---|---|---|---|
| Age, years, mean (SD) | 26.6 (10.8) | 28.9 (11.2) | 26.2 (9.1) |
| Age < 18 years, n (%) | 40 (23.3) | 13 (14.6) | 32 (19.4) |
| Female, n (%) | 93 (54.5) | 44 (49.4) | 91 (55.2) |
| Body mass index, kg/m$^2$, mean (SD) | 21.52 (3.9) | 22.26 (4.2) | 21.07 (3.2) |
| Caucasian, n (%) | 163 (95.3) | 86 (96.6) | 161 (97.6) |
| Hispanic/Latino, n (%) | 5 (2.9) | 3 (3.4) | 4 (2.4) |
| US subjects, n (%) | 54 (31.6) | 31 (34.8) | 53 (32.1) |
| Canadian, European subjects, n (%) | 117 (66.4) | 58 (65.2) | 111 (67.9) |
| CF genotype | | | |
| F508del/F508del, n (%) | 74 (43.3) | 34 (38.2) | 83 (50.3) |
| F508del/Other, n (%) | 70 (40.9) | 38 (42.7) | 56 (33.9) |
| Other/Other and unknown, n (%) | 27 (15.8) | 17 (19.1) | 26 (15.8) |
| FEV1 % predicted, mean (SD) | 61.4 (17.4) | 61.2 (18.4) | 58.7 (17.8) |
| $FEV_1$ % predicted ≥ 70%, n (%) | 46 (27.1) | 21 (25.5) | 35 (20.7) |
| $FEV_1$ % predicted < 70%, n (%) | 124 (72.9) | 65 (75.6) | 134 (79.3) |
| # PEx in last year, oral or IV ABx | | | |
| 2 | 75 (43.9) | 43 (48.3) | 75 (45.5) |
| 3 | 70 (40.9) | 30 (33.7) | 63 (38.2) |
| ≥ 4 | 25 (14.6) | 16 (18.0) | 26 (15.8) |
| Background treatments | | | |
| Azithromycin | 80 (46.8) | 42 (47.2) | 80 (48.5) |
| Other prophylactic Abx | 55 (32.2) | 40 (44.9) | 44 (26.7) |
| Dornase alfa | 150 (87.7) | 70 (78.7) | 138 (83.6) |
| CFTR modulators | 46 (26.9) | 21 (23.6) | 57 (34.5) |

- This was refractory group of subjects with significant impairment of FEV1 % predicted and ≥ 2 PEx in the last year, despite background treatment with drugs reported to reduce PEx

**Table 3. PEx Event Rates per Subject per 28 weeks**

| PEx Event Rates | Event Rate per Subject per 28 Weeks: Placebo N = 171 | Lenabasum 5 N = 89 | Lenabasum 20 N = 165 |
|---|---|---|---|
| Primary PEx definition | 0.85 | 0.76 | 0.90 |
| Primary PEx definition, IV Abx | 0.47 | 0.41 | 0.46 |
| Secondary PEx definition | 1.02 | 0.92 | 1.04 |
| Secondary PEx definition, IV Abx | 0.55 | 0.48 | 0.53 |

- No statistically significant differences between lenabasum and PBO groups
- A high proportion of PEx (~50%) were treated with IV ABx

**Table 4. Change in FEV1 % Predicted**

| Outcome | Event Rate per Subject per 28 Weeks: Placebo N = 171 | Lenabasum 5 N = 89 | Lenabasum 20 N = 165 |
|---|---|---|---|
| Baseline, mean (SD) | 61.37 (17.4) | 61.21 (18.4) | 58.67 (17.8) |
| Week 28, mean (SD) | 61.02 (18.5) | 61.18 (20.6) | 58.88 (19.5) |
| Δ FEV1 % predicted, mean (SD) | -0.09 (8.6) | -0.44 (9.3) | 0.44 (8.4) |
| LS mean difference (SE) | | -0.37 (1.1) | 0.43 (1.0) |

- No statistically significant differences between lenabasum and PBO groups
- Little change from baseline FEV1 % predicted in PBO group over 28 weeks

**Table 5. Incidence of Adverse Events (AEs)**

| Adverse Event | Event Rate per Subject per 28 Weeks, n (%): Placebo N = 171 | Lenabasum 5 N = 89 | Lenabasum 20 N = 165 |
|---|---|---|---|
| Any AE | 151 (88.3) | 80 (89.9) | 151 (91.5) |
| Serious AEs (SAEs) | 50 (29.2) | 25 (28.1) | 50 (30.3) |
| Severe AEs | 22 (12.9) | 12 (13.5) | 16 (9.7) |
| AE causing study drug withdrawal | 5 (2.9) | 2 (2.2) | 11 (6.7) |
| Deaths | 0 | 0 | 0 |

- Slightly higher rate of AEs causing study drug discontinuation in lenabasum 20 mg group

**Table 6. Non-PEx-related AEs ≥ 2% more frequent in lenabasum 20 mg than PBO groups**

| Adverse Event | Event Rate per Subject per 28 Weeks, n (%): Placebo N = 171 | Lenabasum 5 mg N = 89 | Lenabasum 20 mg N = 165 |
|---|---|---|---|
| Headache | 16 (9.4) | 11 (12.4) | 22 (13.3) |
| Fatigue | 16 (9.4) | 8 (9.0) | 20 (12.1) |
| Dizziness | 6 (3.5) | 5 (5.6) | 13 (7.9) |
| Constipation | 5 (2.9) | 2 (2.2) | 9 (5.5) |
| Dry mouth | 4 (2.3) | 2 (2.2) | 8 (4.8) |
| Night sweats | 1 (0.6) | 0 | 5 (3.0) |
| Myalgia | 0 | 2 (2.2) | 4 (2.4) |
| Cognitive disorder | 0 | 0 | 4 (2.4) |

- No new safety signals

**Table 7. Preliminary PEx Rates in PBO Group, by Geography**

| Countries | N | # PEx last yr | CFTR Rx, % | PEx rate per Subject per 28 Weeks: 1° PEX def | 1° PEX def IV ABx | 2° PEX def | 2° PEX def IV ABx |
|---|---|---|---|---|---|---|---|
| US | 54 | 2.7 | 59% | 1.12 | 0.72 | 1.28 | 0.87 |
| Other countries | 79 | 3.0 | 19% | 1.00 | 0.47 | 1.22 | 0.51 |
| 5 E. Europ. Countries | 38 | 2.5 | 0% | 0.16 | 0.14 | 0.22 | 0.16 |

5 Eastern European countries dosed 21% of all subjects in the study and reported PEx rates ~15% of those reported in other countries

**Table 8. Preliminary Post-hoc PEx Rates in Placebo Group, using Primary PEx Definition, by Baseline Characteristics**

| Characteristic, N = 133 | Rate | Characteristic, N = 133 | Rate |
|---|---|---|---|
| All | 1.05 | CFTR-modulators, n = 46 | 0.97 |
| FEV1 < 70%, n = 102 | 1.12 | No CFTR-modulators, n = 87 | 1.09 |
| FEV1 ≥ 70%-<90%, n = 23 | 0.98 | Azithromycin, n = 65 | 1.02 |
| FEV1 ≥ 90%, n = 8 | 0.39 | No azithromycin, n = 68 | 1.06 |
| 2 PEx last year, n = 56 | 0.76 | Pseudomonas in sputum, n = 82 | 1.12 |
| 3 PEx last year, n = 52 | 1.23 | Staph in sputum, n = 30 | 1.07 |
| 4-7 PEx last year, n = 24 | 1.35 | No pseudomonas or staph, n =21 | 0.81 |
| | | Inhaled prophylactic ABx, n = 72 | 0.99 |
| | | No inhal. prophylactic ABx, n= 61 | 1.12 |

Excludes subjects in 5 "low PEx rate" Eastern European countries

**Table 9. Preliminary Post-hoc PEx, by Baseline FEV1 and CFTR Modulator Use**

| Treatment | N | CFTR Modu | 1° PEX def | 1° PEX def IV ABx | 2° PEX def | 2° PEX def IV ABx |
|---|---|---|---|---|---|---|
| **FEV1 % predicted ≥ 40 to < 70%** | | | | | | |
| Placebo | 61 | | 1.21 | 0.64 | 1.45 | 0.71 |
| Lenabasum 5 mg | 31 | No | 0.80 (34% RR) | 0.47 (27% RR) | 0.84 (42% RR) | 0.49 (31% RR) |
| Lenabasum 20 mg | 49 | | 1.08 | 0.56 | 1.30 | 0.67 |
| Placebo | 30 | | 0.96 | 0.67 | 1.10 | 0.78 |
| Lenabasum 5 mg | 12 | Yes | 0.66 (31% RR) | 0.41 (39% RR) | 0.74 (33% RR) | 0.49 (37% RR) |
| Lenabasum 20 mg | 30 | | 1.05 | 0.56 | 1.22 | 0.70 |
| **FEV1 % predicted ≥ 70 to < 90%** | | | | | | |
| Placebo | 12 | | 0.74 | 0.33 | 0.91 | 0.33 |
| Lenabasum 5 mg | 8 | No | 0.36 (51% RR) | 0.36 | 0.49 (46% RR) | 0.36 |
| Lenabasum 20 mg | 17 | | 1.04 | 0.37 | 1.28 | 0.43 |
| Placebo | 11 | | 1.24 | 0.35 | 1.42 | 0.44 |
| Lenabasum 5 mg | 6 | Yes | 1.01 | 0.17 (51% RR) | 1.01 (29% RR) | 0.17 (61% RR) |
| Lenabasum 20 mg | 10 | | 0.60 (52% RR) | 0.24 (31% RR) | 0.71 (50% RR) | 0.24 (45% RR) |

- Excludes subjects in 5 "low PEx rate" Eastern European countries
- RR = relative reduction in PEx rate compared to PBO PEx rate

## Conclusions

- This is the first Phase 3 trial to target the endocannabinoid system as a non-immunosuppressive, anti-inflammatory treatment for people with CF and recurrent PEx
- The primary efficacy endpoint was not met
- Enrolled subjects were a refractory group of CF patients, with low baseline FEV1% predicted (~60%) and 2-7 total PEx in the previous year, despite intensive background treatment with drugs to reduce PEx, such as CFTR-modulators, azithromycin, prophylactic antibiotics, and dornase alfa
- Subjects in the PBO group had the expected clinical course, with increasing rates of PEx as FEV1% predicted decreased, numbers of PEx in the previous year increased, and treatment with CFTR-modulators was not given
- Subjects in 5 Eastern European countries had unexpectedly low PEx rates, ~15% that in other countries. This low rate may reflect differences in what physicians in various geographies call a PEx or would treat with Abx, or may reflect improvement in care or background treatment compliance with monthly visits after enrollment
- Including subjects from countries except these 5, the overall rate of PEx in the PBO group was 1.09 in subjects not receiving CFTR modulators and 0.97 in subjects receiving them, indicating that high unmet medical need remains for additional treatments to lessen recurrent PEx in refractory subjects with multiple PEx in the prior year
- Post-hoc analyses in subjects with similar FEV1% predicted at baseline and similar treatment with CFTR-modulators suggested evidence of clinical benefit of lenabasum
- Lenabasum was administered safely in this study, was well tolerated, and its overall safety profile remains unchanged

## Thank You


- The people with CF who participated in this study
- Trial investigators and study staff at sites
- Leadership of the Cystic Fibrosis Foundation and the Cystic Fibrosis Foundation Therapeutics Development Network
- Members of the Steering Committee
- Members of the Data Monitoring Committee


## Disclosures


- Dr. Chmiel reports grants from Corbus Pharmaceuticals and grants from Cystic Fibrosis Foundation during the conduct of the study; and grants and personal fees from Cystic Fibrosis Foundation, grants from NIH, personal fees from American Board of Pediatrics outside the submitted work
- This study was sponsored by Corbus Pharmaceuticals, Inc. and funded in part by the Cystic Fibrosis Foundation


Presented at the North American Cystic Foundation Conference, October 7-23, 2020