A Randomized, Double-Blind, Placebo Controlled, Multicenter Phase 2a Study to Assess Safety, Daily Respiratory Symptoms, Pharmacokinetics, and Biomarker Variations after Administration of either YPL-001, or Placebo in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease

G.J. Criner[1], M. T. Dransfield[2], S. Arora[3], T. J. Rogers[4], J.F. Pritchard[5], C. Engel[6], J. Batonga[6], F. Vickers[5], Y. Lee[7], J. Yoo[7], S. Lew[7], F. A. Fakih[8]

[1]Thoracic Surgery and Medicine, Temple Univ, Philadelphia, PA, United States, [2]Univ of Alabama Birmingham & Birmingham VA Med Ctr, Birmingham, AL, United States, [3]Aventiv Research, Columbus, OH, United States, [4]CILR, Temple UnivSch of Med, Philadelphia, PA, United States, [5]Celerion, Inc, Lincoln, NE, United States, [6]Celerion, Inc., Montreal, QC, Canada, [7]Yungjin Pharm. CO., LTD., Seoul, Korea, [8]Florida Pulmonary Consultants & Sleep Disorder Cen, Winter Park, FL, United States

Background

YPL-001 is an oral dosage form of the extract from the plant Speedwell used in traditional Asian medicine to treat respiratory inflammatory diseases including chronic obstructive pulmonary disease (COPD). This botanical drug product is a mixture of 5 identified active iridoids and other related compounds. Biological activity is considered to be from the mixture and not from one component.

Preclinical Results:

- YPL-001 inhibited neutrophil accumulation in bronchoalveolar lavage (BAL) fluid and several pro-inflammatory cytokines and chemokines (including interleukin [IL]- 8) and activated the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) anti-oxidative pathway.
- YPL-001 may down-regulate neutrophil influx and production of tumor necrosis factor alpha (TNF-α), IL-1β IL-6, chemokine ligand-1 (CXCL-1), and macrophage inflammatory protein-2 (MIP-2).

Phase 1 Results:

- YPL-001 was well tolerated in healthy subjects following single (up to 320 mg) and multiple (up to 240 mg twice daily [BID]) oral doses with no serious adverse events (AEs).
- Verproside and picroside II, the main active iridoids of YPL-001, are rapidly absorbed and cleared rapidly from plasma, with mean $t_{1/2}$ <2.5 hours.

Objectives and Hypothesis

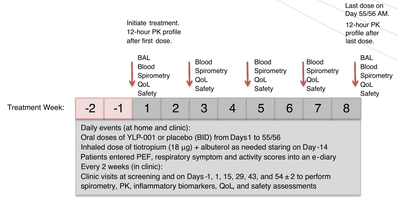
The primary and secondary objectives were to assess safety, tolerability, and the number and magnitude of respiratory symptoms of 2 oral doses of YPL-001 versus placebo administered for 8 weeks in moderate to severe COPD patients.

Hypothesis: YPL-001 will improve respiratory symptoms in patients without any significant AEs.

Exploratory objectives were to assess BAL and blood inflammatory biomarkers, spirometry measurements, quality of life (QoL) scores, and verproside and picroside II pharmacokinetic (PK) plasma profiles after YPL-001 BID.

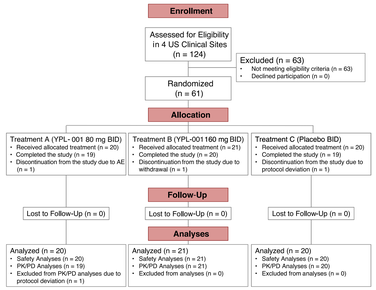
Methods

Study Timeline:



- Patients were adult males and females with moderate to severe COPD (conform to the severity classification for Global Initiative for Chronic Obstructive Lung Disease [GOLD] Stage 2-3) with a predominant bronchitic component.
- Safety assessments included physical examinations, vital signs, pulse oximetry, electrocardiograms (ECGs), laboratory tests, and AEs.
- Assessment of respiratory symptoms was performed daily through patient self-reported peak expiratory flow (PEF), major (estimated sputum quality and quantity) and minor (cough, wheeze, sore throat, nasal congestion, nasal discharge, and body temperature above 100°F) symptoms of COPD exacerbation, dyspnea (Modified Borg Dyspnea Scale scores), and activity (Duke Activity Status Index [DASI]) using an electronic diary (e-diary). Patients with significant respiratory distress were defined as having weekly mean COPD Symptom Scores ≥2 as captured from each patient in their e-diary.
- Spirometry measurements (forced expiratory volume in one second [FEV_1], forced vital capacity [FVC], FEV_1/FVC, and inspiratory capacity [IC]), QoL assessments (Baseline Dyspnea Index [BDI]/Transition Dyspnea Index [TDI], COPD Assessment Test [CAT]), and blood samples for inflammatory biomarkers were collected every 2 weeks.
- Serial blood samples were collected for 12 hours following the first and last dose for PK assessment of verproside and picroside II.
- BAL samples were also collected prior to and after 8 weeks of treatment to assess inflammatory biomarkers.
- Data were summarized using descriptive statistics or frequency counts for qualitative data. Within-treatment comparisons were performed for each treatment on change from baseline data using the Wilcoxon Signed Rank test. Between-treatment comparisons (active versus placebo) on change from baseline data were performed using the Wilcoxon Rank Sum test. p-values (within and between) were presented along with descriptive statistics. Change was considered significant when p<0.05.

Study Population:



Demographics:

Trait	Category/Statistics	Treatment A YPL -001 80 mg	Treatment B YPL-001 160 mg	Treatment C Placebo	Total
Sex	Female	6 (40%)	8 (38%)	9 (45%)	25 (41%)
	Male	12 (60%)	13 (62%)	11 (55%)	36 (59%)
Primary Race	Black or African American	5 (25%)	6 (29%)	5 (25%)	16 (26%)
	White	15 (75%)	15 (71%)	15 (75%)	45 (74%)
Ethnicity	Hispanic or Latino	1 (5%)	0 (0%)	0 (0%)	1 (2%)
	Not Hispanic or Latino	19 (95%)	21 (100%)	20 (100%)	60 (98%)
Age at Dosing (yrs)	Mean	60.4	65.7	61.7	62.6
	SD	6.50	8.66	7.95	7.98
Weight (kg)	Mean	85.62	81.39	75.08	80.71
	SD	15.342	16.089	12.246	15.069
Height (cm)	Mean	173.9	170.7	169.9	171.5
	SD	9.04	11.28	11.72	10.71
BMI (kg/m²)	Mean	28.34	27.77	26.19	27.44
	SD	4.759	3.838	4.711	4.465
Smoking Status	Current Smokers	10 (50%)	11 (52%)	9 (45%)	30 (49%)
	Former Smokers	10 (50%)	10 (48%)	11 (55%)	31 (51%)

Treatment A: Multiple oral doses of YPL-001 80 mg BID on Days 1 – 55 and QD on Day 56 AM
Treatment B: Multiple oral doses of YPL-001 160 mg BID on Days 1 - 55 and QD on Day 56 AM
Treatment C: Multiple oral doses of placebo BID on Days 1- 55 and QD on Day 56 AM

BMI: Body Mass Index

Results

All 61 subjects were included in the safety analyses and there were 60 subjects included in PK, PD and symptom monitoring analyses.

Primary Objective:

- There were no discernable treatment-related or time-related trends in the laboratory, vital sign (including pulse oximetry), ECG, or physical examination assessments.
- 55 AEs were reported in 52% of patients overall (50% of patients in the YPL-001 80 mg group, 38% in the YPL-001 160 mg group, and 70% in the placebo group).

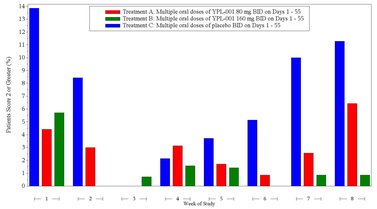
Respiratory Adverse Events*	Treatment A YPL -001 80 mg	Treatment B YPL -001 160 mg	Treatment C Placebo	Total
Other COPD related AEs including Exacerbation	3 (15%)	2 (10%)	5 (25%)	10 (16%)
Cough	0 (0%)	2 (10%)	5 (25%)	7 (11%)
Oropharyngeal pain	1 (5%)	0 (0%)	1 (5%)	2 (3%)
Dyspnea	1 (5%)	0 (0%)	0 (0%)	1 (2%)
Rhinitis allergic	0 (0%)	0 (0%)	1 (5%)	1 (2%)
Rhinorrhea	0 (0%)	0 (0%)	1 (5%)	1 (2%)
Bronchitis	1 (5%)	0 (0%)	1 (5%)	2 (3%)
Upper respiratory tract infection	0 (0%)	0 (0%)	2 (10%)	2 (3%)
Bronchopneumonia	1 (5%)	0 (0%)	0 (0%)	1 (2%)

Treatment A: Multiple oral doses of YPL-001 80 mg BID on Days 1- 55 and QD on Day 56 AM
Treatment B: Multiple oral doses of YPL-001 160 mg BID on Days 1 - 55 and QD on Day 56 AM
Treatment C: Multiple oral doses of placebo BID on Days 1- 55 and QD on Day 56 AM
*Adverse events are coded using MedDRA Version 18.0

Secondary Objective:

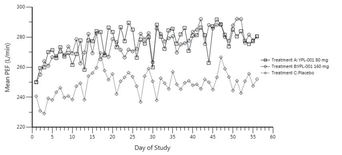
- There was a dose-related trend in reduction in the percentage of patients with weekly mean scores of 2 or greater, consistent with an effect of YPL-001 treatment on reducing the incidence of respiratory exacerbations.

Percent Patients with Mean COPD Symptom Scores of ≥ 2 Following Multiple Oral YPL-001 Doses of 80 and 160 mg and Placebo



- Mean daily PEF values in patients receiving YPL-001 increased from 250-255 L/min at baseline to 278-283 L/min following 8 weeks of treatment whereas patients who received placebo saw a difference of less than 3%, from 241 L/min to 248 L/min.

Mean PEF Recorded Versus Time Following Multiple Oral YPL-001 Doses of 80 and 160 mg and Placebo

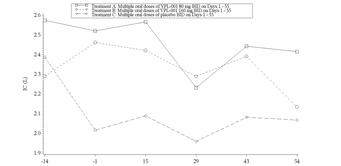


- There were no discernable treatment differences in dyspnea (Modified Borg Dyspnea Scale) and activity (DASI) scores.

Exploratory Objectives

- Spirometry: Despite no apparent treatment-related changes in FEV_1, FVC, and FEV_1/FVC there was a possible treatment-related effect of YPL-001 on increasing IC over the 8-week treatment period.

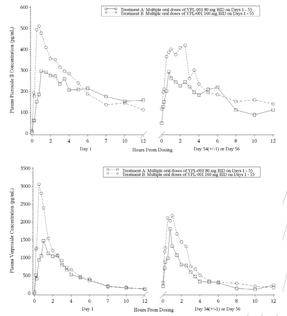
Mean IC Pre-Bronchodilator versus Time Following Multiple Oral YPL-001 Doses of 80 and 160 mg and Placebo



- QoL assessments (BDI/TDI and CAT) were unchanged except for small improvements in chest tightness scores following administration of 80 mg YPL-001.
- BAL and plasma inflammatory biomarkers concentrations were highly variable throughout the study. There were no treatment related differences in BAL biomarkers.
- For IL-8 and MCP-1, the plasma inflammatory biomarkers increase from baseline appeared to be reduced following 80 mg and/or 160 mg YPL-001 administration.

Pharmacokinetics: verproside and picroside II exposure was consistent with previous studies. PK was similar to that observed in healthy subjects with quick absorption and rapid elimination ($t_{1/2}$ < 2.5 hours after both doses). Exposure appeared to be non-linear and no significant accumulation was observed after multiple doses.

Verproside and Picroside II Concentrations Following Single (Day 1) and Multiple (Day 54±2) Doses of YPL-001 80 or 160 mg



Summary

- Oral doses of YPL-001 were safe and well tolerated in patients with moderate to severe COPD.
- YPL-001 may reduce respiratory exacerbations associated with COPD by improving maximum ventilatory capacity as indicated by a 10-15% treatment-associated increase in PEF and improvements in inspiratory capacity. The increase in PEF would be considered clinically relevant in COPD patients.
- Other spirometry results established that YPL-001 is not a bronchodilator nor does it interfere with the effects of albuterol. This indicates that YPL-001 could be used in conjunction with albuterol without compromising bronchodilation.
- YPL-001 did not appear to have any major effects on inflammatory cells and biomarkers of inflammatory response in either BAL, blood, or plasma. Any mild effects of YPL- 001 on these parameters could be easily lost in the large inter-subject variability among many of the measures collected in this study.

Conclusion

Observed data are consistent with the historical use of this herbal product in traditional Asian medicine for treatment of inflammatory diseases of the respiratory tract including COPD and provide a basis to consider future studies at higher doses and longer duration.

Clinical Research supported by Yungjin Pharm. CO., LTD., Seoul Korea