Single and Multiple Dose Pharmacokinetics of YPL-001, a Novel Botanical Drug Product in Development for the Treatment of Respiratory Inflammatory Diseases.

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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. Current long term control medications for the treatment of COPD include corticosteroids, cromolyn sodium, immunomodulators, long acting beta agonists, methylxanthines, and leukotriene modifiers. YPL-001 belongs most closely with the leukotriene modifier class of drug.

Preclinical Results:

- YPL-001 was well tolerated in a panel of standard animal toxicology studies.
- Based on NOAEL values of 180 mg/kg/day and 1000 mg/kg/day established in rats and dogs, respectively, in 4-week repeated dose oral toxicology studies, the human equivalent doses were calculated to be 28.8 mg/kg and 540 mg/kg, respectively (i.e., 2016 mg and 37800 mg, respectively based on a 70 kg human).
- After oral administration of YPL-001 at 12.5, 25, and 50 mg/kg doses (5.225, 10.45, and 20.9 mg/kg as verproside) to rats, verproside was rapidly absorbed. AUC and Cmax of verproside increased linearly with YPL-001 dose. Other parameters of verproside were also comparable among the three oral doses studied, indicating that the pharmacokinetic (PK) parameters of verproside were independent of doses.
- 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).

Rationale

Assess single-dose and multiple-dose PK of verproside and picroside II, 2 of the active iridoids components of YPL-001, in healthy subjects and in COPD patients to allow recommendations on dose levels and dosing intervals in future studies.

Methods

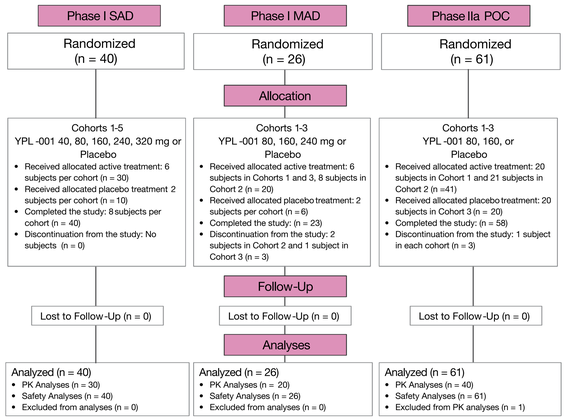
Study Design:

Study Design	Single ascending dose (SAD)	Multiple ascending dose (MAD)	Proof of Concept (POC)
Population	Healthy Subjects	Healthy Subjects	COPD Patients
Dose	Cohort 1: 40 mg YPL-001 or Placebo	Cohort 1: 80 mg YPL-001 BID or Placebo	Cohort 1: 80 mg YPL-001 BID
	Cohort 2: 80 mg or Placebo	Cohort 2: 160 mg YPL-001 BID or Placebo	Cohort 2: 160 mg YPL-001 BID
	Cohort 3: 160 mg or Placebo	Cohort 3: 240 mg YPL-001 BID or Placebo	Cohort 3: Placebo BID
	Cohort 4: 240 mg or Placebo		
	Cohort 5 : 320 mg or Placebo		
Dosing regimen	Single doses under fasting conditions with Cohort 3 subjects crossing over to fed conditions after a 14day washout	Multiple doses under fasting conditions administered from Day 1 through Day 14	Multiple doses under fasting conditions administered from Day 1 through Day 55/56
Study Assessments	Safety PK (Day 1)	Safety PK (Days 1 and 14)	Safety PK (Days 1 and 55/56)

BID: twice a day (every 12 hours)

- Healthy adult male and female subjects were enrolled in the SAD and MAD studies.
- Adult male and female patients 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 were enrolled in the POC study.
- Safety assessments included physical examinations, vital signs, pulse oximetry, electrocardiograms (ECGs), laboratory tests, and adverse events (AEs). Additionally, in the POC study, assessment of respiratory symptoms was performed daily.
- Serial blood and urine samples were collected for 72 hours postdose in the SAD study for PK assessment of verproside only.
- Serial blood samples were collected for at least 12 hours following the first and last dose in the MAD and POC studies for PK assessment of verproside and picroside II.
- Statistical assessment of dose proportionality for the verproside and picroside II PK parameters AUC and Cmax were explored using the Power Model in the MAD and SAD studies.
- Food-effect in the SAD study was assessed using analyses of variance performed on the ln-transformed AUC and Cmax for verproside.

Study Population:

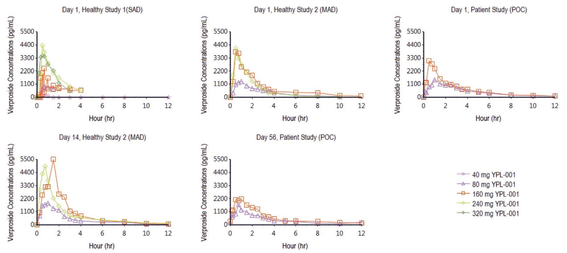


Results

Verproside and Picroside II Pharmacokinetics:

- Verproside and picroside II plasma PK were characterized by rapid absorption (Tmax $\leq$ 1 hour) and rapid oral clearance (t1/2 < 2.5 hours) over single doses up to 320 mg and multiple doses up to 240 mg BID of YPL 001 under fasting conditions.
- Verproside and picroside II exposure increased in a dose-dependent manner following single doses up to 240 mg and following multiple doses up to 160 mg BID. No further increase in exposure at higher doses was observed.
- Following multiple doses of YPL-001, modest accumulation of verproside and picroside II was observed.
- Exposure in patients was similar to healthy subjects.
- Following single-dose administration under fed conditions a 44-58% decrease in verproside exposure was observed.
- A high inter-subject variability was observed in plasma concentrations and PK parameters for both compounds.
- Urine verproside concentrations were negligible.

Verproside Concentrations Following Single and Multiple Doses of YPL-001 40 to 320 mg



VERPROSIDE SINGLE-DOSE PK PARAMETERS (Mean ± SD)

DAY 1

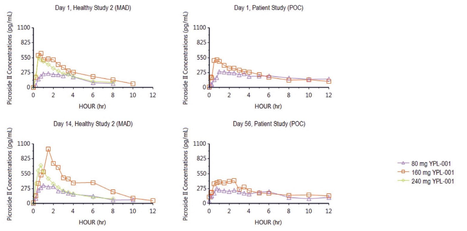
Study	SAD					MAD			POC	
Dose Level	40 mg N=1	80 mg N=6	160 mg N=6	240 mg N=6	320 mg N=6	80 mg N=6	160 mg N=8	240 mg N=6	80 mg N=18	160 mg N=20
AUC_{0-t} (pg*hr/mL)	742	752 ± 381	2561 ± 1795	5457 ± 5016	5361 ± 867	3232 ± 2869	8021 ± 5801	6673 ± 4479	4566 ± 4290	6936 ± 5931
AUC_{0-inf} (pg*hr/mL)	.	.	3805 ± 1824	8220 ± 5333	6216 ± 778	3348 ± 2917	8300 ± 6348	6833 ± 4478	5963 ± 5096	7452 ± 6462
C_{max} (pg/mL)	1190	1140 ± 328	2900 ± 1760	4780 ± 5660	4490 ± 1440	1599 ±757	4875 ± 2820	4265 ± 2354	2135 ± 1449.5	3573 ± 2822
T_{max} (hr)*	0.4969	0.668 (0.52, 1.00)	0.507 (0.33, 0.67)	0.5867 (0.35, 1.50)	0.5057 (0.35, 1.50)	0.875 (0.50, 2.50)	0.502 (0.30, 1.50)	0.503 (0.50, 1.00)	0.875 (0.17, 4.00)	0.750 (0.25, 4.00)
$t_{½}$ (hr)	.	.	0.68 ± 0.263	0.92 ± 0.176	0.71 ± 0.100	1.12 ± 0.493	1.31 ± 0.473	1.36 ± 0.146	1.71 ± 0.662	1.69 ± 0.658

VERPROSIDE MULTIPLE-DOSE PK PARAMETERS (Mean ± SD)

		DAY 14			DAY 56	
		N=6	N=8	N=6	N=17	N=20
AUC_{0-t} (pg*hr/mL)		4596 ± 4127	10770 ± 11489	9566 ± 9298	4178 ± 4558	6918± 5686
AUCtau(pg*hr/mL)		4709 ± 4080	10860 ± 11424	9658 ± 9246	4374 ± 4646	6977 ± 5644
C_{max_ss} (pg/mL)		2414 ± 1281	6737 ± 7342	5458 ± 4387	2228 ± 2332	2888 ± 2221
T_{max_ss} (hr)*		0.756 (0.252, 2.00)	0.759 (0.329, 1.50)	0.528 (0.272, 0.751)	0.750 (0.17, 3.00)	0.750 (0.25, 2.00)
RAUC		1.59 ± 0.557	1.55 ± 0.878	1.52 ± 0.464	1.31 ± 1.211	1.31 ± 1.138

. = Value missing or not reportable
* = T_{max} is presented as median (minimum, maximum)

Picroside II Concentrations Following Single and Multiple Doses of YPL-001 80 to 240 mg



PICROSIDE II SINGLE-DOSE PK PARAMETERS (Mean ± SD)

DAY 1

Study	MAD			POC	
Dose Level	80 mg N=6	160 mg N=8	240 mg N=6	80 mg N=16	160 mg N=20
AUC_{0-t} (pg*hr/mL)	850 ± 877	2212 ± 1801	1548 ± 1119	1431± 1658	2078± 1889
AUC_{0-inf} (pg*hr/mL)	1973± 918	2960± 1726	1907± 1170	2375± 2403	2351± 2082
C_{max} (pg/mL)	305± 210	842± 526	624± 333	411± 324	618± 543
T_{max} (hr)*	0.875 (0.499, 2.50)	0.626 (0.303, 2.03)	0.753 (0.501, 2.50)	1.000 (0.17, 5.00)	0.625 (0.25, 5.00)
$t_{½}$ (hr)	1.81± 0.588	1.68± 0.298	1.59± 0.577	2.177 ± 0.8656	2.221 ± 0.9263

PICROSIDE II MULTIPLE-DOSE PK PARAMETERS (Mean ± SD)

	DAY 14			DAY 56	
	N=6	N=6	N=5	N=16	N=20
AUC_{0-t} (pg*hr/mL)	1124± 1044	3024± 3877	1804± 949	1207± 1433	1949± 1858
AUCtau(pg*hr/mL)	2556± 599	4287± 4369	1985± 1024	1517± 1496	2432± 1810
C_{max_ss} (pg/mL)	419± 240	1116± 1391	751± 490	370± 341	491± 337
T_{max_ss} (hr)*	0.756 (0.252, 2.00)	0.759 (0.329, 1.50)	0.748 (0.524, 0.751)	0.750 (0.17, 3.50)	1.000 (0.17, 2.00)
RAUC	1.39± 0.325	1.57± 1.01	1.54± 0.440	1.094 ± 0.67100	1.085 ± 0.81768

* = T_{max} is presented as median (minimum, maximum)

Safety:

- All AEs observed in healthy subjects were mild to moderate and the majority were unlikely related or unrelated to treatment.
- In the POC study, 52% of patients experienced AEs, with the majority of these following placebo.

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

- There was a dose-related reduction in the percentage of COPD patients with weekly mean COPD symptom scores ≥ 2 in patients receiving YPL-001 compared to placebo.

Summary

- Verproside and picroside II exposure appeared to increase in a dose-dependent manner until the 240 mg BID dose level, after which no further increases in exposure were observed suggesting capacity-limited absorption.
- The 240 mg dose of YPL-001 is expected to contain amounts of identified compounds relative to those observed in traditional Chinese medicine.

Amount (mg) of Identified Compounds in YPL-001 in Proposed Clinical Dose Versus Traditional Chinese Medicine Use

Identified Compounds in YPL-001	1.40 g (Single Dose) Traditional Chinese Medicine	2.80 g/d (Divided Dose) Traditional Chinese Medicine[a]	240 mg (Single Dose) in Clinical Study[b]
Verproside	47.94	95.88	86.88- 91.92
Veratric acid	2.10	4.20	3.24 - 6.24
Catalpolside	3.43	6.86	10.08 - 10.38
Picroside II	3.77	7.54	11.76- 12.24
Isovanilloyl catalpol	3.53	7.06	12.78- 14.16
6-O-veratroyl catalpol	7.88	15.76	10.86 -16.44
Total (mg)	68.65	137.30	142.5 - 144.48

[a]Traditional medicine dosage from Chinese Medical Great Dictionary, Zhong Yao Da Ci Dian.
[b]Extrapolations based on batch analyses of a 40 mg dose

Conclusion

Multiple doses of YPL-001 up to 240 mg BID in healthy subjects and multiple doses of YPL-001 up to 160 mg BID in patients with moderate to severe COPD were safe and well tolerated. Beneficial therapeutic effects seen in patients were consistent with traditional use in Asian medicine. The PK profiles of verproside and picroside II and the beneficial therapeutic effects observed in the POC study provide a basis for future studies of longer duration at doses up to 240 mg BID.

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