LP-001, a novel long-acting and most cost-effective EPO in CKD anemia

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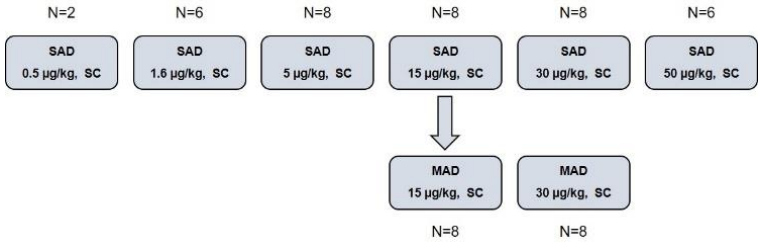
Methods

- Anemia is one of the most common and morbid complications in chronic kidney disease (CKD), and is associated with a reduced quality of life, and an increased morbidity and mortality. The prevalence of anemia raised with the progression of CKD: 8.4% at stage 1 to 53.4% at stage 5 in US.
- Erythropoiesis-stimulating agent (ESA) was a major advance that led to widespread improvement in anemia and to a reduction in the need for blood transfusion. In addition, numerous studies have indicated that ESA therapy results in an improvement in the patient's quality of life.
- Annual direct costs associated with CKD management rose upon progression from stage G3a to G5. Mean annual costs per patient of hemodialysis is $57,334, while of peritoneal dialysis is $49,490.
- Thus, a cost-effective ESA that target primary prevention and disease progression are essential to reduce the economical burden.

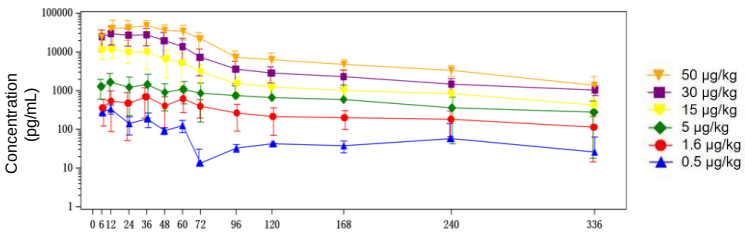
Methods

- Materials: UT-7 cell lines was purchased from Cobioer Biosciences (Nanjing, China). 32D cell lines was produced in-house. Epoetin alfa and Darbepoetin alfa were purchased from Kyowa Kirin Co., Ltd. (Tokyo, Japan). Carboplatin was purchased from Qilu Pharmaceutical Co., Ltd. (Shandong, China). Crl:CD (SD) rats were purchased from Beijing Vital River Laboratory Animal Technology Co., Ltd.(Beijing, China) .
- After 24 hours of starvation, LP-001, epoetin alpha, and nesp were added to 32D cells and UT-7 cells, respectively. After 3 days, the proliferation of 32D cells and UT-7 cells was detected using CCK-8 assay kit.
- Carboplatin induced anemia test in rats, cyclophosphamide induced anemia in cynomolgus monkeys: 45 mg/kg carboplatin and 90 mg/kg cyclophosphamide were administered to rats and cynomolgus monkeys respectively. Then NESP® (2 μg/kg) and different concentration of LP-001 were administrated.The erythropoiesis effect was observed and compared in 2 μg/kg NESP® group with LP-001 groups
- A randomized, double-blind, single-ascending-dose Phase I clinical study (CTR20222179/ NCT06294275) was conducted. 38 healthy subjects were randomly divided into six groups to receive a single subcutaneous dose of 0.5 μg/kg, 1.6 μg/kg, 5 μg/kg, 15 μg/kg, 30 μg/kg and 50 μg/kg respectively. 16 healthy subjects were randomly divided into six groups to receive a multiple subcutaneous dose of 15 μg/kg and 30 μg/kg respectively. Safety, pharmacokinetics, and pharmacodynamics (reticulocyte count) profile was evaluated.

Phase I Clinical study scheme



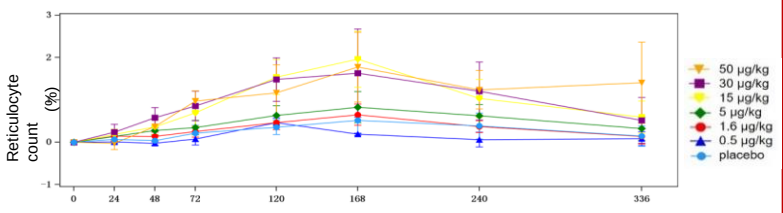
PK profile of single S.C. injection of LP-001 in healthy subjects



PK parameters

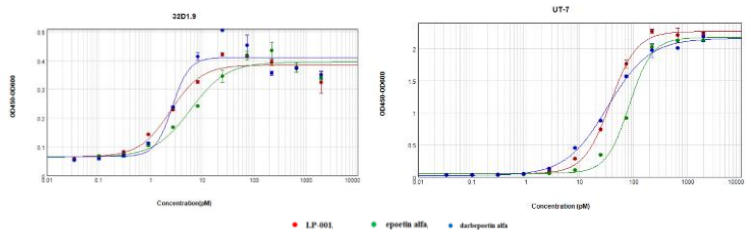
	1.6 μg/kg (N=6)	5 μg/kg (N=8)	15 μg/kg (N=8)	30 μg/kg (N=8)	50 μg/kg (N=6)
C_{max} (pg/mL)	782.7±485.1	2191.9±1207.9	13137.1±6433.6	32074.8±14704.5	50677.2±21426.6
AUC_{0-t} (h*pg/mL)	87194.463±29348.370	213956.448±152259.030	848183.213±335085.232	2102178.098±869758.012	3850839.333±1240802.310
$t_{1/2}$(h)	65.795±27.344 (about 2.7 days)	92.830±49.328 (about 3.9 days)	107.242±20.717 (about 4.5 days)	104.672±8.269 (about 4.4 days)	90.763±34.464 (about 3.8 days)

PD profile (reticulocyte count), Safety and ADA



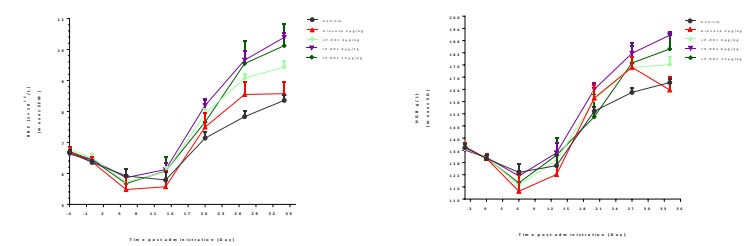
LP-001 appears to show good safety profile. Only one Grade 3 TEAE was reported (blood creatine kinase increased) that was unrelated to LP-001 by clinical evaluation.
Non subjects was found to have ADA during the study.

In parallele comparison of the different EPOs on proliferation of 32D and UT-7 cell lines

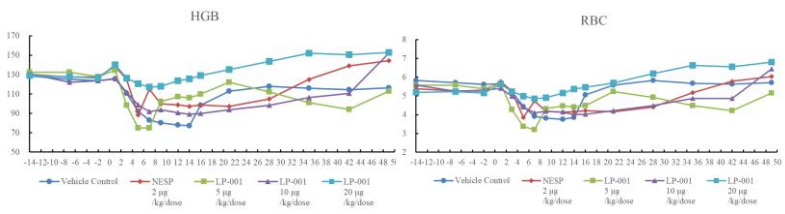


	LP-001	epoetin alfa	darbepoetin alfa
32D	2.433 pM（0.265 ng/mL）	5.924 pM（0.181 ng/mL）	2.623 pM（0.097 ng/mL）
UT-7	37.14 pM（4.048 ng/mL）	82.87 pM（2.536 ng/mL）	32.85 pM（1.215 ng/mL）

LP-001 and NESP® in a carboplatin induced anemia in rats



LP-001 and NESP® in Cyclophosphamide Induced Anemia in Cynomolgus Monkeys



Conclusion

- LP-001 has a bioactivity comparable to Aranesp in both cell based assay (UT-7) and in-vivo animal models (normal SD rats, carboplatin induced anemia in SD rats and with cyclophosphamide induced anemia in cynomolgus monkey.
- In SAD of phase I study, LP-001 exhibited a non-linear PK characteristic with T1/2 ranging from 65.8 hrs to 107hrs, which is comparable to Aranesp. No ADA and grade 3 or above AE were observed.
- The pre-clinical and phase I study of LP-001 suggests that this novel long-acting EPO has a comparable glycosylation form and half-life to Aranesp. Moreover, it can improve the EPO level more smoothly therefore renders a potential safer and cost-effective ESA that might be alternative for CKD treatment.