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# Pharmacokinetics of LBPT and its primary metabolites, as well as tolerability in the first-in-human study

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ABSTRACT

*Background:* LBPT is a novel platelet-activating factor (PAF) receptor antagonist that is developed for the treatment of rheumatoid arthritis. The purpose of this first-in-human study was to evaluate the tolerability and safety of LBPT, to investigate the pharmacokinetics of LBPT and its primary metabolites, as well as to assess the food effect on the pharmacokinetics in healthy Chinese subjects.

*Materials and Methods:* LBPT was evaluated in 2 clinical studies. The first study was a double blind, placebo-controlled and ascending dose study. Eighty-five healthy Chinese subjects received oral dose of 2, 4, 6, 8, 15, 25, 50, 75, 100, 125, 150, 225, 300, 400 or 500 mg of LBPT or placebo. The pharmacokinetics of LBPT and its primary metabolites were investigated in the last 4 dose cohorts. The tolerability was evaluated by monitoring adverse events (AEs), physical examinations, 12-lead electrocardiograms (ECG) and laboratory tests. The second study was an open-label, 2-period cross-over study with a washout interval of 3 days. Twelve subjects received 300 mg of LBPT after an overnight fasting or a high-fat breakfast. The pharmacokinetics of LBPT in subjects under fasted and fed conditions were compared.

*Results:* LBPT was well tolerated up to 500 mg-dose and there were no serious AEs in the study. The incidence and severity of AEs were closely related to dose. Following single oral administration of 225, 300, 400 and 500 mg of LBPT, plasma $C_{max}$ was reached at 0.5 h and the mean $t_{1/2}$ was 0.6–1.6 h. Plasma exposure increased with dose escalation but proportionality was not observed. LBPT was eliminated in forms of metabolites and 20–40% of the given dose was recovered in urine. Compared with the subjects under fasting conditions, AUC and $C_{max}$ were lower and $t_{max}$ was delayed in the fed subjects.

*Conclusion:* LBPT was well tolerated in healthy subjects with a pattern of dose-related AEs. The pharmacokinetics was non-linear and was impacted by food intake.



## 1. Introduction

Rheumatoid arthritis (RA) is a chronic and generally progressive autoimmune disease that causes functional disability, significant pain and joint destruction (Choi et al., 2002; Gabriel, 2001). This disease is ranked as the 42nd highest contributor to global disability of the 291 conditions studied, just below malaria and above iodine deficiency (Cross et al., 2014). It is estimated to affect 0.5–1.0% of the population worldwide and increases in prevalence with age (Alamanos et al., 2006; Chopra and Abdel-Nasser, 2008). Only disease-modifying antirheumatic drugs can interfere with the disease process (Smolen et al., 2007). In the past few years, new target therapies interfering with B cells, T cells, interleukin-6 receptor and the tumor necrosis factor (TNF) have revolutionized the treatment of RA with impressive clinical benefits (Edwards et al., 2004; Ehrenstein et al., 2004; Baslund et al., 2005; Fischer et al., 2015). However, not all patients respond, or patients who exhibited an initial response may lose response due to the development of anti-drug antibodies (Smolen et al., 2007). There is still uncertainty as to how long the available anti-rheumatic biologicals can be continuously employed as RA therapies (Isaacs, 2009; Manadan and Block, 2008). Therefore new agents are urgently needed for the treatment of RA.

Platelet-activating factor (PAF, 1-*O*-alkyl-2-*sn*-glycero-3-phosphocholine) is a polar phospholipids mediator that is released from a variety of inflammatory cells (Zimmerman et al., 1990; Ishii and Shimizu, 2000). PAF regulates the function of a variety of cells in the peripheral tissues and in the nervous system by acting as both inter- and intracellular mediators. Its cellular effects are mainly mediated by a heterotrimeric G-coupled protein receptor (Zhu et al., 2006; Wang et al., 1994; Golino et al., 1993). Apart from its potent ability to platelet activation, PAF plays critical roles in allergic and inflammatory reactions at different pathological conditions (Edwards and Constantinescu, 2009;

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Pałgan and Bartuzi, 2015; Kasperska-Zajac et al., 2008; Tsuda et al., 2011). The involvements of PAF in critical inflammatory events such as neutrophil chemo attraction and nociception, strongly suggest the potential of PAF receptors pathway in the treatment of inflammatory diseases (Pałgan and Bartuzi, 2015; Tsuda et al., 2011; Palacios et al., 1999; Guerrero et al., 2013).

LBPT, (*E*)-ethyl 1-(5-(4-chlorophenyl)-3-oxopent-4-enyl) piperidine-4-carboxylate, is a first-in-class PAF receptor antagonist developed by Institute of Materia Medica of Chinese Academy of Medical Sciences (Beijing, China). Preclinical studies showed that LBPT produced significant activity of anti-inflammation and gastric mucosa protecting property in animals with acute, chronic or immune-mediated inflammation (Supplementary Data). These pre-clinical studies included inhibition effect on mouse croton oil ear inflammation, carrageenan-induced rat granuloma and paw swelling, cotton pellet granuloma in rats, as well as rat adjuvant-induced arthritis. Besides, in rats with collagen type II arthritis, significant relief of inflammation in soft tissue around the middle of the joint was observed through X-ray and pathological examination. Moreover, LBPT exhibited comparable or even better anti-inflammation effect in all the animal studies compared with naproxen and diclofenac sodium. Of note, at variance with diclofenac sodium, LBPT also provided favorable gastric mucosa protecting activity in the alcohol and indomethacin induced gastric ulcer rat models. With regard to LBPT metabolism and excretion, a preclinical study identified five primary metabolites in rat plasma and urine: oxidized, reduced and de-ethyl metabolites (Fig. 1). Excretion studies indicated that parent LBPT was not observed in urine, however the accumulated urine excretion of the five metabolites accounted for 79.7 ± 8.75% of the given dose.

Currently LBPT is being evaluated in Phase II trials for the treatment of RA in China. The present studies were designed to evaluate the tolerability and safety of LBPT, to characterize the pharmacokinetics of LBPT and its primary metabolites, to investigate the impact of food on the pharmacokinetics in heathy Chinese volunteers.

## 2. Material and Methods

### 2.1. Chemicals and Drugs

Chemical standards of LBPT and its five metabolites (Fig. 1) were provided by Institute of Materia Medica, Chinese Academy of Medical Sciences (Beijing, China). Acetonitrile and methanol of HPLC grade were purchased from Honeywell Burdick& Jackson (Muskegon, MI, USA). Ammonium formate was purchased from Sigma-Aldrich chemicals (St. Louis, MO, USA). HPLC grade water was prepared using a Milli Q system. LBPT tablets (2, 15, 25, 50 and 100 mg/tablet) and placebo tablets were provided by the Institute of Material Medica, Chinese Academy of Medical Sciences (Beijing, China).

### 2.2. Subjects

This study was conducted in accordance with Good Clinical Practice regulations, the ethical principles stated in the Declaration of Helsinki and other applicable regulatory requirements. This study was registered at Center for Drug Evaluation (CDE) of China Food Drug Administration (CFDA) (No. 2008L03753). Approval of the study was obtained from the Ethical Committee of the Peking Union Medical College Hospital (Beijing, China) prior to subject enrollment. All the subjects provided written informed consent after the nature of the study was fully explained.

The subjects were enrolled based on the following inclusion criteria: men and women of Han Chinese ethnicity between 18 and 40 years of age with a body mass index of 19 to 25 kg/m$^2$; no evidence of clinically significant abnormalities in cardiac, hepatic, renal, pulmonary, neurological, gastrointestinal, hematological and psychiatric function as determined by medical history, physical examination and laboratory screens. Pregnant and lactating women were excluded from the study. Female subjects were required to be surgically incapable of pregnancy, or practice effective double-barrier birth control methods. Exclusion criteria included a history of allergy to drugs; participation in a clinical drug study or blood donation within a period of 3 months; positive test results for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV); positive for drugs of abuse; a history of alcohol abuse.

### 2.3. Study Design

LBPT was evaluated in two phase I clinical studies. The first study (study 1) was a double blind, placebo-controlled, parallel and dose escalation study designed characterize the safety, tolerability and pharmacokinetics of LBPT and its metabolites in healthy Chinese subjects. This study consisted of 3 phases: the screening phase (14 days prior to the first dose), a treatment phase (3 days) and the safety follow-up phase (7 days after completion of the last dose). Eighty-five eligible Chinese subjects were enrolled and randomized to one of the treatment groups using a computer-generated randomization schedule (Table 1). The subjects received single doses of 2, 4, 6, 8, 15, 25, 50, 75, 100, 125, 150, 225, 300, 400 or 500 mg of LBPT tablets or placebo with 200 mL of water at 8:00 after an overnight fasting (at least 10 h). The maximum recommended starting dose (MRSD) for this study was selected to be 10-fold lower than the human equivalent dose (HED) calculated from

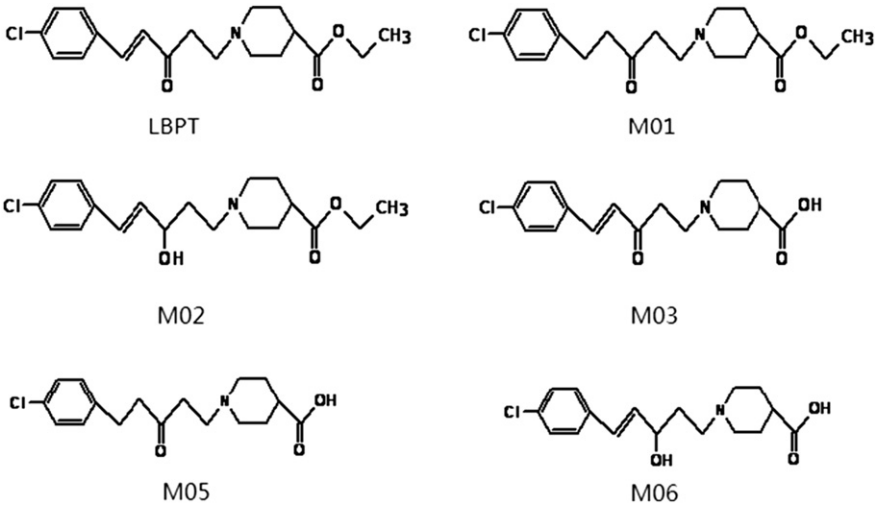


**Fig. 1.** Chemical structures of LBPT and its five major metabolites: M01, M02, M03, M05, M06.