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CLINICAL TRIAL REPORT

# A Randomized, Double-Blind, Parallel-Group Phase I Study Comparing the Pharmacokinetics, Safety, and Immunogenicity of CMAB015, a Candidate Secukinumab Biosimilar, with Its Reference Product Cosentyx® in Healthy Chinese Male Subjects

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**Purpose:** Secukinumab, a monoclonal antibody targeting interleukin (IL)-17A, is approved for the treatment of psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, enthesitis-related arthritis, and hidradenitis suppurativa. This study compared the pharmacokinetics (PK), safety, and immunogenicity of CMAB015, a candidate secukinumab biosimilar, with the reference product secukinumab (Cosentyx®) in healthy Chinese male subjects.

**Patients and methods:** This double-blind, parallel-group study randomized healthy Chinese male subjects (N=130) to receive either a single dose of 150 mg CMAB015 or secukinumab subcutaneously. Primary study endpoints were PK parameters such as the maximum concentration ($C_{max}$) and area under the curve from zero to infinity ($AUC_{0\text{-}inf}$), while safety and immunogenicity were secondary endpoints.

**Results:** The 90% confidence intervals (CIs) of the geometric mean ratios (GMRs) of $C_{max}$ and $AUC_{0\text{-}inf}$ for CMAB015 to secukinumab were all within the bioequivalence limits (80.00–125.00%). Other PK parameters were comparable between the groups. The safety profile of CMAB015 was similar to that of secukinumab, with no serious adverse events related to treatment. The incidence of TEAEs was slightly higher in the CMAB015 group, but these events were mild to moderate in severity and did not lead to any withdrawals from the study. Immunogenicity analysis revealed low rates of anti-drug antibody (ADA) positivity, with similar rates between CMAB015 and secukinumab.

**Conclusion:** This study demonstrated equivalent PK, comparable safety, and immunogenicity of CMAB015 to secukinumab in healthy Chinese male subjects. These findings support further clinical evaluation of CMAB015 as a secukinumab biosimilar.

**Trial Registration:** The trial was registered on Clinicaltrials.gov (Identifier No. NCT05734482) and Chinadrugtrials.org.cn (Identifier No. CTR20230105).

**Keywords:** CMAB015, secukinumab, biosimilar, pharmacokinetics, safety, immunogenicity

## Introduction

Interleukin-17A (IL-17A) is a pro-inflammatory cytokine belonging to the IL-17 family, known for its pivotal role in orchestrating inflammatory and immune responses.[1,2] Developed by Novartis, secukinumab is a fully human monoclonal antibody that specifically targets and neutralizes IL-17A, thereby interrupting the inflammatory cascade driven by this cytokine.[3] The efficacy and safety of secukinumab have been well established in clinical trials, leading to its approval for



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the treatment of psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis, enthesitis-related arthritis, and hidradenitis suppurativa.[4–8] In particular, Phase III clinical trials have demonstrated the effectiveness of secukinumab in Chinese patients with moderate to severe plaque psoriasis, highlighting its potential as a valuable treatment option in this population.[9] Since its initial approval in Japan in December 2014, secukinumab has received regulatory approval in numerous countries, including the United States and the European Union, underscoring its global significance in the management of IL-17A-driven diseases.[10]

The emergence of biosimilars offers a promising avenue for expanding access to effective biologic therapies while addressing cost considerations. A biosimilar is a biological product that is highly similar to an approved originator or reference product, with no clinically meaningful differences in safety, purity, or potency.[11] Biosimilars have the potential to increase treatment options for patients and healthcare providers, offering a more affordable alternative to costly biologic therapies.[12] The development and approval of biosimilars follow a well-regulated process in many countries. The European Medicines Agency (EMA), the US Food and Drug Administration (FDA), and the World Health Organization (WHO) have all developed guidelines outlining the scientific considerations for biosimilar development and evaluation.

CMAB015 is one of the first biosimilars of secukinumab, which developed by Taizhou Mabtech Pharmaceutical Co. LTD. It shares the same primary structure as secukinumab (Cosentyx®), with 1344 amino acid residues. Its light chain (κ chain) comprises 215 amino acid residues, and its heavy chain (γ-ammonia chain) comprises 457 amino acid residues, resulting in a molecular weight of approximately 151 kDa. Other quality attributes, such as high-order structure and bioactivity, are also similar to secukinumab. In particular, preclinical studies have shown that CMAB015 exhibits comparable pharmacodynamics, pharmacokinetics (PK), and safety profiles to secukinumab.

In alignment with regulatory guidelines set forth by the National Medical Products Administration (NMPA), the EMA, and the US FDA, this phase I study was designed to assess the PK characteristics, safety, and immunogenicity of CMAB015 compared to secukinumab. By demonstrating the biosimilarity of CMAB015 to secukinumab, this study aims to provide valuable insights into the potential clinical utility of CMAB015 as a biosimilar of secukinumab.

# Methods

## Ethics and Trial Registration

This clinical study adhered to the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and local regulatory requirements. Prior to enrollment, all subjects provided written informed consent. The final protocol, any amendments, and informed consent documents were reviewed and approved by the Institutional Review Board of the Second Hospital of Anhui Medical University. The trial was registered on Clinicaltrials.gov (Identifier No. NCT05734482) and Chinadrugtrials.org.cn (Identifier No. CTR20230105).

## Study Population

Healthy Chinese male volunteers aged 18 to 45 years, weighing between ≥ 50 kg and ≤ 75 kg, with a body mass index (BMI) of ≥ 18 and < 28 kg/m$^2$ were eligible for the enrollment. All subjects were required to have no abnormalities or clinical significance in vital signs, physical examination, electrocardiogram (ECG), chest radiography, abdominal B ultrasound, blood routine, urine routine, blood biochemistry, etc. The main exclusion criteria included any prior or current presence of clinically significant diseases, current presence of active infection, prior or current presence of inflammatory bowel disease, a history of malignant tumors within the last 5 years (except completely resected basal cell or squamous cell carcinoma in situ), a history of allergy to anti-IL-17 antibody active ingredients, excipients, or latex, and previous exposure to anti-IL-17 antibody therapy.

## Study Design

The study was a randomized, double-blind, parallel-controlled, single-dose study conducted at the Second Hospital of Anhui Medical University. Assuming a coefficient of variation (CV) within the subjects of 32% and a geometric mean ratio (GMR) of CMAB015 to secukinumab of 0.95, 65 male subjects were enrolled in each group (130 male subjects in

total) to achieve 90% power at a 5% significance level by two one-sided tests, considering a dropout rate of 10%. Subjects completed screening within 14 days prior to drug administration, and observations were made for 112 days after drug administration. All eligible subjects were randomly assigned in a 1:1 ratio to the treatment group (CMAB015) or control group (secukinumab). 65 subjects in each group were given a single subcutaneous injection of 150 mg CMAB015 or secukinumab in the upper arm, respectively, according to the grouping.

## Pharmacokinetic Evaluations

PK parameters were calculated using Phoenix WinNonlin Version 8.3.5 to accurately reflect drug metabolism in the human body. Non-compartmental analysis (NCA) was employed based on the individual blood concentration and actual sampling time to calculate PK parameters. The primary PK parameters maximum concentration ($C_{max}$) and area under the curve from zero to infinity ($AUC_{0\text{-}inf}$) were compared between the treatment group (CMAB015) and control group (secukinumab). The secondary PK parameters included area under the curve from time 0 to the last measured ($AUC_{0\text{-}t}$), time to maximum concentration ($T_{max}$), terminal half-life ($t_{½}$), terminal rate constant ($\lambda_z$), systemic clearance (CL/F), and apparent volume of distribution ($V_d$/F) were also evaluated.

Blood samples for PK evaluation were collected at pre-dose (within 1 h before dosing), and at 24 h (D2 ± 1 h), 48 h (D3 ± 1 h), 72 h (D4 ± 2 h), 96 h (D5 ± 2 h), 120 h (D6 ± 2 h), 144 h (D7 ± 2 h), 168 h (D8 ± 2 h), 192 h (D9 ± 2 h), 336 h (D15 ± 8 h), 672 h (D29 ± 24 h), 1008 h (D43 ± 48 h), 1344 h (D57 ± 48 h), 1680 h (D71 ± 48 h), 2016 h (D85 ± 72 h), 2352 h (D99 ± 72 h) and 2688 h (D113 ± 72 h) following the study drug administration. Blood (3 mL) was collected at each time point, and the serum concentration of CMAB015 or secukinumab was analyzed by enzyme-linked immunosorbent assay (ELISA) at United-Power Pharma Tech (Tianjin) Co., Ltd.

## Immunogenicity Evaluations

Immunogenicity was assessed by comparing CMAB015 and secukinumab. Blood samples were collected for immunogenicity evaluation at pre-dose and at 336 h (D15 ± 8 h), 672 h (D29 ± 24 h), 1344 h (D57 ± 48 h), and 2688 h (D113 ± 72 h) following drug administration. Samples positive for anti-drug antibodies (ADA) were further tested for the presence of neutralizing antibodies (Nabs), and the titers of positive ADA samples were evaluated. ADA and Nabs in human serum were identified using a Meso Scale Diagnostics (MSD) bridging-electrochemiluminescent immunoassay (ECLIA) at United-Power Pharma Tech (Tianjin) Co., Ltd.

## Safety Assessments

Safety assessments included monitoring adverse events (AEs), vital signs, physical examinations, clinical laboratory tests, 12-lead ECGs, and injection site reactions. All AEs were coded using MedDRA Version 25.1 and summarized by system organ class (SOC) and preferred term (PT). The severity of AEs was graded according to the common terminology criteria for adverse events (CTCAE V5.0).

## Statistical Analyses Method

Bioequivalence between CMAB015 and secukinumab was determined if the 90% CIs of GMRs for primary PK parameters ($C_{max}$ and $AUC_{0\text{-}inf}$) fell within the range of 80.00%-125.00%. Statistical analyses were conducted using an analysis of variance (ANOVA) model on the logarithmic scale. Other statistical tests were performed using SAS® 9.4 (SAS Institute Inc., Cary, NC, USA). A similarity test of $AUC_{0\text{-}t}$ was performed similar to the primary endpoint, and the nonparametric Wilcoxon rank-sum tests were used for $T_{max}$, $t_{1/2}$, $\lambda_z$, CL/F, and Vd/F. A significance level of $P < 0.05$ was considered statistically significant unless otherwise stated. Safety and anti-drug antibody data sets were used for safety and immunogenicity evaluations, respectively.

# Results

## Subject Disposition, Demographic and Baseline Characteristics

A total of 300 subjects were screened, with 130 successfully passing the screening and 170 failing. The primary reasons for screening failures were that 165 subjects did not meet the inclusion criteria or met the exclusion criteria, and 5 subjects were excluded for other reasons. Following screening, 130 eligible healthy male subjects were enrolled and randomized: 65 to the CMAB015 group and 65 to the secukinumab group. However, 4 subjects in the CMAB015 group did not complete the study due to unforeseen factors (Figure 1). All 130 subjects were included in the analysis of baseline demographic data. In the CMAB015 group, 61 subjects were Han Chinese, and 4 were from other ethnic groups, with a mean age (SD) of 29.8 (6.74) years, mean weight (SD) of 64.64 (5.996) kg, mean height (SD) of 171.76 (6.324) cm, and mean BMI (SD) of 21.97 (2.424) kg/m.$^2$ In the secukinumab group, all healthy male subjects were Han Chinese, with a mean age (SD) of 29.1 (6.75) years, mean weight (SD) of 64.22 (6.065) kg, mean height (SD) of 171.42 (4.697) cm, and mean BMI (SD) of 21.87 (2.066) kg/m$^2$ (Table 1). Baseline characteristics were comparable between the CMAB015 and secukinumab groups.

## Pharmacokinetic Evaluations

Based on the summary data of serum concentration at each scheduled blood collection time point, the mean serum concentration-time profiles of CMAB015 and secukinumab were similar throughout the entire sampling period following a single subcutaneous injection (Figure 2). Primary and secondary PK parameters were comparable between the two groups (Table 2). The GMRs for CMAB015/secukinumab of $C_{max}$ and $AUC_{0\text{-}inf}$ in the study were 104.05% and 95.70%, respectively. The 90% CIs of GMRs for CMAB015/secukinumab of $C_{max}$, $AUC_{0\text{-}inf}$ and $AUC_{0\text{-}t}$ were all within the predefined bioequivalence margin of 80.00–125.00% (Table 3). Additionally, as shown in Table 4, there were no significant differences in secondary PK parameters $T_{max}$, $t_{½}$, $\lambda_z$, CL/F, and $V_d$/F between the CMAB015 group and the secukinumab group ($P > 0.05$).

## Safety Evaluations

All AEs that occurred throughout the study were summarized in Table 5. A total of 101 (77.7%) subjects experienced 246 AEs, all of which were treatment-emergent adverse events (TEAEs). Among these, 88 (67.7%) subjects experienced 199

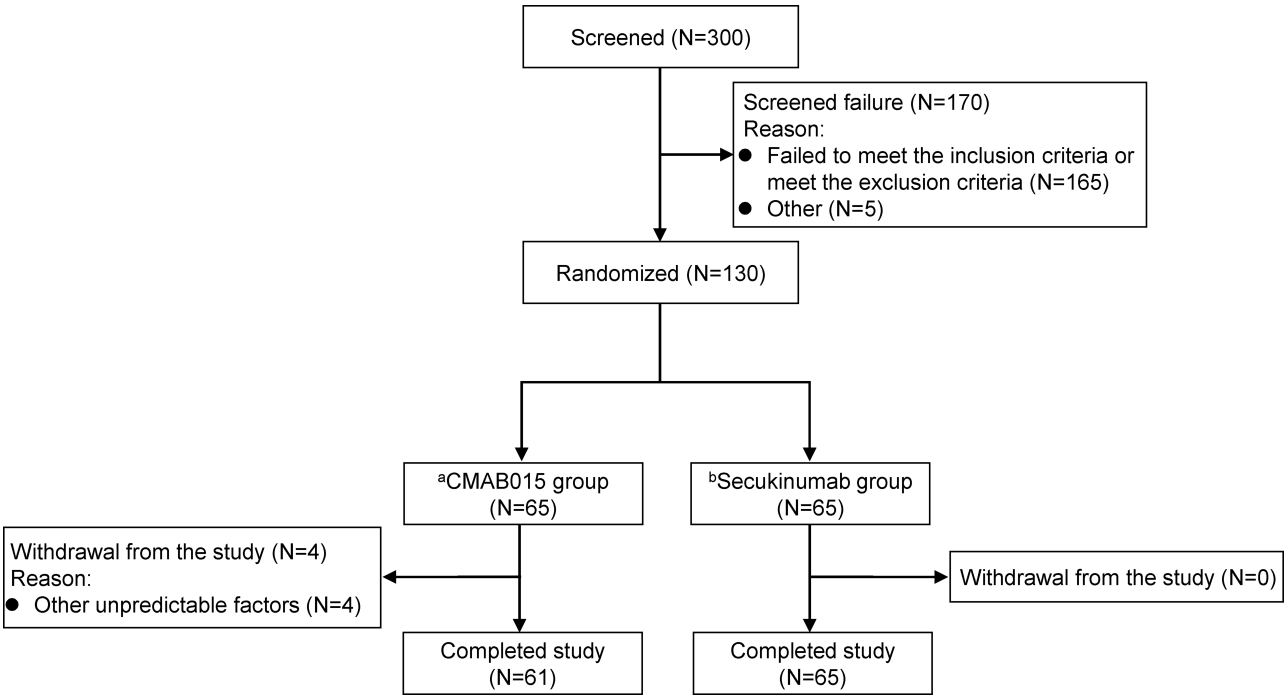


**Figure 1** Study design and subject flow. [a]Subjects who received CMAB015 treatment. [b]Subjects who received secukinumab treatment. N indicates the number of subjects.

**Table 1** Summary of Demographics

| Parameter | CMAB015 Group (N=65) | Secukinumab Group (N=65) | Total (N=130) |
|---|---|---|---|
| **Age (years)[a]** | | | |
| Number (Missing) | 65 (0) | 65 (0) | 130 (0) |
| Mean (SD) | 29.8 (6.74) | 29.1 (6.75) | 29.4 (6.73) |
| Median (Q1, Q3) | 29.0 (25.0, 35.0) | 27.0 (24.0, 34.0) | 28.5 (24.0, 34.0) |
| Min, Max | 19, 44 | 18, 44 | 18, 44 |
| **Ethnicity** | | | |
| Han | 61 (93.8%) | 65 (100%) | 126 (96.9%) |
| Other | 4 (6.2%) | 0 | 4 (3.1%) |
| Total (Missing) | 65 (0) | 65 (0) | 130 (0) |
| **Weight (kg)** | | | |
| Number (Missing) | 65 (0) | 65 (0) | 130 (0) |
| Mean (SD) | 64.64 (5.996) | 64.22 (6.065) | 64.43 (6.011) |
| Median (Q1, Q3) | 64.50 (59.80, 68.90) | 64.70 (58.60, 68.40) | 64.65 (59.30, 68.90) |
| Min, Max | 53.1, 74.3 | 53.0, 74.2 | 53.0, 74.3 |
| **Height (cm)** | | | |
| Number (Missing) | 65 (0) | 65 (0) | 130 (0) |
| Mean (SD) | 171.76 (6.324) | 171.42 (4.697) | 171.59 (5.551) |
| Median (Q1, Q3) | 171.50 (166.00, 176.50) | 172.00 (168.00, 175.00) | 172.00 (167.00, 175.50) |
| Min, Max | 159.5, 184.5 | 161.0, 183.0 | 159.5, 184.5 |
| **BMI ($kg/m^2$)[b]** | | | |
| Number (Missing) | 65 (0) | 65 (0) | 130 (0) |
| Mean (SD) | 21.97 (2.424) | 21.87 (2.066) | 21.92 (2.244) |
| Median (Q1, Q3) | 21.30 (20.20, 23.90) | 22.30 (20.10, 23.50) | 21.45 (20.20, 23.60) |
| Min, Max | 18.1, 27.2 | 18.1, 26.0 | 18.1, 27.2 |

**Notes**: (1) Percentages were calculated using the number of people in each group as the denominator. (2) The baseline value was defined as the last non-missing observation before dosing. [a]Age (years) = (Date of informed consent signing - Birthday + 1) / 365.25. [b]BMI ($kg/m^2$) = Weight (kg) / (Height (cm) / 100)$^2$.

treatment-related adverse events (TRAEs), which were TEAEs related to the study drug. Specifically, 53 (81.5%) subjects in the CMAB015 group experienced 136 TEAEs, and 48 (73.8%) subjects experienced 111 TRAEs. Similarly, in the secukinumab group, 48 (73.8%) subjects experienced 110 TEAEs and 40 (61.5%) subjects experienced 88 TRAEs. 17 (13.1%) subjects experienced 18 important TEAEs, and 15 (11.5%) subjects experienced 16 important TRAEs. The incidence of TEAEs and TRAEs was slightly higher in the CMAB015 group, but no serious adverse events, allergic reactions, or injection site reactions occurred in either group.

The occurrence of TEAEs is detailed in Table 6. The common TEAEs, reported in ≥ 5% of subjects treated with either CMAB015 or secukinumab, were as follows: proteinuria, blood uric acid increased, white blood cell count increased, alanine aminotransferase increased, aspartate aminotransferase increased, neutrophil count decreased, white blood cell count decreased, infection and infectious diseases, heart organ diseases, respiratory system, chest and mediastinal diseases, and diseases of gastrointestinal system. Amongst, proteinuria with the highest incidence was reported in both treatment groups. The occurrence of TEAEs was similar between groups, with no significant differences in distribution or incidence.

The safety profile of CMAB015 was similar to that of secukinumab, with no serious adverse events related to treatment. The incidence of TEAEs was slightly higher in the CMAB015 group, but these events were mild to moderate in severity and did not lead to any withdrawals from the study.

## Immunogenicity Evaluations

4 (3.1%) subjects tested positive for ADA. Among them, 2 (3.1%) subjects in the CMAB015 group were ADA positive on Day 15, and 1 (1.5%) subject was ADA positive on Day 29. In the secukinumab group, 1 (1.5%) subject tested ADA positive on Day 15 (Table S1). The ADA titers of the positive subjects were 1. There was no significant difference in

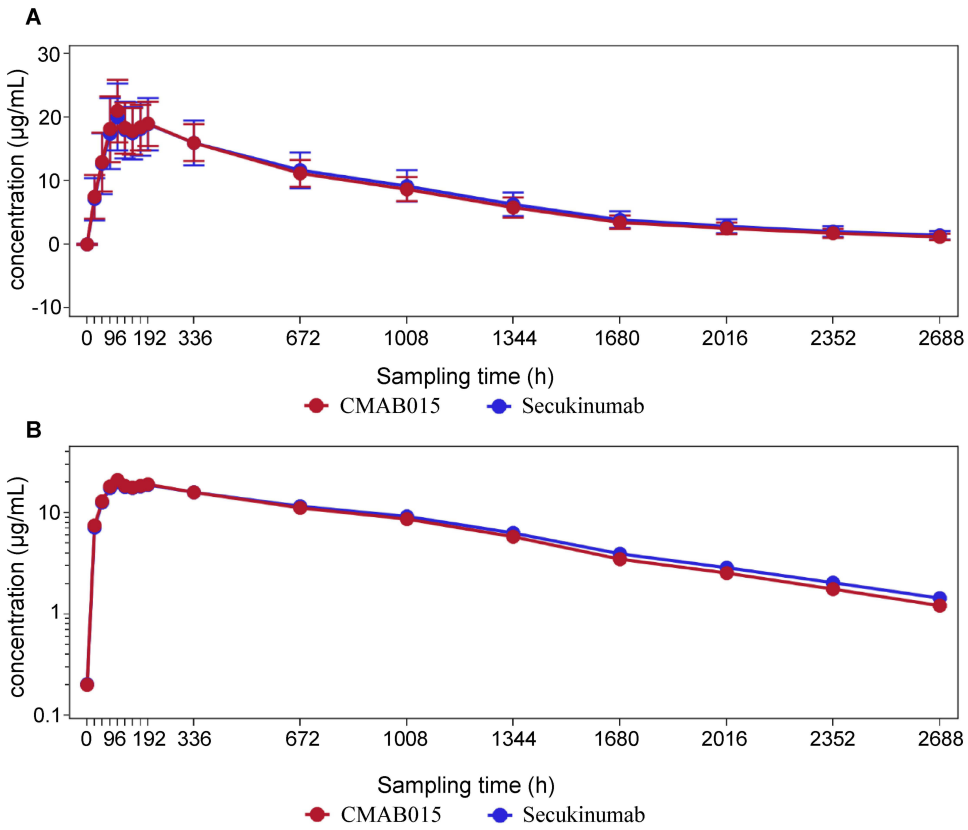


**Figure 2** Mean serum concentration-time profiles following a single subcutaneous injection of CMAB015 or secukinumab. (**A**) Mean serum concentration-time profiles (±SD) in linear scales. (**B**) Mean serum concentration-time profiles in semi-log scales.

ADA occurrence between the two groups at the Day 15 and Day 29 visits post-administration. All subjects tested negative for ADA at baseline, and none tested positive for Nabs. According to the statistical analysis plan's definition of treatment-induced antibody positivity (ADA negative at baseline and positive after the study drug), the overall ADA positivity was considered treatment-induced antibody positive. In conclusion, the immunogenicity of healthy subjects was essentially similar in both groups.

## Discussion

IL-17A is considered a pivotal proinflammatory cytokine in the pathogenesis of various diseases, including psoriasis, psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis.[13] Secukinumab, a selective anti-IL17A monoclonal antibody, has demonstrated efficacy and safety in treating these conditions.[14–18] Biosimilars of secukinumab, such as CMAB015, offer cost-effective alternatives that are equivalent in efficacy and safety, providing patients with psoriasis or ankylosing spondylitis with more treatment options.

The primary aim of biosimilar PK studies is to confirm the consistency of PK profiles between the test and reference drugs in a sensitive and homogeneous population. The NMPA guidelines emphasize selecting the most sensitive population for comparative studies of PK and pharmacodynamic properties. Healthy subjects are considered the most sensitive population for PK studies due to their low variability, making them suitable for single-dose PK studies under ethical considerations. Female subjects' PK parameters are susceptible to hormonal fluctuations, and subjects aged 18 to 45 years can offer a better representation of drug efficacy and safety, which is why only eligible healthy male subjects aged 18 to 45 years were enrolled and randomized in this study.

This Phase I clinical trial was a randomized, double-blind, parallel-group, single-dose study comparing the PK, safety, and immunogenicity of CMAB015, a biosimilar of secukinumab, with its reference drug secukinumab. The trial demonstrated that the 90% CIs of the GMRs of CMAB015 to secukinumab for $C_{max}$ and $AUC_{0\text{-inf}}$ were all within the standard bioequivalence

**Table 2** Pharmacokinetic Parameters of CMAB015 and Secukinumab - PK Parameter Analysis Set

| Group | Statistical Magnitude | $C_{max}$ (μg/mL) | $AUC_{0-inf}$ (h*μg/mL) | $AUC_{0-t}$ (h*μg/mL) | $T_{max}$ (h) | $t_{1/2}$ (h) | $\lambda_z$ ($h^{-1}$) | CL/F (mL/h) | Vd/F (mL) | $AUC_{\_\%Extrap}$ (%) |
|---|---|---|---|---|---|---|---|---|---|---|
| **CMAB015 group** | Number | 65 | 62 | 65 | 65 | 62[a] | 62[a] | 62[a] | 62[a] | 62[a] |
| | Mean | 21.60 | 20,548.666 | 19,142.748 | 113.7072 | 617.3361 | 0.0011 | 7.6131 | 6678.1849 | 5.450 |
| | SD | 4.71 | 4124.884 | 3864.313 | 37.5369 | 93.2107 | 0.0002 | 1.6533 | 1267.8308 | 2.581 |
| | CV | 21.79 | 20.07 | 20.19 | 33.01 | 15.10 | 15.84 | 21.72 | 18.98 | 47.36 |
| | Median | 21.50 | 20,814.602 | 19,537.949 | 95.9833 | 611.2085 | 0.0011 | 7.2066 | 6556.1400 | 5.345 |
| | Min | 12.1 | 12,495.24 | 10,518.26 | 71.9833 | 435.694 | 0.001 | 4.670 | 4030.108 | 1.54 |
| | Max | 34.7 | 32,120.77 | 30,115.40 | 191.9833 | 833.843 | 0.002 | 12.005 | 10,261.878 | 16.64 |
| | Geometric mean | 21.10 | 20,132.650 | 18,747.080 | 108.7461 | 610.2528 | 0.0011 | 7.4506 | 6559.5586 | 4.907 |
| | Geometric CV | 22.28 | 20.89 | 21.15 | 29.36 | 15.54 | 15.54 | 20.89 | 19.39 | 49.63 |
| **Secukinumab group** | Number | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 | 65 |
| | Mean | 20.86 | 21,675.872 | 20,250.952 | 135.5190 | 656.5381 | 0.0011 | 7.3424 | 6825.1246 | 6.228 |
| | SD | 4.91 | 5507.410 | 4817.218 | 63.0677 | 102.2085 | 0.0002 | 1.8013 | 1458.3600 | 2.407 |
| | CV | 23.52 | 25.41 | 23.79 | 46.54 | 15.57 | 14.65 | 24.53 | 21.37 | 38.65 |
| | Median | 20.90 | 21,465.625 | 20,074.136 | 95.9833 | 648.8537 | 0.0011 | 6.9879 | 6722.4651 | 6.174 |
| | Min | 11.3 | 12,064.76 | 11,891.90 | 71.9833 | 465.000 | 0.001 | 3.497 | 4228.104 | 1.43 |
| | Max | 31.4 | 42,895.84 | 37,463.47 | 337.7333 | 974.695 | 0.001 | 12.433 | 10,936.106 | 12.66 |
| | Geometric mean | 20.28 | 21,036.729 | 19,720.131 | 124.2460 | 649.1335 | 0.0011 | 7.1304 | 6677.6188 | 5.751 |
| | Geometric CV | 24.72 | 24.89 | 23.43 | 41.89 | 15.11 | 15.11 | 24.89 | 21.23 | 43.95 |

**Notes**: [a]3 Subjects in CMAB015 group had $AUC_{\_\%Extrap}$ > 20%, then the respective other PK parameters ($t_{1/2}$, $\lambda_z$, $AUC_{0-inf}$, CL/F, Vd/F, $AUC_{\_\%Extrap}$) were not performed descriptive statistical analysis.

**Table 3** Similarity Analysis of $C_{max}$, $AUC_{0-Inf}$ and $AUC_{0-t}$

| PK Parameters | N1:N2 | Geometric Mean of CMAB015 Group | Geometric Mean of Secukinumab Group | GMR (CMAB015 Group/ Secukinumab Group) | GMR (90% CI) |
|---|---|---|---|---|---|
| $C_{max}$ (μg/mL) | 65:65 | 21.10 | 20.28 | 104.05% | 97.26–111.31% |
| $AUC_{0-inf}$ (h*μg/mL) | 62:65 | 20,132.65 | 21,036.73 | 95.70% | 89.52–102.32% |
| $AUC_{0-t}$ (h*ug/mL) | 65:65 | 18,747.08 | 19,720.13 | 95.07% | 89.17%-101.36% |

**Notes**: N1: Subjects of CMAB015 group; N2: Subjects of secukinumab group; CI = Confidence interval; GMR = Geometric mean ratio. Variance analysis model was used to analyze the PK parameters following the natural logarithmic transformation. 3 Subjects in CMAB015 group had $AUC_{\_\%Extrap}$ > 20%, then the respective AUC0-inf was not included in the similarity analysis.

**Table 4** Comparison of Secondary Pharmacokinetic Parameters

| PK Parameters | N1:N2 | Median (Q1, Q3) of CMAB015 Group | Median (Q1, Q3) of Secukinumab Group | Statistical Magnitude | *P* value |
|---|---|---|---|---|---|
| $T_{max}$ (h) | 65:65 | 95.9833 (95.9833, 119.9833) | 95.9833 (95.9833, 191.9833) | 1.967[T] | 0.051[T] |
| $t_{1/2}$ (h) | 62:65 | 611.2085 (540.9398, 687.5034) | 648.8537 (577.4123, 692.8254) | −1.681[T] | 0.095[T] |
| $\lambda_z$ ($h^{-1}$) | 62:65 | 0.0011 (0.0010, 0.0013) | 0.0011 (0.0010, 0.0012) | 1.660[T] | 0.099[T] |
| CL/F (mL/h) | 62:65 | 7.2066 (6.6033, 8.1680) | 6.9879 (6.1492, 8.2442) | 0.991[T] | 0.324[T] |
| $V_d$/F (mL) | 62:65 | 6556.1400 (5804.1877, 7601.4152) | 6722.4651 (5682.6037, 7580.4246) | −0.234[T] | 0.815[T] |

**Notes**: N1: Subjects of CMAB015 group; N2: Subjects of secukinumab group. [T] Wilcoxon rank-sum test for two-sided *P*-values based on t-distribution approximation. 3 Subjects in CMAB015 group had $AUC_{\_\%Extrap}$ > 20%, then the respective other PK parameters ($t_{1/2}$, $\lambda_z$, CL/F, Vd/F) were not included in the comparison.

range of 80.00% to 125.00%. These results indicate that CMAB015 has similar PK profiles to secukinumab when administered as a single subcutaneous injection of 150 mg in healthy Chinese male volunteers. The number of subjects positive for ADAs was small (3 in the CMAB015 group and 1 in the secukinumab group), therefore, the impact of immunogenicity status (ADA negative or positive) on PK parameters was insufficient to reach a definitive conclusion.

**Table 5** Summary of Adverse Events

| Adverse events | CMAB015 group (N=65) | | Secukinumab group (N=65) | | Total (N=130) | |
|---|---|---|---|---|---|---|
| | Number of cases (%) | Number of AEs | Number of cases (%) | Number of AEs | Number of cases (%) | Number of AEs |
| All AEs | 53 (81.5) | 136 | 48 (73.8) | 110 | 101 (77.7) | 246 |
| All TEAEs | 53 (81.5) | 136 | 48 (73.8) | 110 | 101 (77.7) | 246 |
| CTCAE≥Grade 3 TEAEs | 2 (3.1) | 2 | 2 (3.1) | 2 | 4 (3.1) | 4 |
| CTCAE≥Grade 3 TRAEs | 1 (1.5) | 1 | 2 (3.1) | 2 | 3 (2.3) | 3 |
| TRAEs | 48 (73.8) | 111 | 40 (61.5) | 88 | 88 (67.7) | 199 |
| TESAEs | 1 (1.5) | 1 | 0 | 0 | 1 (0.8) | 1 |
| TRSAEs | 0 | 0 | 0 | 0 | 0 | 0 |
| TEAEs leading to withdrawal | 0 | 0 | 0 | 0 | 0 | 0 |
| TRAEs leading to withdrawal | 0 | 0 | 0 | 0 | 0 | 0 |
| AESI | 18 (27.7) | 21 | 10 (15.4) | 11 | 28 (21.5) | 32 |
| AESI related to study drug | 18 (27.7) | 21 | 10 (15.4) | 11 | 28 (21.5) | 32 |
| Important TEAEs | 11 (16.9) | 12 | 6 (9.2) | 6 | 17 (13.1) | 18 |
| Important TRAEs | 9 (13.8) | 10 | 6 (9.2) | 6 | 15 (11.5) | 16 |
| SUSAR | 0 | 0 | 0 | 0 | 0 | 0 |
| Hypersensitivity | 0 | 0 | 0 | 0 | 0 | 0 |
| Injection site reaction | 0 | 0 | 0 | 0 | 0 | 0 |
| TEAE leading to death | 0 | 0 | 0 | 0 | 0 | 0 |

**Abbreviations**: AEs, adverse events; TEAEs, treatment emergent adverse events; TRAEs, treatment related adverse events; CTCAE, common terminology criteria for adverse events; TESAEs, treatment emergent serious adverse events; TRSAEs, treatment related serious adverse events; AESI, adverse events of special interest; SUSAR, suspicious and unexpected serious adverse reactions.

**Table 6** The Incidence of TEAEs Were Summarized by SOC and PT

| SOC/PT | CMAB015 Group (N=65) | | Secukinumab Group (N=65) | | Total (N=130) | |
|---|---|---|---|---|---|---|
| | Number of Cases (%) | Number of AEs | Number of Cases (%) | Number of AEs | Number of Cases (%) | Number of AEs |
| Various inspection | 44 (67.7) | 89 | 32 (49.2) | 66 | 76 (58.5) | 155 |
| Proteinuria | 23 (35.4) | 30 | 13 (20.0) | 20 | 36 (27.7) | 50 |
| Blood uric acid increased | 11 (16.9) | 17 | 11 (16.9) | 14 | 22 (16.9) | 31 |
| White blood cell count increased | 3 (4.6) | 3 | 4 (6.2) | 6 | 7 (5.4) | 9 |
| Alanine aminotransferase increased | 4 (6.2) | 5 | 3 (4.6) | 5 | 7 (5.4) | 10 |
| Aspartate aminotransferase increased | 4 (6.2) | 4 | 3 (4.6) | 3 | 7 (5.4) | 7 |
| Blood pressure increased | 3 (4.6) | 3 | 3 (4.6) | 4 | 6 (4.6) | 7 |
| Neutrophil count decreased | 5 (7.7) | 7 | 1 (1.5) | 1 | 6 (4.6) | 8 |
| White blood cell count decreased | 4 (6.2) | 5 | 0 | 0 | 4 (3.1) | 5 |
| Antinuclear antibody positive | 0 | 0 | 4 (6.2) | 4 | 4 (3.1) | 4 |
| Urine red blood cell positive | 2 (3.1) | 2 | 1 (1.5) | 1 | 3 (2.3) | 3 |
| Platelet count increased | 0 | 0 | 3 (4.6) | 3 | 3 (2.3) | 3 |
| γ-glutamyltransferase increased | 2 (3.1) | 3 | 0 | 0 | 2 (1.5) | 3 |
| Lymphocyte count decreased | 0 | 0 | 2 (3.1) | 2 | 2 (1.5) | 2 |
| Heart rate increased | 1 (1.5) | 1 | 1 (1.5) | 1 | 2 (1.5) | 2 |
| Blood bilirubin increased | 2 (3.1) | 2 | 0 | 0 | 2 (1.5) | 2 |
| Blood unconjugated bilirubin increased | 2 (3.1) | 2 | 0 | 0 | 2 (1.5) | 2 |
| Conjugated bilirubin increased | 1 (1.5) | 2 | 0 | 0 | 1 (0.8) | 2 |
| Urine occult blood positive | 1 (1.5) | 1 | 0 | 0 | 1 (0.8) | 1 |
| Urine glucose present | 1 (1.5) | 1 | 0 | 0 | 1 (0.8) | 1 |
| Platelet count decreased | 0 | 0 | 1 (1.5) | 2 | 1 (0.8) | 2 |
| Blood pressure decreased | 1 (1.5) | 1 | 0 | 0 | 1 (0.8) | 1 |

(*Continued*)

**Table 6** (Continued).

| SOC/PT | CMAB015 Group (N=65) | | Secukinumab Group (N=65) | | Total (N=130) | |
|---|---|---|---|---|---|---|
| | Number of Cases (%) | Number of AEs | Number of Cases (%) | Number of AEs | Number of Cases (%) | Number of AEs |
| Infection and infectious diseases | 14 (21.5) | 15 | 9 (13.8) | 10 | 23 (17.7) | 25 |
| Heart organ diseases | 10 (15.4) | 13 | 5 (7.7) | 11 | 15 (11.5) | 24 |
| Respiratory system, chest and mediastinal diseases | 5 (7.7) | 6 | 6 (9.2) | 7 | 11 (8.5) | 13 |
| Diseases of gastrointestinal system | 4 (6.2) | 7 | 6 (9.2) | 9 | 10 (7.7) | 16 |
| All kinds of nervous system disorders | 3 (4.6) | 3 | 2 (3.1) | 3 | 5 (3.8) | 6 |
| Diseases of skin and subcutaneous tissue | 1 (1.5) | 1 | 2 (3.1) | 2 | 3 (2.3) | 3 |
| Psychiatric category | 1 (1.5) | 1 | 1 (1.5) | 1 | 2 (1.5) | 2 |
| Metabolic and nutritional diseases | 0 | 0 | 1 (1.5) | 1 | 1 (0.8) | 1 |
| Various musculoskeletal and connective tissue disorders | 1 (1.5) | 1 | 0 | 0 | 1 (0.8) | 1 |

**Abbreviations**: AEs, adverse events; TEAEs, treatment emergent adverse events; SOC, system organ class; PT, preferred term.

Additionally, both CMAB015 and secukinumab are large molecule drugs with a molecular weight of approximately 151 kDa. Moreover, since the absorption, distribution, metabolism, and excretion processes of monoclonal antibody drugs and small molecule drugs differ significantly, and the concomitant drugs did not affect the activity or quantity of protease relevant to the study drugs, it is reasonable to assume that the concomitant drugs did not impact the PK characteristics of CMAB015 and secukinumab. Overall, the PK parameters of CMAB015 and secukinumab remained within an acceptable range. In conclusion, CMAB015 and secukinumab exhibited similar PK profiles in healthy male subjects.

Previous studies have reported that AEs occurred in 55–65% of secukinumab recipients and 56–62% of placebo recipients in patients with psoriatic arthritis.[19–22] Additionally, it has been demonstrated that secukinumab at doses of 150 and 300 mg is well tolerated in Chinese patients with moderate-to-severe plaque psoriasis.[23] In our study, AEs or TEAEs occurred in 81.5% of CMAB015 recipients and 73.8% of secukinumab recipients, and TRAEs occurred in 73.8% of CMAB015 recipients and 61.5% of secukinumab recipients. The incidence of TEAEs was slightly higher in the CMAB015 group; however, these events were mild to moderate in severity and did not result in any study withdrawals. It is not uncommon for biosimilars to exhibit a slightly higher incidence of TEAEs compared to their reference biologics, often due to random chance, particularly in trials with relatively small sample sizes. Nonetheless, the observed differences in TEAE rates were minor and fell within the expected margins of clinical equivalence. Analysis based on the SOC, PT, and CTCAE classification showed that the incidence of TEAEs and TRAEs between the two groups was consistent with the results of the full data analysis. There were no reports of allergic reactions, adverse injection site reactions, TEAEs leading to withdrawal from the study, or TEAEs leading to death in either group. However, some differences were noted in the incidence of AESI and important AEs between the CMAB015 and secukinumab groups. The incidence of AESI was 27.7% in the CMAB015 group and 15.4% in the secukinumab group. Similarly, the incidence of important AEs was 16.9% in the CMAB015 group and 9.2% in the secukinumab group. Although the incidence of AESI and important AEs was slightly higher in the CMAB015 group than in the secukinumab group, the actual situation should be further investigated in a larger sample size study. In conclusion, a single subcutaneous injection of either CMAB015 or secukinumab resulted in an overall good and similar safety profile in healthy Chinese male subjects.

As a monoclonal antibody, secukinumab carries the potential for immunogenicity. Previous reports indicated that among patients with moderate-to-severe plaque psoriasis treated with secukinumab and with evaluable samples (n=1163), 8 patients (0.7%) tested positive for ADAs, while all patients were negative for Nabs.[24] Another clinic trial found that 5 (0.35%) of 1414 patients with psoriatic arthritis and 8 (0.69%) of 1164 patients with ankylosing spondylitis treated with secukinumab respectively developed positive for ADAs, while all patients were negative for Nabs.[25] Additionally, it was found that the presence of ADAs was not associated with any AEs or PK.[25] In our study, 3 subjects in the CMAB015

group and 1 subject in the secukinumab group showed positive ADAs with relatively low titers, and all ADA-positive subjects in our study were Nab-negative. The immunogenicity profile of CMAB015 mirrored that of secukinumab, with a limited impact on PK parameters and safety profile in healthy Chinese male subjects following a single subcutaneous injection. The exact correlation will be further explored in future larger sample size studies.

## Conclusions

This study illustrated the equivalent PK profiles of the secukinumab biosimilar (CMAB015) and the reference product (secukinumab) in healthy Chinese male subjects after a single subcutaneous injection. Moreover, the safety profiles and immunogenicity of CMAB015 were similar to those of secukinumab. These findings support the further development of CMAB015 as a biosimilar to secukinumab and its potential to provide an effective and affordable treatment option for patients with inflammatory diseases.

## Data Sharing Statement

The datasets used and analyzed during the current study will be available from the corresponding author on reasonable request.

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## Disclosure

Chenguang Wang, Tianshu Yang, Xunmin Zhang, Yong Shan, Sheng Hou, and Hao Wang are affiliated with Taizhou Mabtech Pharmaceutical Co. Ltd. The authors report no other conflicts of interest in this work.

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