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ORIGINAL RESEARCH

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Anti-C5a Antibody BDB-001 for Severe COVID-19: A Randomized, Double-Blind, Placebo-Controlled Phase 1 Clinical Trial in Healthy Chinese Adults

Guiling Chen · Nan Li · Xiahong Dai · Shiyan Tu · Zhenwei Shen · Kaiqi Wu · Tinghan Jin · Jiajun Wu · Conggao Peng · Guoping Sheng · Mengfei Zhu · Lingling Tang · Lanjuan Li

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ABSTRACT

Introduction: Severe Coronavirus Disease 2019 (COVID-19) progresses with inflammation and coagulation, due to an overactive complement system. Complement component 5a (C5a) plays a key role in the complement system to trigger a powerful "cytokine and chemokine storm" in viral infection. BDB-001, a recombinant human immunoglobulin G4 (IgG4) that specially binds to C5a, has the potential to inhibit the C5a-triggered cytokine storm in treating COVID-19 patients and other inflammation diseases. Here, we have explored its safety, tolerability, pharmacokinetics, and pharmacodynamics in healthy adults. This trial is registered with http://www.chinadrugtrials.org.cn/(CTR20200429).

Methods: Thirty-two enrolled participants were randomized into three single-dose cohorts (2, 4, and 8 mg/kg) and 1 multi-dose cohort (4 mg/kg), and received either BDB-001 or placebo (3:1) double-blindly. The safety and tolerability after administration were evaluated for 21 days for single-dose cohorts and 28 days for the multi-dose cohort. The pharmacokinetics of

Guiling Chen, Nan Li and Xiahong Dai share first authorship.

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G. Chen · N. Li · X. Dai · K. Wu · T. Jin · J. Wu · C. Peng · G. Sheng (✉) · M. Zhu (✉) · L. Tang (✉)
Phase I Clinical Trial Unit, Shulan (Hangzhou) Hospital Affiliated to Zhejiang Shuren University Shulan International Medical College, Dongxin Road, 848, Hangzhou 310000, China
e-mail: guoping.sheng@shulan.com

M. Zhu
e-mail: mengfei.zhu@shulan.com

L. Tang
e-mail: lingling.tang@shulan.com

S. Tu
The First Clinical Medical College of Lanzhou University, Lanzhou, Gansu, China

Z. Shen
Zhejiang Shuren University, Hangzhou, Zhejiang, China

L. Li (✉)
State Key Laboratory for Diagnosis and Treatment of Infectious Diseases, National Clinical Research Center for Infectious Diseases, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Diseases, The First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310003, Zhejiang, China
e-mail: ljli@zju.edu.cn

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BDB-001 in plasma and pharmacodynamics as free C5a in plasma were analyzed.
Results: The incidence of drug-related adverse events (AEs) was low, and all AEs were mild or moderate: neither AEs ≥ 3 (NCI-Common Terminology Criteria For Adverse Events, CTCAE 5.0) nor serious adverse events (SAEs) were found. The area under the concentration–time curve from time zero to 480 h ($AUC_{0\text{-}480h}$), that from time zero to infinity (AUC_{inf}), and peak plasma concentration ©$_{max}$) increased dose-dependently from 2 to 8 mg/kg in the single-dose cohorts and were characterized by a nonlinear pharmacokinetics of target-mediated drug disposal (TMDD). The accumulation index by $AUC_{0\text{-}tau}$ after five administrations (4 mg/kg) from the multi-dose cohort was 6.42, suggesting an accumulation effect. Furthermore, inhibition of C5a at the plasma level was observed.
Conclusion: The results of this phase I study supported that BDB-001 is a potent anti-C5a inhibitor with safety, tolerability, and no immunogenicity.
Trial Registration Number: CTR20200429.

Keywords: Severe COVID-19; Complement system; C5a; Phase 1; Clinical trial

Key Summary Points

- Severe Coronavirus Disease 2019 (COVID-19) progresses with inflammation and coagulation, due to an overactive complement system, such as a C5a-trigged cytokine storm.
- BDB-001 is a recombinant human immunoglobulin G4 (IgG4) that specially binds to C5a. It has a low incidence of drug-related adverse events (AEs), and all AEs were mild or moderate.
- Pharmacokinetics analysis of BDB-001 showed typical nonlinear pharmacokinetics of target-mediated drug disposal (TMDD) and accumulation effect. Pharmacodynamics of BDB-001 showed inhibition of C5a at the plasma level.
- The results of this phase I study support that BDB-001 is a potent anti-C5a inhibitor with safety, tolerability, and non-immunogenicity, and is worth of further studies in COVID-19 patients. This may eventually be applied to other C5-related clinical challenges, including but not limited to, virus-mediated acute respiratory distress syndrome.

INTRODUCTION

Coronavirus Disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, may be accompanied by severe respiratory inflammation, progress to acute respiratory distress syndrome (ARDS) and multi-organ failure, and lead to high fatality rates [1–3]. Complement deposition on endothelial cells and high level of blood complement component 5a (C5a) have been found in severe COVID-19 patients [4–7]. Experimental studies have shown that SARS-CoV-2 activated the complement system and illustrated the association of the C5a-C5aR1 signaling with COVID-19-triggered inflammation [5, 7, 8]. These data suggest that the overactivation of the complement system leads to ARDS and multi-organ failure in severe COVID-19 patients, and that the therapies targeting complement pathways have the potential to reduce pro-inflammatory cytokines, lessen lung pathology, and improve the survival rate of COVID-19 patients.

Complement activation involves several important molecules, such as C3, C5, C3a, and C5a, to be recruited and activated. These molecules modulate the responses of targeted innate and adaptive immune cells [9, 10]. Among them, C5a functions in coagulation system activation [11–13] by promoting the immune cells' recruitment and activation, the pro-inflammatory cytokines release from endothelial cells and neutrophils, and the oxidative radical formation thus damages tissue. For example, C5a stimulated the expression of interleukin-6 (IL-6), IL-8, IL-10, interferon-γ

(IFN-γ) and tumor necrosis factor-α (TNF-α) [14–16]. These data denote the key role of C5a in complement-driven ARDS and multi-organ failure during severe pathogenic SARS-CoV-2 infection. Therefore, inhibiting C5a is considered a strategy to alleviate the respiratory inflammation and to increase the survival of severe COVID-19 patients [17–20].

BDB-001, developed by Staidson (Beijing) Biopharma, is a recombinant human immunoglobulin G4 (IgG4) antibody that specially binds to C5a. In our preclinical in vitro study, it blocked a series of biological functions of C5a, such as chemotaxis of neutrophils, release of intracellular bacteriolysis, and increased level of inflammatory cytokines. Moreover, there was no influence on C5 cleavage and the membrane attack complex. The blockade of C5a does not disrupt neutrophils while preventing their activation, which helps the repair of a functional neutrophil population in COVID-19 patients. A clinical study with a similar C5a antibody, IFX-1, exhibited its safety and efficacy [19–21]. Here, we perform a double-blinded randomized phase 1 study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of anti-C5a antibody BDB-001 in healthy adults. We concluded that intravenous administration of BDB-001 single doses of 2, 4, or 8 mg/kg or multiple doses of 4 mg/kg were well tolerated and had the potential to inhibit C5 function.

METHODS

Participants and Study Design

This is a single-center, double-blind, randomized, placebo-controlled, phase 1 clinical trial held in Zhejiang, China. Thirty-two enrolled participants were randomly and sequentially allocated to three single-dose-escalation cohorts at 2, 4, and 8 mg/kg, and one multi-dose cohort at 4 mg/kg.

Participants were recruited and screened for eligibility. Inclusion criteria includes age between 18 and 55 years old, healthy condition confirmed by a physical examination and a series of clinical laboratory tests (total protein; hepatitis B and C serology; HIV; full blood count; kidney and liver function tests; urinary screen for protein, blood, and glucose; and pregnancy test for women of childbearing potential), and informed consent to adopt contraceptives according to the protocol requirements. Participants were excluded with any history of receiving COVID-19 related or unrelated vaccines or experimental drugs, medical history of severe diseases or drug abuse, heavy smoking, heavy drinking or alcoholics, current pregnancy or breast-feeding, or body mass index beyond the range of $18 \sim 28\ kg/m^2$.

The protocol and informed consent were reviewed and approved by the Clinical Trial Ethics Committee of our hospital. All participants signed informed consents before the screening. This study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

Randomization and Masking

Each enrolled participant was assigned a randomization code generated by SAS (v9.4), according to the order of the screening numbers. In single-dose cohorts, 24 participants were randomly assigned (8:8:8) into 3 blocks (2 mg/kg, 4 mg/kg, 8 mg/kg), and in each block they were further randomly assigned (3:1) to receive either the BDB-001 (Staidson Biopharma) or placebo. In the multi-dose cohort, two sentinels were randomly assigned (1:1) into BDB-001 (4 mg/kg) or placebo, and the remaining 6 participants were randomly assigned (5:1).

BDB-001 was supplied as a 10-ml solution at 10 mg/ml, stored at 2–8 °C and in lightproof condition. The BDB-001 and the placebo were identical in appearance, and the treatment allocation was double blinded.

Dose Escalation

This study applied three single-dose levels, of 2, 4 to 8 mg/kg, followed by a 4-mg/kg multi-dose cohort. The study started from the lowest single-dose cohort and proceeded to the next dose level only after safety assessment was satisfied according to the set criteria for dose escalation.

The termination criteria were: (1) more than ½ participants had drug-related adverse events (AEs), determined to be ≥ 2 grade [Common Terminology Criteria for Adverse Events (CTCAE) 5.0], (2) more than 1/4 participants had drug-related AEs, determined to be 3–4 grade (CTCAE 5.0), or (3) at least one drug-related serious adverse event (SAE). The follow-up assessments were scheduled on days 7, 14, and 21 for the single-dose cohorts or on days 14, 21, and 28 for the multi-dose cohort.

Study Procedures

The dose for each participant was calculated according to his/her body weight, and then mixed with 250 mL normal saline for intravenous infusion over 60 min. In cohort 1, 8 participants were randomly assigned (3:1) to receive a single intravenous dose of 2 mg/kg BDB-001 or placebo. Participants stayed in the hospital and were monitored for safety assessment for 4 days. After a success with cohort 1, cohort 2 (4 mg/kg) was proceeded with, followed by cohort 3 (8 mg/kg). In cohort 4, two sentinels were randomly assigned (1:1) to receive 4 mg/kg of BDB-001 or placebo on days 1, 2, 3, 5, and 7. After a successful safety assessment for 10 days, the remaining 6 participants were randomly assigned (5:1) to receive 4 mg/kg of BDB-001 or placebo on the same schedule, and follow-up assessments on days 14, 21, and 28.

For the safety assessments, laboratory tests included white blood cell count, differential hematocrit, hemoglobin, platelets, alanine aminotransferase, aspartate aminotransferase, creatinine, and total bilirubin, which were obtained prior to infusion and afterwards on days 4, 7, 14, and 21 for the single-dose cohorts, or on days 3, 5, 7, 10, 14, 21, and 28 for the multi-dose cohort. All AEs occurring during the trial were documented and evaluated. AEs were coded using the *Medical Dictionary for Regulatory Activities 23.0* (MedDRA 23.0), and severity was graded using the CTCAE 5.0. All AEs were assessed its correlation with drug, severity, and grade. The anti-drug antibody level at each time points (before administration and on days 7 and 21 after administration for the single-dose cohorts, and before administration and on days 1, 7, 14, and 28 for the multi-dose cohort) were calculated with the MSD-electro chemiluminescence platform, and the 95% confidence interval was calculated by the Clopper–Pearson method.

Outcomes

The primary endpoint was safety and tolerability of BDB-001 in healthy adults, which was quantified by the number and proportion of treatment emergent adverse events and any anomaly in the test results and adverse medical events. The secondary endpoints include pharmacokinetics, pharmacodynamics, and anti-drug antibodies against BDB-001. Pharmacokinetic parameters were calculated and analyzed after quantifying the concentration of BDB-001 in the plasma of participants after receiving the intravenous infusion. The area under the concentration–time curve from time zero to infinity (AUC_{inf}), the area under the concentration–time curve from time zero to 480 h ($AUC_{0\text{-}480\ h}$), systemic clearance (CL), peak plasma concentration (C_{max}), elimination rate constant (kel), elimination half-life ($t_{½}$), time to achieve C_{max} (T_{max}), volume of distribution at terminal phase (Vz), mean residence time–time curve from time zero to time of last quantifiable concentration (MRT_{last}), and percentage of residual area ($AUC_{\_\%Extrap}$) were calculated accordingly, as previously described (22). We also included the inflammatory cytokines (IL-6, IL-8, IL-10, IFN-γ, and TNF-α) as an exploratory objective.

Statistical Analyses

The analyses of safety, pharmacodynamics, pharmacokinetics, and inflammatory cytokines were summarized using descriptive measures, such as counts, means, confidence intervals (CIs), and frequencies. The differences across cohorts were determined using Student's *t*-test, ANOVA, or chi-square tests, as appropriate. Unless otherwise stated, all statistical tests were two-sided with $\alpha = 0.05$, and two-sided 95% CIs

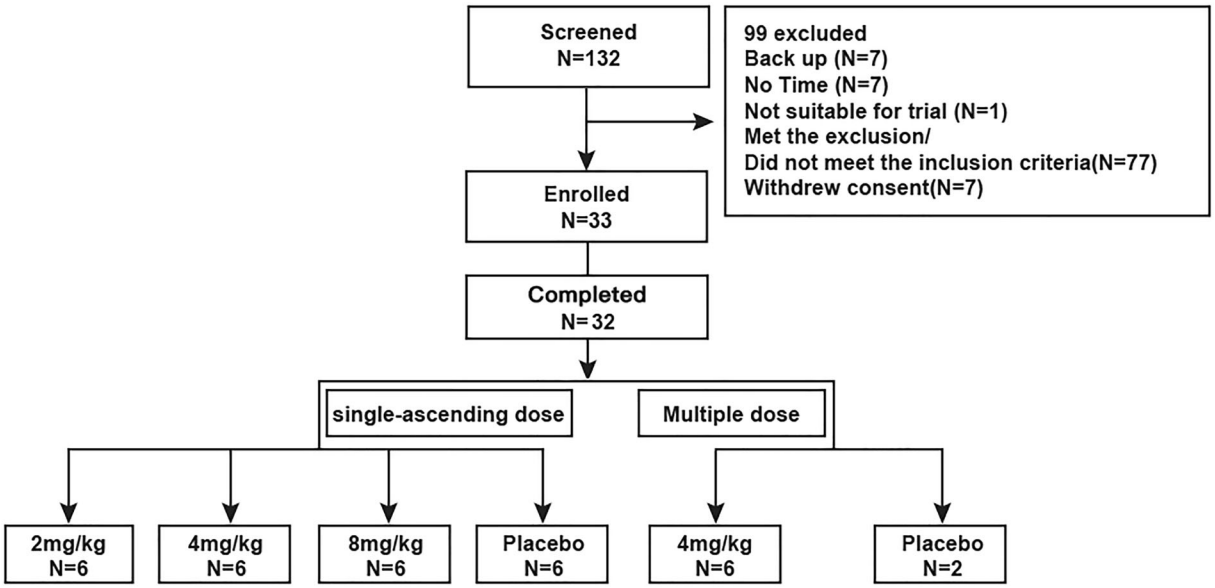

Fig. 1 Flow chart of participant enrollment and assignment

were calculated. If the P value was ≥ 0.001, it was rounded to 3 decimal places; if the P value was < 0.001, it was reported as < 0.001.

RESULTS

Baseline Characteristics of Participants

From the total of 132 screened participants, 33 were eligible and enrolled. One enrolled participant assigned to cohort 2 voluntarily withdrew from the study before administration, while the remaining 32 participants completed the study (Fig. 1). Participants were randomly assigned into one of the four cohorts to receive either BDB-001 (6 participants each cohort) or placebo (2 participants each cohort) as described in Methods. All the baseline characteristics of participants were similar among the four cohorts (Table S1).

Safety and Tolerability

All 32 participants finished the safety assessment. The safety and tolerability were evaluated, including AEs, electrocardiogram results, vital sign measurement, physical examination, and laboratory assessments. In total, 12 drug-related AEs were reported: 7 occurred in 3 participants [50.00% (3/6)] in cohort 1 receiving 2 mg/kg of BDB-001, 4 occurred in 2 participants [33.33% (2/6)] in cohort 2 receiving 4 mg/kg of BDB-001, none in cohort 3 receiving 8 mg/kg of BDB-001 (Table 1), 1 in 1 participant [16.67% (1/6)] in cohort 4 receiving BDB-001, and 4 in 2 participants [100% (2/2)] in cohort 4 receiving placebo (Table 2). No AEs was found in participants receiving placebo in cohorts 1–3. The occurrence of AEs was not dose-dependent, because the incidence rates of drug-related AE were 50.00% ($n = 3$), 33.33% ($n = 2$), and 0% in the single-dose cohorts receiving 2, 4, and 8 mg/kg of BDB-001, respectively (Table 1), and the incidence rate was 16.67% ($n = 6$) and 100.00% ($n = 2$), respectively, in the multi-dose cohort receiving 4 mg/kg of BDB-001 and placebo. The most frequent AEs were blood bilirubin increase ($n = 2$, in the 2-mg/kg single-dose and the 4-mg/kg multi-dose cohorts), white blood cell count decrease ($n = 2$, in the 2-mg/kg and 4-mg/kg single-dose cohorts), and neutrophil count decrease ($n = 2$, in the 2-mg/kg and 4-mg/kg single-dose cohorts).

Most AEs were mild or moderate (CTCAE 5.0 $\leq$ 2). There were 22 grade 1 AEs and 2 grade

Table 1 Incidence and frequency of drug-related adverse events occurred after single administration, single dose

SOC	2 mg/kg (n = 6)			4 mg/kg (n = 6)			8 mg/kg (n = 6)			Placebo (n = 6)			Total (n = 24)			
PT	No. of AEs	No. of participants	Incidence (%)	No. of AEs	No. of participants	Incidence (%)	No. of AEs	No. of participants	Incidence (%)	No. of AEs	No. of participants	Incidence (%)	No. of AEs	No. of participants	Incidence (%)	P value
Total	7	3	50.00	4	2	33.33	0	0	0.00	0	0	0.00	11	5	20.83	0.11
Investigations	6	3	50.00	4	2	33.33	0	0	0.00	0	0	0.00	10	5	20.83	0.11
White blood cell count decreased	1	1	16.67	1	1	16.67	0	0	0.00	0	0	0.00	2	2	8.33	1.00
Neutrophil count decreased	1	1	16.67	1	1	16.67	0	0	0.00	0	0	0.00	2	2	8.33	1.00
White blood cells urine positive	0	0	0.00	1	1	16.67	0	0	0.00	0	0	0.00	1	1	4.17	1.00
Urine leukocyte esterase positive	0	0	0.00	1	1	16.67	0	0	0.00	0	0	0.00	1	1	4.17	1.00
Urine bilirubin increased	1	1	16.67	0	0	0.00	0	0	0.00	0	0	0.00	1	1	4.17	1.00
Urobilinogen urine increased	1	1	16.67	0	0	0.00	0	0	0.00	0	0	0.00	1	1	4.17	1.00
Peripheral pulse decreased	1	1	16.67	0	0	0.00	0	0	0.00	0	0	0.00	1	1	4.17	1.00
Blood bilirubin increased	1	1	16.67	0	0	0.00	0	0	0.00	0	0	0.00	1	1	4.17	1.00
Cardiac disorders	1	1	16.67	0	0	0.00	0	0	0.00	0	0	0.00	1	1	4.17	1.00
Sinus bradycardia	1	1	16.67	0	0	0.00	0	0	0.00	0	0	0.00	1	1	4.17	1.00

P values calculated with Fisher probabilities in 2 × 2 table data

(1) AEs are coded with MedDRA 23.0

(2) Drug-related means may be related, possibly related, related

Table 2 Incidence and frequency of drug-related adverse events occurred, multiple doses

SOC	4 mg/kg ($n = 6$)			Placebo ($n = 2$)			Total ($n = 8$)			
PT	No. of AEs	No. of participants	Incidence (%)	No. of AEs	No. of participants	Incidence (%)	No. of AEs	No. of participants	Incidence (%)	*P* value
Total	1	1	16.67	4	2	100.00	5	3	37.50	0.11
Investigations	1	1	16.67	3	2	100.00	4	3	37.50	0.11
Aspartate aminotransferase increased	0	0	0.00	1	1	50.00	1	1	12.50	0.25
Peripheral pulse decreased	0	0	0.00	1	1	50.00	1	1	12.50	0.25
Blood bilirubin increased	1	1	16.67	0	0	0.00	1	1	12.50	1.00
Blood creatine phosphokinase increased	0	0	0.00	1	1	50.00	1	1	12.50	0.25
Cardiac disorders	0	0	0.00	1	1	50.00	1	1	12.50	0.25
Atrioventricular block first degree	0	0	0.00	1	1	50.00	1	1	12.50	0.25

P values calculated with Fisher probabilities in 2 × 2 table data

(1) AEs are coded with MedDRA 23.0

(2) Drug-related means may be related, possibly related, related

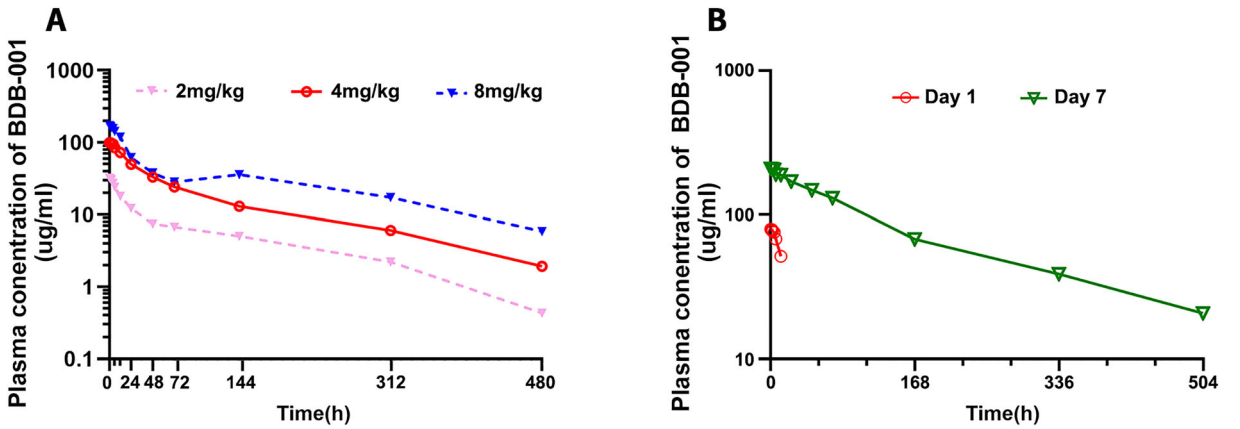

Fig. 2 Pharmacokinetics of BDB-001 administration. The plasma concentration of BDB-001 in single-dose cohorts (**A**) or multi-dose cohort (**B**) at the indicated time after infusion were determined. Median values from each group are plotted

Table 3 Pharmacokinetic parameters for single—ascending dose

PK	2 mg/kg ($n = 6$)	4 mg/kg ($n = 4$)	8 mg/kg ($n = 6$)
AUC_{inf} (h × ug/ml)	1895.63 (302.01)	7360.16 (1673.82)	19,484.61 (2080.51)
$AUC_{0\text{-}480\ h}$ (h × ug/ml)	1851.55 (266.74)	7026.80 (1489.68)	17,960.90 (1732.35)
C_{max} (ug/ml)	42.96 (5.66)	100.11 (11.37)	231.88 (27.83)
CL (mL/h/kg)	1.08 (0.19)	0.56 (0.11)	0.41 (0.04)
kel (1/h)	0.01 (0.003)	0.01 (0.001)	0.01 (0.001)
$t_{½}$ (h)	81.90 (24.63)	114.88 (17.72)	131.18 (16.53)
T_{max} (h)	1.00 (1.00–1.50)	1.25 (1.00–4.00)	1.01 (1.00–1.50)
V_z (mL/kg)	124.49 (28.96)	91.66 (14.34)	77.87 (7.60)
$AUC_{\_\%Extrap}$ (%)	2.11 (2.44)	4.31 (1.66)	7.71 (2.82)
MRT_{last} (h)	73.63 (13.57)	107.88 (13.11)	144.36 (8.76)

Values are shown as mean values (SD), except for T_{max} as median(min–max)
AUC_{inf} area under the concentration–time curve from time zero to infinity, $AUC_{0\text{-}480h}$ area under the concentration–time curve from time zero to 480 (h), *CL* systemic clearance, C_{max} peak plasma concentration, *kel* elimination rate constant, $t_{½}$ elimination half-life, T_{max} time to achieve C_{max}, *Vz* volume of distribution at terminal phase, MRT_{last} mean residence time–time curve from time zero to time of last quantifiable concentration, $AUC\_\%Extrap$ percentage of the area under the curve that has been derived after extrapolation or percentage residual area

2 AEs. No SAE nor suspicious and unexpected serious adverse reactions were observed. No participant required medical attention, and all participants fully recovered without sequelae by the end of the study (Tables S2, S3). There were 4 cases of dose errors occurring in cohort 2 (4 mg/kg): one participant received a lower dosage of 2.9 mg/kg, and three were given higher dosages of 4.9, 4.7, and 4.6 mg/kg, respectively. Because the results from all groups showed that they were well tolerated, these dosage deviations contributed little influence

Table 4 Pharmacokinetic parameters for multiple doses

PK	$AUC_{0-\tau,ss}$ (h × ug/ml)	$AUC_{inf,ss}$ (h × ug/ml)	$C_{max,ss}$ (ug/ml)	$C_{min,ss}$ (ug/ml)	$C_{avg,ss}$ (ug/ml)	$T_{max,ss}$ (h)	$t_{½}$ (h)	CL_{ss} (mL/h/kg)	Kel_{ss} (1/h)	$V_{z,s}$ (mL/kg)	$MRT_{inf,ss}$ (h)	Rac (AUC)	DF (%)
4 mg/kg (n = 6)	11,053.60 (1069.59)	54,450.56 (7340.56)	281.42 (32.34)	164.36 (18.06)	230.28 (22.28)	1.50 (1.00, 4.02)	191.05 (20.31)	0.36 (0.03)	0.004 (0.00)	76.25 (5.12)	209.80 (11.53)	6.42 (0.66)	50.83 (5.41)

Values are shown as mean values (SD), except for $T_{max,ss}$ as median (min–max)

$AUC_{0-\tau,ss}$ area under the concentration–time curve from time zero to t (h) at steady state, $AUC_{inf,ss}$ area under the concentration–time curve from time zero to infinity at steady state, $C_{max,ss}$ peak plasma concentration at steady state, $C_{min,ss}$ minimum concentration at steady state, $C_{avg,ss}$ average concentration at steady state, $T_{max,ss}$ time to achieve C_{max} at steady state, $t_{½}$ elimination half-life, CL_{ss} systemic clearance at steady state, kel_{ss} elimination rate constant at steady state, V_{ss} The volume of at steady state, $MRT_{inf,ss}$ mean residence time–time curve from time zero to infinity at steady state, *Rac (AUC)* accumulation Index by AUC_{0-tau}, *DF (%)* % degree of fluctuation

on the safety assessment. Moreover, the results of 24 participants' anti-drug antibody were negative.

Pharmacokinetics

Excluding 4 cases with dose error in cohort 2 (4 mg/kg, single-dose), 28 participants were included in the pharmacokinetic and pharmacodynamic analyses. The curves of plasma concentration of BDB-001 in three single-dose cohorts exhibited a similar profile, which started with a rapid decrease within 24 h after the intravenous infusion, followed by a slow elimination phase until 144–480 h (Fig. 2A). Across the dose range from 2 to 8 mg/kg, pharmacokinetics profiles were dose-dependent (Fig. 2A). Plasma concentration of BDB-001 decreased rapidly in a dose-dependent manner from 0 to 72 h after administration, which may reflect an effective binding with C5a, a characteristic of target-mediated drug disposal (TMDD).

The pharmacokinetic parameters are summarized in Table 3 for the single-dose cohorts and Table 4 for the multi-dose cohort. Among the single-dose cohorts, mean $AUC_{0\text{-}480\ h}$, C_{max}, $t_{½}$, and MRT_{last} increased from low to high doses, reached a maximum in the 8-mg/kg cohort, while the mean T_{max} remained similar (1–1.25 h) between different doses (Table 3). After 5 intravenous infusions of BDB-001 (multi-dose cohort), TMDD were also observed, as the plasma concentration of BDB-001 decreased rapidly after administration (Fig. 2B; Table 4). $T_{½}$ in the multi-dose cohort were larger than that in the single dose of 4 mg/kg (mean ± SD: 191 ± 20 vs. 115 ± 15, $P < 0.01$), and there was a faster clearance at day 1 and a slower clearance at day 7 (Fig. 2B). Moreover, the accumulation index by $AUC_{0\text{-}tau}$ [Rac (AUC)] of BDB-001 was 6.418 (mean ± SD: 6.418 ± 0.660) after 5 doses of 4 mg/kg. All these indicated the accumulation of BDB-001 in vivo.

Pharmacodynamics

The effect of BDB-001 on the target was modeled with the plasma-free C5a level, which

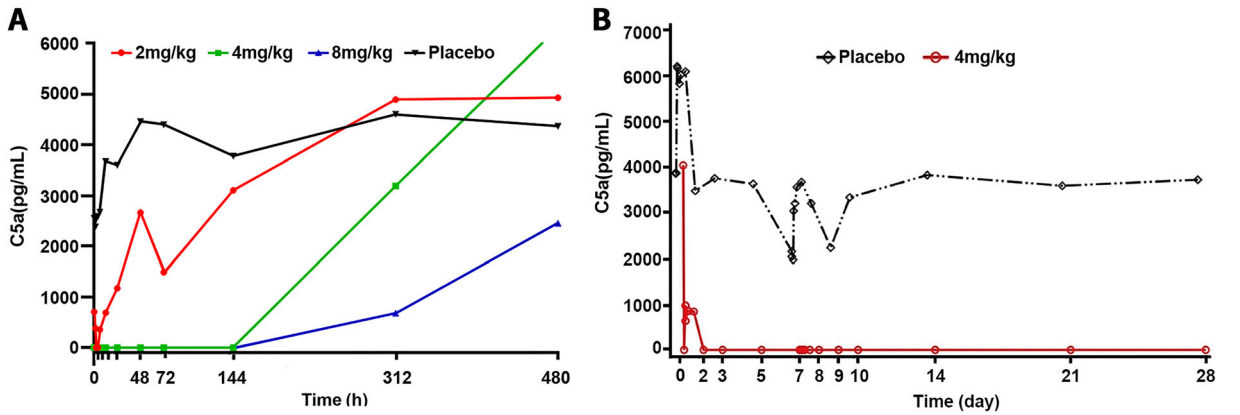

Fig. 3 Pharmacodynamics of BDB-001 administration. The plasma concentration of free C5a in single-dose cohorts (**A**) or multi-dose cohort (**B**) at the indicated time after infusion were determined. Median values from each group are plotted

reversely reflected the fixation of C5a by BDB-001. Plasma-free C5a decreased in a dose-dependent manner after intravenous infusion of BDB-001, while it maintained a similar level in the placebo group (Fig. 3A, B). In all the single-dose cohorts, the median C5a level were below the limit of quantitative value (BLQ) between 1.5 and 12 h after infusion. The median C5a level remained under the BLQ until 144 h and 312 h in the 4- and 8-mg/kg cohorts, respectively. These data suggest that the binding of C5a and BDB-001 increased along with the dose (Tables S4, S5), and the effective binding lasted 12, 144, and 312 h incrementally with 2, 4, and 8 mg/kg of BDB-001 administration, respectively. After 5 intravenous infusions of 4 mg/kg BDB-001 on days 1, 2, 3, 5, and 7, plasma concentration of BDB-001 was always more than 20 μg/mL, and the C5a level was under the BLQ at all time points (Figs. 2B, 3B). Combined with the pharmacokinetic analysis of BDB-001 plasma concentration, this suggests that the lowest effective plasma concentration of BDB-001 was approximately 20 μg/mL, and that a single dose of BDB-001 in 4 mg/kg had a long-time inhibition effect.

In single-dose cohorts, there was no statistically significant difference between groups in the cytokine levels of IL-6, IL-8, IL-10, IFN-γ, and TNF-α at any time point (Table S6). Also, none of the cytokine levels showed a significant difference between BDB-001 and the placebo groups at all time points in the multi-dose cohort, suggesting that BDB-001 did not cause the release of inflammatory cytokines after its administration.

DISCUSSION

Overactive complement system in the lung and other organs is one cause of SARS-CoV-2-induced atypical ARDS and thrombotic microangiopathy. Targeting C5a, C5, or C5aR1 is expected to improve the survival rate of COVID-19 patients. In this phase 1 clinical trial, we have demonstrated that BDB-001, an anti-C5a antibody, was well-tolerated in healthy Chinese volunteers, confirming the safety of the anti-C5a antibody from other studies [17–21]. All AEs were mild or moderate, and participants recovered without medical attention or sequelae. Although previous studies raised concerns with increased abnormal bilirubin [22], we observed only 2 cases at grade 1. The severity or frequency of AEs did not show any dose-dependent trend, nor a significant difference from the placebo group.

Pharmacokinetics parameters, such as the $AUC_{0\text{-}480\ h}$, AUC_{inf} and C_{max}, increased dose-dependently, confirming the characteristics of TMDD. The rapid decrease of BDB-001 concentration after the intravenous infusion is associated with a rapid decrease of free C5a in the plasma, indicating its binding to C5a. The binding to C5a leads to its fast clearance at a low

dose, whereas a slower clearance was noted at higher doses. Accordingly, T_{max}, $T_{½}$, MRT_{last} increased from low to high doses. Importantly, plasma-free C5a decreased in a dose-dependent manner. Accumulation effect in vivo was confirmed after 5 doses of 4 mg/kg infusion.

In this study, we utilized a double-blind randomization strategy to eliminate potential bias. The enrolled participants were balanced in most baseline characteristics among the 4 cohorts and placebo. We used an escalation strategy to evaluate the safety of BDB-001 in single doses of 2, 4, and 8 mg/kg or 5 doses of 4 mg/kg, with no significant drug-related AEs.

In this phase 1 study, we did not directly assess the efficacy of BDB-001, but instead assessed its suppression of serum C5a concentration as pharmacological activity. A previous study showed a significant drop of plasma C5a concentration within 2 h of antibody IFX-1 (vilobelimab) application in severe sepsis patients, which remained depressed (< 10 ng/ml) for 24 h (recovery time 72 h), 72 h (recovery time 5 days), or 5 days (recovery time > 8 days) after receiving two dosages of 2, 4, or 8 mg/kg antibody, respectively [21]. In our study, a single dose of BDB-001 at 4 mg/kg showed a long-time inhibition effect over 6 days, while 5 intravenous infusions at 4 mg/kg suppressed the C5a level under the BLQ for longer than 28 days, a better pharmacological activity than IFX-1. Previous reports have shown that the blockade of C5a is able to completely suppress C5a-elicited inflammation [14–16, 23]. IFX-1 infusion suppressed the elevated C5a level in severe COVID-19 patients to normal for 8 days[20], and improved the survival of patients with severe COVID-19 [19, 24]. Therefore, BDB-001 has the potential to be effective against COVID-related ARDs, by inhibiting the C5a-mediated inflammatory cytokines, and following complement activation often observed in severe COVID-19 patients [4, 5, 7].

In addition to COVID-19, anti-C5a antibody therapy has a broad implication. C5a inhibition by anti-C5a antibody reduced coronary endothelial dysfunction by limiting neutrophil-mediated impairment of endothelium-dependent relaxation after cardiopulmonary bypass and cardioplegic reperfusion [25], and improved burn-induced cardiac dysfunction [26]. C5a inhibition reduced acute lung injury and systemic inflammation by alleviating the excessive activation of inflammatory responses [23, 27], which warrants its further investigation in sepsis [21, 28]. It also demonstrated a substantial improvement in the efficacy of anti-PD-1 antibodies against lung cancer growth and metastasis [29]. These data support the use of BDB-001 being extended to other scenarios caused by C5a-activated systemic inflammation. The first Investigational New Drug application of BDB-001 has been completed for treating t moderate to severe hidradenitis suppurativa.

Several limitations existed in our study. First, as a phase 1 clinical trial, the sample size was small, which can be expanded in consequence studies. Second, participants were recruited from healthy Chinese adults aged 21–45 years. It remains undetermined whether BDB-001 is safe for high-risk populations, such as older adults and those with underlying comorbidities, including but not limit to hypertension, diabetes, or obesity [30], or mild-to-moderate COVID-19 patients as the targeted population for the therapeutic purpose. These populations may present different safety and pharmacokinetic characteristics from healthy people. Further studies including these populations with a large sample size are needed to demonstrate its safety and pharmacokinetic profile more precisely, with great horizons.

CONCLUSIONS

BDB-001 was well tolerated as a single-dose up to 8 mg/kg and a multi-dose up to 5 doses of 4 mg/kg, st which its inhibitory effect on C5a can be observed. Available data warrant further safety and efficacy studies of BDB-001 in COVID-19 patients, to provide a safe and effective recommended dose for the subsequent clinical trials. These results may eventually expand to other C5-related clinical challenges, including but not limited to virus-mediated ARDs.

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Disclosures. Guiling Chen, Nan Li, Xiahong Dai, Shiyan Tu, Zhenwei Shen, Kaiqi Wu, Tinghan Jin, Jiajun Wu, Conggao Peng, Guoping Sheng, Mengfei Zhu, Lingling Tang and Lanjuan Li all confirm that they have no conflicts of interest to declare.

Compliance with Ethics Guidelines. The protocol and informed consent were reviewed and approved by the Clinical Trial Ethics Committee of Shulan (Hangzhou) Hospital. All participants signed informed consents before the screening. This study was conducted in accordance with the principles of Declaration of Helsinki and Good Clinical Practice.

Data Availability. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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