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ORIGINAL RESEARCH ARTICLE

Pharmacokinetics of ABT-122, a TNF-α- and IL-17A-Targeted Dual-Variable Domain Immunoglobulin, in Healthy Subjects and Patients with Rheumatoid Arthritis: Results from Three Phase I Trials

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Abstract

Background and Objective ABT-122 is a dual-variable domain immunoglobulin that neutralizes both tumor necrosis factor-α and interleukin-17A, with the goal of achieving greater clinical efficacy than can be achieved by blocking either cytokine alone. This work characterized the pharmacokinetics of ABT-122 in healthy subjects and in patients with rheumatoid arthritis.

Methods ABT-122 pharmacokinetics was evaluated in three phase I studies. In Study 1, single intravenous (0.1, 0.3, 1, 3, and 10 mg/kg) and subcutaneous (0.3, 1, and 3 mg/kg) doses were evaluated in healthy subjects. In Studies 2 and 3, multiple subcutaneous doses (1 mg/kg every other week or 0.5–3 mg/kg every week) were evaluated for 8 weeks in patients with rheumatoid arthritis on stable methotrexate therapy. Pharmacokinetic data were available from 48 healthy subjects and 31 patients with rheumatoid arthritis.

Results ABT-122 showed multi-exponential disposition with more than dose-proportional exposures at the 0.1–1 mg/kg doses and approximately dose-proportional exposures at doses ≥1 mg/kg. ABT-122 absolute subcutaneous bioavailability was approximately 50% with maximum serum concentrations observed 3–4 days after dosing. Steady state was achieved by week 6 of subcutaneous dosing. ABT-122 maximum serum concentration-to-trough concentration ratio was 2.6 for every other week dosing and 1.3 for every week dosing, corresponding to an effective half-life of 10–18 days. ABT-122 median area under the serum concentration–time curve accumulation ratio was 3.8–4.8 with every week dosing. Measureable antidrug antibodies were observed in all 48 subjects in Study 1 by day 15 post-dose and 19 of 31 ABT-122-treated patients in Studies 2 and 3 [median time to appearance of antidrug antibodies of 64 days (range 15–92 days)]. No dose-limiting toxicities were observed in these studies and the maximum tolerated dose was not identified.

Conclusions Results from these three phase I studies supported testing ABT-122 every week and every other week regimens in phase II trials in subjects with rheumatoid and psoriatic arthritis. Study 2 (EudraCT: 2012-003448-54); Study 3 (NCT01853033)

Key Points

The pharmacokinetics of single and multiple doses of ABT-122, an immunoglobulin that neutralizes both tumor necrosis factor-α and interleukin-17A, was evaluated in healthy subjects and patients with rheumatoid arthritis.

The pharmacokinetic profile of ABT-122 was approximately dose proportional at doses >1 mg/kg. Steady-state serum concentrations were achieved after 6 weeks of subcutaneous dosing. ABT-122 maximum serum concentration-to-trough concentration ratio was 2.6 for every other week dosing and 1.3 for every week dosing, corresponding to an effective half-life of 10–18 days. The ABT-122 median area under the concentration–time curve accumulation ratio was 3.8–4.8 with every week dosing.

ABT-122 has a pharmacokinetic profile that is suitable for every week or every other week subcutaneous dosing.

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1 Introduction

Rheumatoid arthritis (RA) is an autoimmune inflammatory disease affecting the synovium of the joints. Over time, the inflammation causes irreversible damage to the bone and cartilage, causing patients to experience pain and loss of mobility. Approximately 1.5 million people in USA have RA, and it is three times more common in women than men [1, 2]. The global prevalence is estimated to be approximately 1% [3].

Tumor necrosis factor-α (TNF-α) and interleukin 17-A (IL-17) are proinflammatory cytokines implicated in the pathogenesis of RA as well as other inflammatory diseases. Tumor necrosis factor-α and IL-17 are expressed at increased levels in the synovial tissue in patients with RA and both are key factors in the joint inflammation and damage to bone and cartilage that are hallmarks of the disease. Tumor necrosis factor-α blockade is a well-established strategy for the treatment of RA and several anti-TNF-α antibodies are currently approved for this indication [4]. Alternatives to anti-TNF-α antibodies, for example, agents that block IL-17, are also being investigated for the treatment of RA and other inflammatory diseases [5, 6].

Because both TNF-α and IL-17 are implicated in RA, concurrent inhibition of both cytokines is being pursued as a treatment strategy. Several lines of evidence have emerged to suggest that greater clinical response and improved protection against joint damage may be possible with simultaneous neutralization of TNF-α and IL-17 compared with neutralization of either cytokine alone [7–11]. For example, in mouse models of collagen-induced arthritis, combined neutralization of TNF-α and IL-17 inhibited inflammation and reduced mean arthritis score and joint damage more effectively than single neutralization of TNF-α or IL-17 [9]. In addition, when RA synovial fibroblasts were co-incubated with T helper-17 cells ex vivo, expression of proinflammatory cytokines and factors associated with joint destruction were lowest when TNF-α and IL-17 were both inhibited [10]. Furthermore, in a prospective study of subjects with RA, levels of TNF-α and IL-17 messenger RNA in synovial biopsy specimens were synergistically prognostic for worse clinical outcomes [11].

ABT-122 is a novel dual-variable domain immunoglobulin (DVD-Ig^{TM}) of the immunoglobulin G1 class designed to specifically neutralize both TNF-α and IL-17 [12]. ABT-122 is built on an adalimumab backbone and contains two identical κ light chains and two identical immunoglobulin G1 heavy chains, each of which contains two variable domains connected in tandem, enabling dual specificity capable of binding both TNF-α and IL-17 [13]. Together, they form a tetravalent immunoglobulin-like molecule with a molecular weight of 198.5 kD.

Tumor necrosis factor-α typically exists as a soluble homotrimer after being enzymatically cleaved from its cell surface-bound precursor [14], and IL-17 represents a family of dimeric soluble molecules [15]. ABT-122 binds to TNF-α (likely both soluble and membrane-bound forms) and IL-17A, thereby neutralizing TNF-α, IL-17A homodimers, and IL-17A-F heterodimers, but not TNF-α receptors or the other members of the IL-17 family. Data from an ex vivo assay in human fibroblast-like synoviocytes derived from patients with RA showed that ABT-122 fully inhibited IL-6 release from fibroblast-like synoviocytes stimulated by the combination of TNF and IL-17, whereas individual monoclonal antibodies to TNF-α or IL-17 only partially inhibited IL-6 production [16], suggesting that ABT-122 binds to both TNF-α and IL-17. In this same assay, serum from patients receiving ABT-122 retained dual inhibition of TNF-α and IL-17 for up to 3 weeks after single-dose administration [16]. In addition, ABT-122 has shown greater efficacy in a mouse model of collagen-induced arthritis than blockade of either cytokine alone [17, 18]. The ability of ABT-122 to inhibit both cytokines makes it an attractive agent for the potential treatment of RA and other immune-mediated inflammatory diseases. The aim of the three studies described herein was to investigate the pharmacokinetics, safety, and tolerability following single-dose administration of ABT-122 in healthy subjects and multiple-dose administration in patients with RA. This report describes the pharmacokinetic results from these studies. Detailed descriptions of the safety and tolerability results are reported elsewhere [13].

2 Methods

2.1 Study Designs

The studies were conducted in accordance with Good Clinical Practice guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The protocols and informed consent forms were approved by the institutional review boards and participants provided written informed consent before any study-related procedures were performed.

Each study was conducted according to a randomized, double-blind, placebo-controlled design in which participants were assigned to ABT-122 or placebo in a 3:1 ratio. Study 1 was a two-part, single-ascending-dose study conducted in healthy adult subjects (Table 1). In Part I, subjects received a single continuous intravenous (IV) infusion over 2 h of either ABT-122 (0.1, 0.3, 1, 3, or 10 mg/kg) or matching placebo. In Part II, subjects received a single subcutaneous (SC) injection of ABT-122 (0.3, 1, or 3 mg/kg)

Table 1 Overview of ABT-122 studies

Study	Population	*N*	ABT-122 dose	Pharmacokinetic sampling times
Study 1	Healthy subjects	ABT-122: 48 (6 per dose level) Placebo: 16 (2 per dose level)	Part I: single IV dose (0.1, 0.3, 1, 3, or 10 mg/kg) Part II: single SC dose (0.3, 1, or 3 mg/kg)	IV: **0**, 2, 4, 6, 10, 14, and 24 h; days 2, 3, 4, 5, 6, 7, 8, 11, **15**, **22**, **29**, **36**, **43**, **57**, **71**, **85** SC: **0**, 8, and 24 h; days 2, 3, 4, 5, 6, 7, 8, 11, **15**, **22**, **29**, **36**, **43**, **57**, **71**, **85**
Study 2 EudraCT: 2012-003448-54	Patients with stable RA on background MTX	ABT-122: 18 (6 per dose level) Placebo: 7 (2 per dose level [a])	Multiple SC doses 1 mg/kg EOW for 4 doses 1.5 or 3 mg/kg EW for 8 doses	EOW: **0**, 8, and 24 h; days 2, 3, 5, 8, **15**, **29**, **43**, 44, 45, 47, **50**, **57**, **71**, **85** EW: **0**, 8, and 24 h; days 2, 3, 5, 8, **15**, **22**, **29**, **36**, **43**, **50**, 51, 52, 54, **57**, **64**, **78**, **92**
Study 3: NCT01853033	Patients with stable RA on background MTX	ABT-122: 13 (6 per dose level[b]) Placebo: 6 (2 per dose level[c])	Multiple SC doses 0.5[b], 1.5, or 3 mg/kg EW for 8 doses	EW: **0**, 8, and 24 h; days 2, 3, 4–5, 8, **15**, **22**, 23, 24, 25–26, **29**, **36**, **43**, **50**, 51, 52, 53–54, **56–57**, **63–64**, **77–78**, **91–92**

Bold font indicates time points at which serum antidrug antibodies were also measured

EOW every other week, *EW* every week, *IV* intravenous, *MTX* methotrexate, *RA* rheumatoid arthritis, *SC* subcutaneous

[a] Three patients received placebo in the ABT-122 1-mg/kg EOW dose group

[b] Only one patient received ABT-122 0.5 mg/kg EW

[c] One patient received placebo in the ABT-122 0.5-mg/kg EW dose group and three patients received placebo in the ABT-122 3-mg/kg EW dose group

or matching placebo. In both parts, dose escalation proceeded after evaluation of the safety, tolerability, and pharmacokinetic data from the preceding dose level. Subjects were confined to the study site beginning 1–3 days before study drug administration on day 1 and ending on day 8. Subjects then returned to the study site approximately weekly for another 11 weeks for continued safety assessments and pharmacokinetic sampling.

Studies 2 and 3 were multiple-dose studies conducted in patients with stable RA on background therapy with methotrexate (MTX) (Table 1). Patients received SC injections of ABT-122 (1 mg/kg every other week [EOW] for four doses or 1.5 or 3 mg/kg every week [EW] for eight doses in Study 2 and 0.5, 1.5, or 3 mg/kg EW for eight doses in Study 3) or matching placebo. Patients were confined to the study sites for 2–3 days for the first and last doses of study drug, beginning 1 day before the doses were administered. Other doses were administered on an outpatient basis.

2.2 Study Participants

For Study 1, men and women between the ages of 18–55 years, inclusive, with a body mass index of 19–29.9 kg/m^2 and in general good health on the basis of results of medical history, laboratory profile, physical examination, chest X-ray, and 12-lead electrocardiogram were eligible to enroll. For Studies 2 and 3, men and women between the ages of 18–75 years with a body mass index of 19–39 kg/m^2 (Study 2) or 19–35 kg/m^2 (Study 3) who had a diagnosis of RA (based on the 1987 or 2010 American College of Rheumatology/European League Against Rheumatism criteria) for at least 3 months, had been on MTX therapy (7.5–25 mg/week) for at least 3 months, and had been receiving a stable MTX dose for at least 4 weeks before the first dose of study drug were eligible to enroll.

In all studies, potential participants were excluded if they were female and were pregnant or breastfeeding, had any clinically significant condition (other than RA for Studies 2 and 3), abnormalities, infection, or febrile illness, had a positive test result for hepatitis B or C or human immunodeficiency virus, or had a history of, or evidence of, active or latent tuberculosis. For Studies 2 and 3, participants must not have had evidence of an anti-ABT-122 antibody in a pre-study serum sample, a history of diabetes mellitus, or evidence of immunosuppression.

2.3 Pharmacokinetic Sampling and Bioanalytical Methods

Serial blood samples were collected for up to 92 days after a single dose or the last dose of study drug as summarized in Table 1. Serum concentrations of ABT-122 were determined using a validated chimeric electrochemiluminescent immunoassay with step-by-step incubation at

AbbVie (Ludwigshafen, Germany). The assay uses biotinylated TNF-α as a capture reagent and a sulfo-tagged monoclonal antibody against the IL-17 binding site as the detection reagent. The assay detected ABT-122 molecules with at least one free binding site each for TNF-α and IL-17. The lower limit of quantitation for the ABT-122 serum concentration assay was 13.6 ng/mL. Overall precision (% coefficient of variation) was <7.5% and the observed bias was between −6.3 and −3.1%. Samples quantified below the lower limit of quantification were reported as zero.

Serum titers of antidrug antibodies (ADA) were determined using a validated bridging electrochemiluminescent immunoassay with biotinylated ABT-122 as a capture reagent and sulfo-tagged ABT-122 as the detection reagent. The assay detected free anti-ABT-122 antibodies generated by acid dissociation to allow for dissociation of ADA from the drug/ADA complex. Samples were initially screened for the presence of ADA. Samples identified as positive for ADA were then analyzed in a titer-based assay and if necessary, further diluted serially to determine the antibody titer using a dedicated titration cut-point. Antidrug antibody positive samples from the titer-based assay were further analyzed for specificity in a confirmatory assay. Serum samples were considered positive for ADA when the mean signal was greater than the calculated screening cut-point and the suppression in the confirmatory assay was ≥17.1% for healthy subjects and ≥27.7% for patients with RA. The sensitivity at the screening cut-point was 20.7 ng/mL for healthy subject samples and 41.6 ng/mL for RA patient samples.

2.4 Pharmacokinetic and Statistical Analyses

ABT-122 pharmacokinetic parameters were estimated using noncompartmental methods with Phoenix WinNonlin Version 6.3 (Pharsight Corporation, Mountain View, CA, USA). The maximum observed serum concentration (C_{max}), the time to C_{max}, and for multiple dosing, the observed serum concentration at the end of a dosing interval (C_{trough}), were determined directly from the serum concentration–time data. Calculated parameters included the apparent terminal phase elimination rate constant (β), the terminal phase elimination half-life ($t_{1/2}$), and the area under the serum concentration–time curve (AUC) from time 0 to the last measureable concentration (AUC_t) or infinite time (AUC_∞), and for multiple dosing AUC over the dosing interval (AUC_{tau}). The relative bioavailability (F) of ABT-122 following SC administration in Study 1 was determined by analysis of covariance using AUC values for doses administered by IV and SC routes. Dose-normalized C_{max}, C_{trough}, and AUC_{tau} values, and the accumulation ratio (R_{ac}) for C_{max} and AUC, were also determined in the multiple-dose studies (Studies 2 and 3).

Statistical analyses were performed using SAS software Version 9.4 (SAS Institute Inc., Cary, NC, USA). Dose proportionality for ABT-122 exposure was assessed by performing an analysis of covariance on the natural logarithms of dose-normalized C_{max} and AUC from the single-ascending dose study and dose-normalized C_{max}, AUC, and C_{trough} of the last dose interval from the multiple-dose studies. Within the framework of the final model, the hypothesis of no difference between the highest and the lowest dose was tested. In addition, a repeated-measures analysis was performed on the observed C_{trough} values for the second through the last dose to investigate attainment of steady state. Separate analyses were performed for EW and EOW dosing.

2.5 Safety Assessments

Safety was evaluated throughout the study based on assessments of adverse events, vital signs values, physical examinations, laboratory values, and 12-lead electrocardiograms. All participants who received at least one dose of study drug were included in the analyses. Participants who received placebo were pooled into a single group within each study or study part.

3 Results

3.1 Participants

A total of 64 healthy subjects and 44 patients with RA were enrolled in the studies (Table 1). Two subjects in Study 1 were lost to follow-up after the study drug had been administered (one subject in the placebo group after day 58 and one subject in the 3-mg/kg IV group after day 8). One patient in the 1.5-mg/kg SC group in Study 2 and two patients (one placebo and one in the 3-mg/kg SC group) in Study 3 discontinued from the studies because of adverse events prior to receiving the last dose of study drug. Enrollment in the 0.5-mg/kg group was truncated because pharmacokinetic and safety data from a comparable dose (1 mg/kg EOW) had been obtained in a parallel study.

Demographic and baseline disease characteristics for the study participants are summarized in Table 2. The healthy subjects were younger (mean age 35 years) and included more men (70%) than the patients with RA (mean age ~57 years and >60% women).

3.2 ABT-122 Pharmacokinetics

3.2.1 Single Doses in Healthy Subjects

ABT-122 maximum serum concentrations were observed at a median of 4–6 h (range 2–10 h) following a single IV dose and approximately 3–4 days (range: 1–6 days) after a

Table 2 Participant demographics and baseline disease characteristics

Demographic characteristic	Study 1, $N = 64$	Study 2, $N = 25$	Study 3, $N = 19$
Weight, kg; mean (SD), range	75.8 (10.2), 52–98	78.3 (14.5), 48.7–99.3	82.8 (19), 47–119.6
Body mass index, kg/m^2; mean (SD), range	25.4 (2.6), 19.6–30.1	27.7 (4.2), 20.3–34.7	29.8 (5.4), 20–37
Age, years; mean (SD), range	35.4 (11.2), 19–56	57.4 (8.7), 42–73	57.7 (10.3), 38–73
Baseline MTX dose, mg/week; mean (SD), range	NA	15.9 (3.2), 7.5–20	14.7 (5.6), 2.5–25
Sex, *n* (%)			
Male	45 (70.3)	7 (28)	7 (36.8)
Female	19 (29.7)	18 (72)	12 (63.2)
Race, *n* (%)			
Black	16 (25)	0 (0)	4 (21.1)
White	48 (73.4)	25 (100)	15 (78.9)
Other	1 (1.6)	0 (0)	0 (0)
Baseline hs-CRP[a], mg/L; mean (SD), range	NA	4 (4.9), 0.6–22.7	6.9 (11.9), 0.4–42.2
Baseline DAS28-CRP[a]; mean (SD), range	NA	3.8 (1.1), 2.1–5.8	3.1 (1.5), 1.5–5.3

DAS Disease Activity Score, *hs-CRP* high-sensitivity C-reactive protein, *MTX* methotrexate, *NA* not applicable, *SD* standard deviation

[a] Baseline DAS28-CRP scores in patients were calculated using a standard formula (http://www.das-score.nl/) taking into account the concentrations of CRP, the patient's global assessment of disease activity, and the tender joint count and swollen joint count for 28 joints. hs-CRP was measured using standard methods

single SC dose (Fig. 1; Table 3). ABT-122 concentrations declined in a multi-exponential manner thereafter, with harmonic mean $t_{1/2}$ values of approximately 3–6 days with IV or SC dosing. The absolute SC bioavailability of ABT-122 was 48% (95% confidence interval 41–57%).

Based on the analyses of covariance and pairwise comparisons, ABT-122 AUC increased more than dose proportionally in the 0.1–1 mg/kg IV dose range ($p < 0.05$). No significant deviation from dose proportionality ($p > 0.05$) was detected in the increase in ABT-122 AUC in the 1–10 mg/kg IV dose range or in the 0.3–3 mg/kg SC single-dose range (Table 3; Fig. 2). The between-subject variability (% coefficient of variation) in ABT-122 C_{max} and AUC ranged from 9 to 27% following IV administration and from 26 to 51% following SC administration.

Measurable ADA titers were observed at one or more time points in all 48 subjects (100%) who received ABT-122. Of note, three subjects had measureable ADA titers prior to ABT-122 administration (one subject each in the 0.1-mg/kg IV, 10-mg/kg IV, and 3-mg/kg SC groups). All subjects had a detectable titer at the first time point (day 15) of ADA measurement after ABT-122 dosing. None of the subjects on placebo had a positive ADA titer at any time during the study. In general, the titer units were relatively low (<500 units) for most of the subjects (40/48). The magnitude of the ADA titer appeared to be generally lower at higher ABT-122 dose levels (ABT-122 doses >1 mg/kg). One subject (10-mg/kg IV dose group) developed high ADA titers (>8000 titer units) following ABT-122 administration and showed a decrease in ABT-122 serum concentrations; this subject had measurable ADA prior to ABT-122 administration. With the exception of the one subject noted above, no apparent effect of ADAs on the pharmacokinetics of ABT-122 was observed.

3.2.2 *Multiple Dosing in Patients with Rheumatoid Arthritis*

The concentration–time profiles of ABT-122 following EW SC dosing in Studies 2 and 3 combined are shown in Fig. 3a and following EOW SC dosing in Study 2 are shown in Fig. 3b. The steady-state pharmacokinetic parameters are shown in Table 4. Maximum ABT-122 serum concentrations were reached at a median of 2–3 days. The ABT-122 C_{max}-to-C_{trough} ratio was 2.6 for EOW dosing and 1.3 for EW dosing, corresponding to an effective half-life of 10 days with EOW dosing and 18 days with EW dosing. After the last dose, the ABT-122 median accumulation ratio based on AUC was 3.8–4.8 with EW dosing. There was no statistically significant difference between ABT-122 C_{trough} values starting on week 6 and those at later time points based on repeated-measures analysis ($p > 0.05$), indicating that steady state had been achieved by week 6 of dosing (Fig. 3c). ABT-122 exposure did not deviate significantly from dose proportionality in patients with RA (Table 4) in the evaluated dose range.

Nineteen of 31 patients (61%) from Studies 2 and 3 combined who received ABT-122 had detectable ADA titers during the study: 12/18 in Study 2 (four, five, and three patients at ABT-122 doses of 1 mg/kg EOW, 1.5 mg/kg EW, and 3 mg/kg EW, respectively) and 7/13 in Study 3 (one, one, and five patients at ABT-122 doses of 0.5 mg/kg

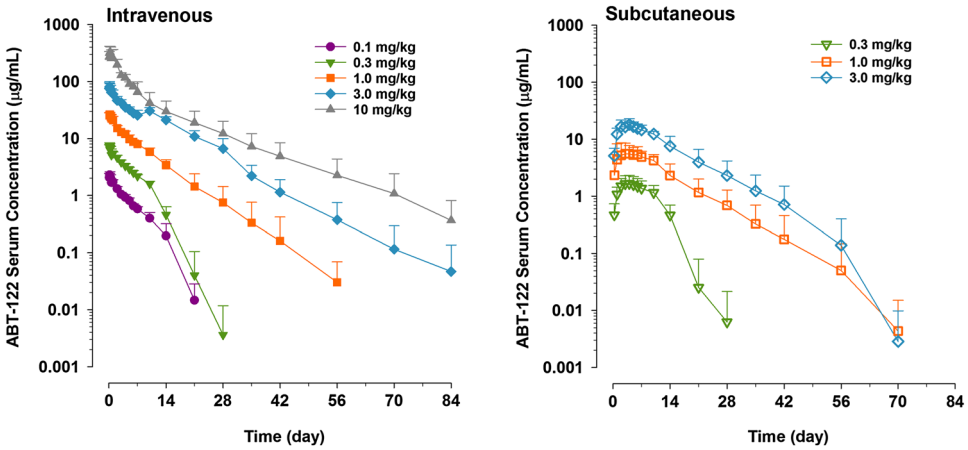

Fig. 1 ABT-122 mean (+standard deviation) serum concentration–time profiles following single intravenous or subcutaneous doses in healthy subjects

EW, 1.5 mg/kg EW, and 3 mg/kg EW, respectively). The median time for appearance of ADAs in patients with RA was 64 days (range 15–92 days) (Fig. 4). No correlation was observed in ADA incidence or time to appearance of ADA across ABT-122 doses. Across all patients with RA, ADA titers were <100 units, except for one patient at an ABT-122 dose of 3 mg/kg EW who developed high ADA titers (>49,700 units) starting on day 15. There was no apparent difference in ABT-122 pharmacokinetic parameters in patients who had detectable titers compared with those who did not, except for one subject at an ABT-122 dose of 3 mg/kg EW, noted above, who developed high ADA titers starting on day 15 with undetectable serum ABT-122 concentrations starting on day 8. This subject also experienced a grade 2 injection-site reaction on day 9 (noted in the safety section below).

3.3 Safety

Across the three studies, 48 healthy subjects and 31 patients with RA received ABT-122 and 16 healthy subjects and 13 patients with RA received placebo. ABT-122 was well tolerated by the healthy subjects and patients with RA in these studies and no dose-limiting toxicities were identified (i.e., the maximum tolerated dose was not identified). For single IV or SC dosing, none of the healthy subjects discontinued from the study because of an adverse event and there were no infusion reactions or injection-site reactions. The treatment-emergent adverse events assessed by the investigator as possibly related to study drug included pruritus, headache, nausea, and hypersensitivity (described as a localized erythema on the face distant from the injection site). No serious or severe adverse events were reported. No clinically meaningful changes in laboratory parameters, vital signs values, or electrocardiogram parameters were observed.

For multiple SC dosing over 8 weeks in patients with RA, there was no clinically meaningful difference in the pattern of adverse events or serious adverse events between ABT-122 and placebo. No dose-limiting toxicities were identified and no systemic hypersensitivity reactions were reported. Additionally, no clinically significant changes in laboratory parameters, vital signs, or electrocardiogram parameters were observed with ABT-122. One patient in Study 2 and two patients in Study 3 experienced adverse events that led to their discontinuation from the studies. In Study 2, rectal carcinoma occurred in one patient with a family history of gastrointestinal cancer. The patient was on ABT-122 1.5-mg/kg EW treatment and the event was considered to be unrelated to ABT-122 by the investigator. The two patients (one on placebo and one on ABT-122 3 mg/kg EW) who discontinued in Study 3 experienced self-limited grade 2 injection-site reactions. The adverse events did not result in any clinical sequelae and resolved spontaneously with symptomatic treatment. A 61-year-old female patient with RA with a history of gallstones in the ABT-122 3-mg/kg dose group experienced a serious adverse event of grade 2 cholecystitis that required a cholecystectomy; the event was not considered to be related to ABT-122. The patient recovered and continued in the study following cholecystectomy. Additional details on the safety, tolerability, and pharmacodynamic results from Studies 2 and 3 are reported elsewhere [13].

4 Discussion

Blockade of TNF-α and IL-17A have been proven to be effective treatment strategies in several autoimmune diseases including RA, psoriasis, and psoriatic arthritis. ABT-122 is a dual TNF-α and IL-17A-targeted dual-variable domain immunoglobulin that neutralizes both cytokines simultaneously with the aim of achieving greater clinical response than would be possible with neutralization of either agent alone. The present studies were the first studies to characterize the pharmacokinetics of single

Table 3 ABT-122 single-dose pharmacokinetic (PK) parameters (mean, % coefficient of variation) in healthy subjects

PK parameter	Intravenous dose groups (mg/kg)					Subcutaneous dose groups (mg/kg)		
	0.1 $N = 6$	0.3 $N = 6$	1 $N = 6$	3 $N = 6$	10 $N = 6$	0.3 $N = 6$	1 $N = 6$	3 $N = 6$
C_{max} (μg/mL)	2.4 (12)	7.5 (13)	27 (9)	82 (23)	348 (27)	1.7 (38)	6.1 (51)	18 (26)
T_{max} (h or day)[a]	4.0 (4.0–6.0)	4.0 (2.0–10.0)	4.0 (2.0–10.0)	4.0 (4.0–6.0)	6.0 (4.0–10.0)	3.0 (2.0–4.0)	4.5 (1.0–6.0)	4.0 (3.0–4.0)
AUC_{∞} (μg·day/mL)	12 (13)	39 (10)	167 (13)	669 (23)	1820 (22)	21 (26)	89 (32)	277 (27)
$t_{1/2}$ (day)[b]	3.6 (31)	2.9 (31)	5.2 (30)	6.3 (32)	3.9 (256)	3.7 (67)	3.1 (164)	3.2 (104)
Clearance (mL/h)	30.9 (20)	25.4 (18)	21.0 (21)	14.4 (28)	18.6 (29)	49.9 (19)	40.5 (31)	34.0 (28)

AUC_{∞} area under the concentration–time curve from time 0 to infinity, *C_{max}* maximum serum concentration, *T_{max}* time to C_{max}, *$t_{1/2}$* terminal phase elimination half-life

[a] Median (range); data are presented in hours for the intravenous dose groups and days for the subcutaneous dose groups

[b] Harmonic mean (pseudo-% coefficient of variation)

ascending IV and SC doses (0.1–10 mg/kg) of ABT-122 in healthy subjects and multiple ascending SC doses (0.5–3 mg/kg) EW or EOW in patients with RA. The dose range of ABT-122 evaluated in these phase I studies encompasses the dose range evaluated in phase II and III studies for other monoclonal antibodies targeting TNF-α or IL-17 individually, such as adalimumab, infliximab, secukinumab, and ixekizumab [19–23].

ABT-122 showed multi-exponential disposition, similar to that of other monoclonal antibodies [24], with more than dose-proportional exposure at lower doses (0.1–1 mg/kg) and approximately dose-proportional exposure at doses ≥1 mg/kg. The more than proportional increase in exposure at the lower range of doses is a typical characteristic of monoclonal antibodies with target-mediated disposition; however, it is also manifested for some drugs as a result of ADAs having higher impact on the exposures at the lower doses. It is noteworthy that several anti-TNF-α antibodies have not consistently shown target-mediated disposition in humans [20, 25].

The absolute bioavailability of ABT-122 with SC dosing was 48%. Maximum serum concentrations were reached 2–4 days after dosing and steady state was achieved by week 6. The effective half-life of ABT-122, calculated based on the C_{max}-to-C_{trough} ratio at steady state, was 10 and 18 days with EOW and EW dosing, respectively. ABT-122 was well tolerated by the healthy subjects and patients with RA in these studies, and overall, its pharmacokinetic profile appears to be favorable for EW or EOW SC administration.

Some differences were noted when ABT-122 pharmacokinetic parameters were compared with those of adalimumab. The pharmacokinetics of adalimumab was dose proportional over the IV dose range of 0.5–10.0 mg/kg [20], whereas ABT-122 pharmacokinetics showed a more than dose-proportional increase in exposure at IV doses <1 mg/kg and a dose proportional increase in exposure at higher doses as previously discussed. The absolute SC bioavailability of ABT-122 (48%) is lower than that of adalimumab (64%). Following single IV doses, ABT-122 clearance (range 30.9–14.4 mL/h) was higher than that of adalimumab (12 mL/h) [20], particularly at the lower ABT-122 doses.

The pharmacokinetics of ABT-122 was generally similar between healthy subjects and patients with RA. Following SC dosing, ABT-122 dose-normalized AUC_{∞} ranged from 69 to 93 μg·day/mL/(mg/kg) in healthy subjects and the dose-normalized AUC_{tau} following the last dose in patients with RA ranged from 61 to 114 μg·day/mL/(mg/kg). The minor differences noted could be owing to a combination of differences in demographic characteristics, with patients with RA being older and having a larger body mass index compared with healthy subjects,

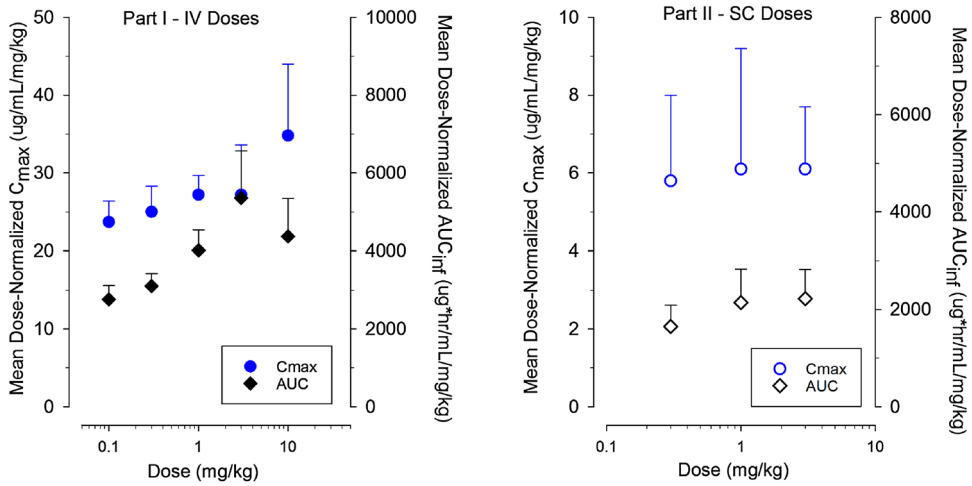

Fig. 2 ABT-122 dose-normalized maximum serum concentration (C_{max}) and areas under the concentration–time curve from time 0 to infinity (AUC_{inf}) [mean + standard deviation] after a single ABT-122 dose in healthy subjects. *IV* intravenous, *SC* subcutaneous

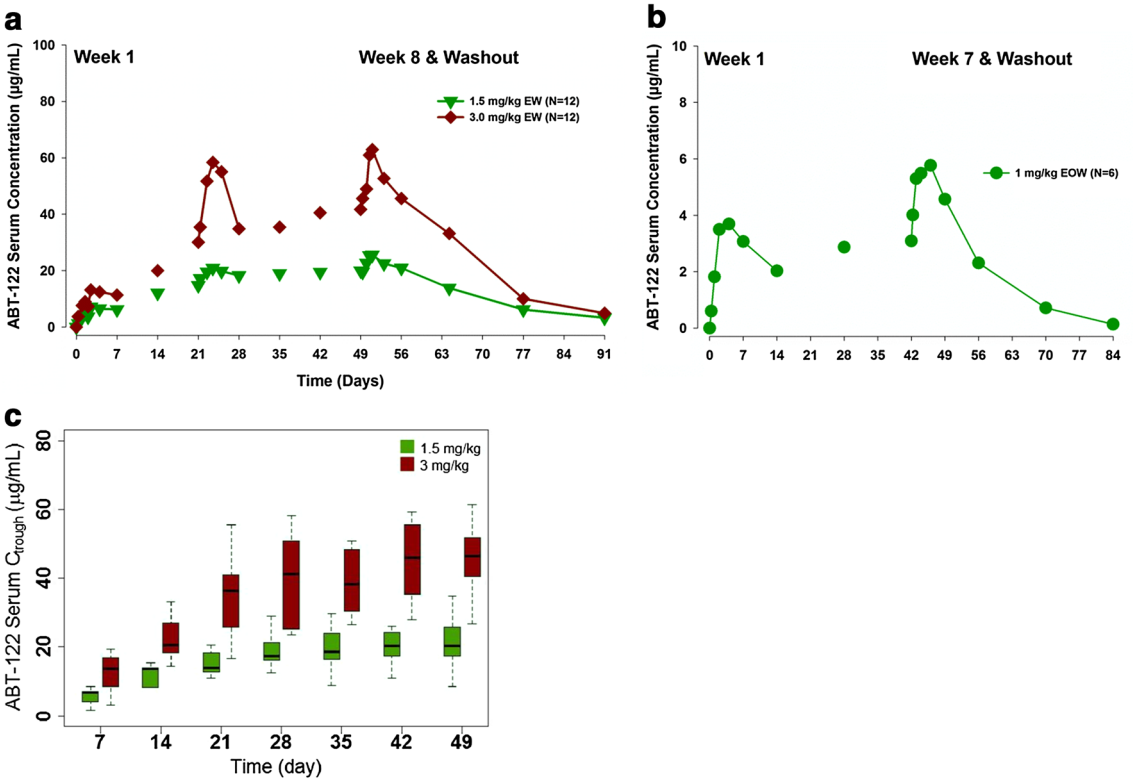

Fig. 3 ABT-122 full serum concentration–time profiles after every week [EW] **a** and every other week [EOW] **b** subcutaneous (SC) dosing and trough concentration–time profiles **c** after EW SC dosing in patients with rheumatoid arthritis. Only one subject received ABT-122 0.5 mg/kg EW; therefore, the data are not shown. For **a**, **b**, data are presented as mean values. For **c**, data are presented as median (*solid line*), interquartile range (*box*), and minimum and maximum (*whiskers*). C_{trough} trough concentration

and also somewhat higher variability generally observed in patients compared with healthy volunteers.

No apparent effect of the presence of ADAs on the pharmacokinetics of ABT-122 was observed in the majority of the subjects and patients across these phase I studies. ADAs to ABT-122 were observed in all healthy subjects who received a single dose of ABT-122, independent of the route of administration; however, in all but one subject, ABT-122 serum exposures were not clearly impacted by ADA formation. Similarly, none of the patients with RA except one showed any clear effect of ADAs on ABT-122 pharmacokinetics. Both the healthy subject and the patient with RA who showed an impact of ADA on ABT-122 pharmacokinetics had very high ADA

Table 4 ABT-122 steady-state pharmacokinetic (PK) parameters (mean, % coefficient of variation) following multiple subcutaneous dosing in patients with rheumatoid arthritis

PK parameter	Dose group			
	1 mg/kg EOW $N = 6$	0.5 mg/kg EW $N = 1$[a]	1.5 mg/kg EW $N = 11$[b]	3 mg/kg EW $N = 11$[b]
C_{max}(μg/mL)	5.96 (37)	2.69	26.4 (32)	66.6 (31)
T_{max} (days)[c]	3 (1–4)	1.5	2 (0–7)	2 (1.5–6.1)
C_{trough} (μg/mL)	2.31 (64)	2.49	21.2 (44)	49.7 (38)
AUC_{tau} (μg·day/mL)	60.5 (39)	15.2	146 (29)	343 (22)
AUC_{tau}/dose (μg·day/mL)/(mg/kg)	60.5 (39)	30.4	97.3 (29)	114 (22)
R_{ac} (AUC)[d]	1.57 (0.79–2.95)	2.16	3.81 (2.56–10.3)	4.81 (2.43–9.96)

AUC_{tau} area under the concentration–time curve during a dosing interval, *C_{max}* maximum serum concentration, *C_{trough}* trough concentration, *EOW* every other week, *EW* every week, *T_{max}* time to C_{max}, *$t_{1/2}$* terminal phase elimination half-life

[a] Only two patients were enrolled in this dose group (one received ABT-122 and one received placebo); data from the patient who received ABT-122 are shown

[b] One patient discontinued from the study prior to receiving the last dose of ABT-122

[c] Median (range); tau is 14 days for EOW dosing and 7 days for EW dosing

[d] R_{ac} = accumulation ratio calculated as $AUC_{tau,\ after\ last\ dose}/AUC_{tau,\ after\ first\ dose}$; presented as median (range)

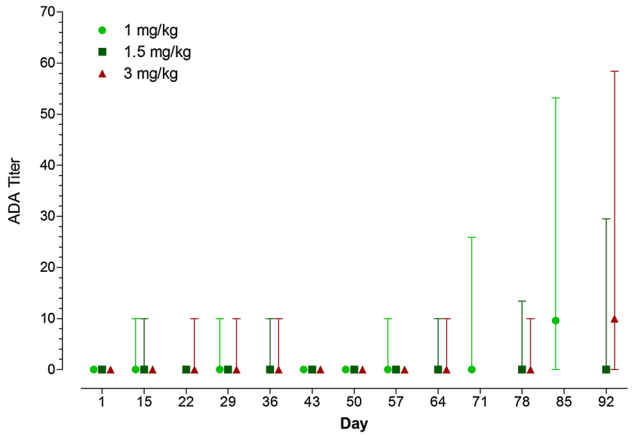

Fig. 4 ABT-122 antidrug antibody (ADA) titers vs. time in the multiple-dose studies in patients with rheumatoid arthritis. Data from Studies 2 and 3 were pooled at each time point, as applicable, and are presented as median and range. One subject in the 3-mg/kg dose group had very high ADA titers from day 15 through 92 (range of 49,700–129,000) and is not included in the plot. In addition, one patient who received a dose of 0.5 mg/kg every week is not shown. The ADA titers for this patient were <30 during the study, except for a value of 83.8 on day 15

titers starting on day 15. A single-dose study generally may not provide an adequate assessment of the effect of ADAs on the pharmacokinetics of monoclonal antibodies, primarily because the generation of ADAs and their effect on exposures may not occur for several weeks after dosing. In addition, it becomes difficult to discern the effect of ADA from between-subject variability in exposure. Data from the multiple-dose studies in patients with RA support the lack of an impact of ADAs on the pharmacokinetics of ABT-122 in the presence of background therapy with MTX. However, these findings are based on a small cohort of 31 patients and need to be confirmed in larger patient cohorts in phase II studies with longer treatment duration. It is noteworthy that compared with healthy subjects, the ADA incidence and titers were substantially lower in patients with RA. Additionally, the appearance of ADAs was delayed in patients with RA compared with healthy subjects; the median time for appearance of ADAs in patients was 64 days (range 15–92 days), whereas all healthy subjects had detectable ADA titers on day 15. These differences can be partially the result of background therapy with stable doses of MTX before the start of ABT-122 dosing in patients with RA.

Participants were monitored throughout the studies for signs and symptoms associated with the clinical profiles of anti-TNF-α and anti-IL-17 monotherapy, which included hypersensitivity reactions and infections. The risk of hypersensitivity reactions was mitigated by enrolling patients with RA who were on stable doses of MTX upon study entry and who continued MTX therapy throughout the study, which was expected to reduce ADA frequency. As expected, ADA frequency in the multiple-dose studies in patients with RA on MTX was lower than that in the single-dose study in healthy subjects, and no systemic hypersensitivity reactions were reported in participants in any of the studies. In addition, the presence of ADAs did not correlate with any systemic or serious adverse event profiles.

Additional limitations of the present studies are related to the small numbers of subjects enrolled and the inclusion

of patients with mild RA rather than the target population of moderate-to-severe active RA. Information on the levels of free and total TNF-α and IL-17 in serum or synovial fluid, which were not measured in these studies, could have enabled further mechanistic understanding of the factors impacting ABT-122 pharmacokinetics and could potentially further guide ABT-122 dosing requirements (based on target coverage or saturation). It is noteworthy that the ABT-122 assay used detects only ABT-122 molecules that have at least one free binding site for both TNF-α and IL-17; as such, other forms of ABT-122, for example, ones in which both binding sites for one or both cytokines are occupied, are not detected by the assay.

Tumor necrosis factor-α and IL-17 have key roles in normal immune defense. Tumor necrosis factor-α plays a critical role in fighting against infections caused by intracellular pathogens, such as tuberculosis, and TNF-α antagonists have been associated with increased risk for infections, including tuberculosis, and other types of serious adverse events [20, 21, 26]. Interleukin-17 is involved in immune defense against extracellular bacterial and fungal pathogens, and recent studies also suggest a role for IL-17 in the regulation of innate and adaptive responses against some intracellular pathogens [27, 28]. It should be noted that ABT-122 neutralizes only two of the six members of the IL-17 family: IL-17A homodimers and IL17-AF heterodimers. Across studies, there were no adverse events of severe or opportunistic infections, suggesting that ABT-122 does not compromise normal immune defense mechanisms to a clinically relevant extent; however, this needs to be further studied in larger clinical trials with longer durations of exposure.

5 Conclusion

Overall, ABT-122 was characterized by a pharmacokinetic profile suitable for EW or EOW SC administration. The incidence of ABT-122 ADAs was lower in RA patients on stable MTX therapy than in healthy subjects. No apparent effect of ADAs on the pharmacokinetics or safety of ABT-122 was observed across these phase I studies. Single IV doses of ABT-122 up to 10 mg/kg in healthy patients and multiple doses of ABT-122 up to 3 mg/kg SC EW for 8 weeks in patients with RA were well tolerated in the studies and no dose-limiting toxicities were identified. The present studies supported advancing ABT-122 to phase II trials in subjects with RA and psoriatic arthritis. Detailed reports of the results of these phase II trials are warranted.

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Compliance with Ethical Standards

Funding The studies were sponsored by AbbVie. AbbVie contributed to the study designs, research, and interpretation of data, and the writing, review, and approval of the publication.

Conflict of interest Amit Khatri, Sandra Goss, Ping Jiang, Heikki Mansikka, and Ahmed A. Othman are employees of AbbVie and may hold AbbVie stock or stock options.

Ethics approval The studies were conducted in accordance with Good Clinical Practice guidelines and the ethical principles that have their origin in the Declaration of Helsinki. The protocols and informed consent forms were approved by the institutional review boards at each site.

Consent to participate All participants provided written informed consent before any study-related procedures were performed.

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