

Mavrilimumab, a human monoclonal antibody targeting GM-CSF receptor- α , in subjects with rheumatoid arthritis: a randomised, double-blind, placebo-controlled, phase I, first-in-human study

Gerd R Burmester,¹ Eugen Feist,¹ Matthew A Sleeman,² Bing Wang,³ Barbara White,⁴ Fabio Magrini²

► Additional data are published online only. To view these files please visit the journal online at (<http://ard.bmj.com>).

¹Department of Rheumatology and Clinical Immunology, Charité – University Medicine Berlin, Berlin, Germany

²MedImmune, Cambridge, UK

³MedImmune, Hayward, California, USA

⁴Formerly with MedImmune, Gaithersburg, Maryland, USA

Correspondence to

Gerd-Rüdiger Burmester, Department of Rheumatology and Clinical Immunology, Charité – University Medicine Berlin, Free University and Humboldt University Berlin, Charitéplatz 1, 10117 Berlin, Germany; gerd.burmester@charite.de

Accepted 1 April 2011

Published Online First
25 May 2011

ABSTRACT

Objective To evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic profiles of mavrilimumab, a human monoclonal antibody targeting the granulocyte-macrophage colony-stimulating factor receptor- α , in subjects with rheumatoid arthritis (RA).

Methods A randomised, double-blind, placebo-controlled, dose-escalating phase I study in subjects with RA who received stable methotrexate treatment for ≥ 3 months before enrolment. Subjects received single intravenous escalating doses of mavrilimumab (0.01–10.0 mg/kg) or placebo.

Results 32 subjects were enrolled in this study (1 unblinded subject at 0.01 mg/kg and another at 0.03 mg/kg were followed by five sequential double-blinded cohorts, $n=6$ each, treated with 0.1, 0.3, 1.0, 3.0 and 10.0 mg/kg, respectively). Adverse events were mild or moderate and were reported with similar frequency across all treatment cohorts. One subject (10.0 mg/kg) experienced moderate face and neck urticaria during infusion that resolved with symptomatic treatment. Systemic clearance of mavrilimumab approached that of endogenous IgG at doses > 1.0 mg/kg; pharmacodynamic activity was confirmed in the 1.0 and 3.0 mg/kg cohorts by suppression of suppressor of cytokine signalling 3 mRNA transcripts. In exploratory analyses, reductions of acute phase reactants were observed in subjects with elevated C-reactive protein (> 5 mg/l) and erythrocyte sedimentation rate (≥ 20.0 mm/h) at baseline. No significant change in Disease Activity Score 28-joint assessment (DAS28) was seen in any of the cohorts. In mavrilimumab-treated subjects ($n=15$) with baseline DAS28 > 3.2 , mean disease activity (DAS28) was significantly reduced at 4 weeks.

Conclusion In this first-in-human study, mavrilimumab showed preliminary evidence of pharmacodynamic activity. Importantly, the safety and pharmacokinetic profiles of mavrilimumab support further clinical studies in RA.

Trial registration number: NCT00771420.

INTRODUCTION

Biological treatments such as tumour necrosis factor (TNF) inhibitors have revolutionised rheumatoid arthritis (RA) treatment over the past decade.^{1–3} However, new treatments are needed for the significant proportion of subjects who fail to achieve the minimum improvement criteria⁴ or experience significant toxicities (eg, serious and opportunistic infection,⁵ tachyphylaxis or development of

resistance) and to provide more subjects with a higher likelihood of achieving disease remission.⁶ While many components of the immune system contribute to the development and progression of RA, it has been shown that treatments reducing CD68+ macrophage numbers in the sublining of the pannus lead to a reduction in disease activity.⁷ Therefore, molecules directly targeting macrophage function may prove beneficial in these refractory subjects.

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a soluble cytokine that promotes the generation, survival and activation of cells from the myeloid compartment, notably neutrophils, eosinophils and macrophages.^{8–11} GM-CSF also regulates numerous functions of mature tissue macrophages, including a number of host defence functions—for example, cell adhesion, expression of pathogen recognition receptors and proinflammatory cytokines (TNF α , interleukin (IL)-12, IL-18, IL-6, monocyte chemoattractant protein 1 and M-CSF), phagocytosis and microbial killing.¹² Furthermore, it is well documented that GM-CSF signalling is critical in maintaining the ability of pulmonary alveolar macrophages to clear surfactant lipids and proteins from the lung surface. For this reason, safety monitoring in this study included a number of tests and assessments to ensure an appropriate evaluation of potential lung toxicities.

Raised levels of GM-CSF and its receptor in the synovial fluid and plasma of subjects with RA and overexpression of GM-CSF receptor within cells of the synovial tissue and on circulating mononuclear cells, as well as the production by chondrocytes,^{13–16} suggest a potential role for this cytokine in RA. Preclinical models have further supported this hypothesis; overexpression of GM-CSF resulted in accelerated and more severe inflammation than in control mice,¹⁷ and direct injection of recombinant GM-CSF into a mouse model of arthritis exacerbated the disease.^{18–19} Conversely, a deficiency in GM-CSF was shown to be protective in several models of induced arthritis.^{20–23} In isolated observations in humans, recombinant GM-CSF administered to subjects undergoing treatment to resolve neutropenia in Felty's syndrome^{24–25} or after chemotherapy²⁵ has also promoted arthritic flares. Taken together, these data suggest that GM-CSF is a key player in arthritis and that blocking this pathway may provide benefit.



This paper is freely available online under the BMJ Journals unlocked scheme, see <http://ard.bmj.com/info/unlocked.dtl>

GM-CSF receptors are heterodimers consisting of a ligand-specific α -subunit (GM-CSFR- α) and a β -chain subunit that is shared with IL-3 and IL-5 receptor.^{26 27} GM-CSFR- α binds to the cytokine with high specificity and low affinity, whereas the common β subunit is responsible for JAK2/STAT3/STAT5 signalling.^{26 28 29} Mavrilimumab, formerly known as CAM-3001, is a novel high-affinity human monoclonal IgG4 antibody (isolated by phage display) against GM-CSFR- α that is a competitive antagonist of GM-CSF signalling.

Currently, no data exist on targeting the innate arm of the immune system via the GM-CSF pathway in RA. We report the results of a first-in-human study evaluating the safety, tolerability, pharmacokinetic and pharmacodynamic profiles of single ascending intravenous doses of mavrilimumab in adult subjects with mild to moderate RA.

SUBJECTS AND METHODS

This study was conducted in accordance with the Declaration of Helsinki (1996) and the International Conference on Harmonisation Guidelines for Good Clinical Practice (topic E6) and was approved by the State of Berlin ethics committee. Each participant gave written informed consent before any protocol-specific activity or study entry.

Subjects

Men and women aged 18–70 years were eligible if they had had RA for ≥ 6 months as defined by the American College of Rheumatology criteria,³⁰ received methotrexate treatment for ≥ 3 months (stable dose of 10–25 mg/week for ≥ 8 weeks) and had a Disease Activity Score 28-joint assessment (DAS28) ≤ 4.8 (mild to moderate) for ≥ 3 months. Exclusion criteria included any form of arthritis other than RA, current or recent serious infection, significant systemic illness or malignancy, neutropenia, use of biological agents for RA within 6 months before the baseline visit and concomitant use of disease-modifying anti-rheumatic drugs other than methotrexate.

Study protocol

This was a randomised, double-blind, placebo-controlled, single-dose-escalating study to evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic profiles of mavrilimumab in subjects with RA. Subjects were randomised to mavrilimumab or placebo cohorts by an interactive voice response system (Perceptive Informatics, Waltham, Massachusetts, USA). The study comprised six cohorts. Because mavrilimumab is an antibody to a cell surface receptor, cohort 1 included two unblinded subjects to evaluate the first two mavrilimumab doses (0.01 and 0.03 mg/kg, one subject each) and to monitor unpredictable side effects before proceeding to the double-blind, randomised arm of the study. No controls were assigned to cohort 1. Cohorts 2–6 included six subjects randomised 5:1 to receive mavrilimumab or placebo, respectively. A safety review board examined the week 1 safety data for each dose cohort (upon completion of the first week of follow-up) in combination with all available safety data from all subjects enrolled in the study.

Treatment

In addition to stable methotrexate treatment, subjects received a single, escalating intravenous dose of mavrilimumab (0.01, 0.03, 0.1, 0.3, 1.0, 3.0 and 10.0 mg/kg) or placebo on study day 0. Infusions lasted ~ 1 h. Subjects were followed up for 24 weeks after infusion.

Outcome measures

Safety and tolerability

Safety profile evaluation included collection of adverse events (AEs) and serious AEs, haematology, blood chemistry laboratory results and vital signs from randomisation through study week 24. AEs were graded by severity and relationship to study drug.

Blood samples for chemistry, complete blood count with differential and platelet counts, and pharmacokinetics and ex vivo pharmacodynamics of mavrilimumab as well as urine samples for urine analysis were collected before dosing, on study days 1, 2 and 3, and then weekly through study week 24, except weeks 16 and 20. Urine samples for pregnancy testing were collected before dosing and at weeks 4, 12 and 24.

The presence of anti-mavrilimumab antibodies in serum was determined using a validated bridging electrochemiluminescent immunoassay. Viral surveillance testing for Epstein–Barr virus and cytomegalovirus was conducted on study day -1 and at study week 6. Lung function tests, such as spirometry and diffusing capacity of lung for carbon monoxide, were conducted at baseline and week 12 to assess for potential lung toxicities after mavrilimumab administration.

Pharmacokinetics and pharmacodynamics

Mavrilimumab concentrations were measured using a validated electrochemiluminescent method with a monoclonal anti-idiotypic antibody as the capture reagent. Non-compartmental pharmacokinetic data analysis was performed using WinNonlin Professional (version 5.2; Pharsight, Mountain View, California, USA). The pharmacodynamic activity of mavrilimumab was assessed at baseline and at 4 and 336 h (2 weeks) after dosing in an ex vivo assay, in which the effect of mavrilimumab on GM-CSF-stimulated expression of suppressor of cytokine signalling 3 (SOCS3) mRNA was investigated. This assay is described in the online supplemental methods.

Clinical RA assessments

Exploratory clinical assessments included DAS28 and its core components (tender and swollen joint counts, erythrocyte sedimentation rate (ESR) or circulating C-reactive protein (CRP) and physician's global assessment of disease activity); subject's global assessment of disease activity, pain and fatigue using a visual analogue scale; and subject's assessment of physical function using the Health Assessment Questionnaire.³¹ RA clinical assessments were undertaken at baseline, week 4 and week 12; ESR and CRP levels were monitored as part of the haematological evaluation at screening, days -1 , 0, 1, 2 and 3, and weeks 1, 2, 3, 4, 5, 6, 8, 10, 12 and 24. Exploratory subanalyses were based on subjects with either a baseline DAS28 > 3.2 or circulating CRP levels > 5 mg/l.

Statistical analysis

Data were analysed by descriptive statistics. Exploratory subanalyses of subjects with a DAS28 score > 3.2 were conducted using a paired t test to compare scores at baseline and week 4. Subanalysis of subjects with CRP > 5 mg/l was conducted using a repeated analysis of variance with Bonferroni-corrected p value. $p < 0.05$ indicated statistical significance. All analyses were determined using GraphPad Prism Software (version 8.2 Prism; GraphPad Software, La Jolla, California, USA).

RESULTS

Subjects

Thirty-two subjects with mild to moderate RA were enrolled. All enrolled subjects completed all planned evaluations and

were included in the safety analyses. One subject (10.0 mg/kg cohort) who experienced moderate face and neck urticaria during infusion did not receive the full mavrilimumab dose and was excluded from the pharmacokinetic analysis. Twenty-seven subjects were randomised to the mavrilimumab cohorts, and five were randomised to placebo. Cohort 1 (n = 2) received open-label active medication (0.01 or 0.03 mg/kg). The remaining subjects were randomised to receive 0.1, 0.3, 1.0, 3.0 and 10.0 mavrilimumab (n = 5/cohort) or placebo (n = 1/cohort). Table 1 shows subjects' baseline demographic characteristics.

Safety and tolerability profile

Adverse events

Over the 6-month study period, 69 AEs were reported in 20 mavrilimumab subjects (74%), and 13 were reported in four placebo subjects (80%). The most commonly reported AEs across cohorts were nasopharyngitis, headache, diarrhoea and back pain (table 2). The majority of AEs were mild, and none resulted in study withdrawal. One subject (10.0 mg/kg mavrilimumab group) did not receive the full infusion owing to grade 2 urticaria of the face and neck that occurred ~15 min after the infusion started. This event led to discontinuation of the infusion. The event was resolved promptly, with no sequelae, after

symptomatic treatment. No relationship was apparent between mavrilimumab dose and the severity or frequency of any AEs.

Eleven treatment-related AEs were reported. A total of six treatment-related AEs were observed across the six mavrilimumab cohorts, including one AE in the 10.0 mg/kg cohort (urticaria), three AEs in the 0.3 mg/kg cohort (headache, migraine, nausea) and two AEs in the 0.1 mg/kg cohort (diarrhoea, peripheral oedema). No treatment-related AEs were reported in the 3.0 or 1.0 mg/kg groups. Five treatment-related AEs in the placebo cohort included nausea, vomiting and headache (n = 1); paraesthesia (n = 1); and headache (n = 1). No abnormal haematology was reported as an AE, and no clinically significant changes in leucocyte, neutrophil or monocyte levels were observed between the placebo and mavrilimumab cohorts irrespective of dose (see online supplementary figure S1). No change was observed with lymphocytes (data not shown). No differences in lung function were seen (see online supplementary table S1).

Serious AEs

Two non-treatment-related serious AEs were reported: one subject was hospitalised for bilateral inguinal hernia repair 4 months after dosing (0.03 mg/kg cohort), and one subject (61-year-old woman, 3.0 mg/kg cohort) was reported to have

Table 1 Subject demographic characteristics at baseline

Parameter	Placebo (n = 5)	All mavrilimumab (n = 27)	Mavrilimumab (mg/kg)						
			0.01 (n = 1)	0.03 (n = 1)	0.1 (n = 5)	0.3 (n = 5)	1.0 (n = 5)	3.0 (n = 5)	10.0 (n = 5)
No. of subjects who completed the study	5	27	1	1	5	5	5	5	5
Age (years)	53 ± 6.8	53 ± 10.4	67	33	47 ± 5.8	55 ± 4.3	46 ± 13.8	57 ± 6.1	58 ± 10.5
Gender, n									
Male	0	4	0	1	0	1	0	1	1
Female	5	23	1	0	5	4	5	4	4
White race, n (%)	5 (100)	27 (100)	1 (100)	1 (100)	5 (100)	5 (100)	5 (100)	5 (100)	5 (100)
Methotrexate (mg/day)	14.0 ± 2.2	16 ± 3.2	20.0	15.0	16.0 ± 5.7	16.0 ± 2.2	16.0 ± 2.2	15.0 ± 3.5	16.0 ± 2.2
DAS28	3.79 ± 1.0	3.35 ± 0.9	4.35	3.46	3.08 ± 0.5	3.91 ± 0.4	3.58 ± 0.8	3.29 ± 1.4	2.69 ± 0.9
Tender joints	4 ± 3.6	3 ± 2.9	3	4	1 ± 1.0	4 ± 2.7	3 ± 3.3	3 ± 2.3	3 ± 4.7
Swollen joints	2 ± 1.5	1 ± 1.2	0	1	0 ± 0.0	1 ± 0.5	2 ± 2.5	1 ± 0.9	0 ± 0.5
CRP (mg/l)	5.7 ± 6.0	6.6 ± 9.4	47.8	4.1	4.7 ± 3.7	5.1 ± 3.3	6.4 ± 6.1	7.3 ± 7.4	1.7 ± 0.5
ESR (mm/h)	17.0 ± 7.5	18.0 ± 12.4	50.0	10.0	25.0 ± 13.2	18.0 ± 11.6	16.0 ± 3.6	19.0 ± 12.7	6.0 ± 1.6
Weight (kg)	73.9 ± 15.9	76.7 ± 16.7	85.6	86.1	66.1 ± 21.3	71.6 ± 14.4	82.0 ± 16.9	79.1 ± 18.8	80.7 ± 15.3
HAQ (score 0–3)	1.60 ± 0.41	1.61 ± 0.33	1.50	1.250	1.700 ± 0.29	1.775 ± 0.45	1.600 ± 0.14	1.525 ± 0.37	1.550 ± 0.44

Medical history terms were classified according to the terminology of the Medical Dictionary for Regulatory Activities (version 11). Values are mean ± SD unless otherwise noted. CRP, C-reactive protein; DAS28, Disease Activity Score 28-joint assessment; ESR, erythrocyte sedimentation rate; HAQ, Health Assessment Questionnaire.

Table 2 Incidence of adverse events by frequency (reported by more than one subject)

Adverse event	Treatment group			
	Placebo (n = 5)		Mavrilimumab* (n = 27)	
	No of AEs	No (%) of subjects	No of AEs	No (%) of subjects
Total	13	4 (80)	69	20 (74)
Nasopharyngitis	3	2 (40)	11	10 (37)
Headache	2	2 (40)	7	5 (19)
Diarrhoea	1	1 (20)	5	5 (19)
Back pain	1	1 (20)	4	4 (15)
Peripheral oedema	0	0	3	3 (11)
Nausea	1	1 (20)	2	2 (7)
Bronchitis	0	0	2	2 (7)
Dizziness	0	0	2	2 (7)
Hypertension	0	0	2	2 (7)
Pharyngolaryngeal pain	0	0	2	2 (7)
Vomiting	1	1 (20)	1	1 (4)

*All doses. AEs were classified according to the terminology of the Medical Dictionary for Regulatory Activities (version 11). AE, adverse event.

carcinoma of the right breast at the week 8 visit. The subject had detected a lump in her right breast before randomisation but did not report it to her doctor until 3 days after receiving the study drug. No clinical viral infection events were reported, and no subject experienced clinically significant laboratory abnormalities or changes in vital signs during the study. No subjects developed anti-mavrilimumab antibodies during the study and safety follow-up periods.

Pharmacokinetics

The mean pharmacokinetic profiles of mavrilimumab after a single intravenous dose are shown in figure 1. All pharmacokinetic observations at the last visit (day 168) were below the assay limit of measurement. Non-compartmental pharmacokinetic parameters are summarised in table 3.

Although there was a dose-proportional increase in maximum observed concentration, the increase in area under the curve was more than dose proportional. Systemic clearance decreased from 88.8 to 3.15 ml/kg/day when the dose was increased from 0.01 to 10.0 mg/kg. Accordingly, the half-life was more prolonged in higher-dose cohorts. At the highest dose level investigated (10.0 mg/kg), the elimination half-life of mavrilimumab was ~15 days.

The distribution volume of mavrilimumab could not be accurately determined because the pharmacokinetics of mavi-

limumab was not linear at lower dose levels. However, the estimated steady-state volume of distribution was slightly greater than the serum volume in subjects receiving the 10.0 mg/kg dose.

Pharmacodynamics

Quantitative RT-PCR showed a three- to fourfold increase (mean 3.274 ± 1.42 ; 95% CI 2.42 to 4.13) in the levels of SOCS3 mRNA transcript compared with the levels of 18S mRNA transcript in ex vivo stimulated leucocytes from the placebo and 0.3, 1.0 and 3.0 mg/kg mavrilimumab cohorts before dosing. Four hours after dosing, the induction of SOCS3 mRNA by GM-CSF was inhibited by 90% and 84% in the 1.0 and 3.0 mg/kg cohorts, respectively ($p \leq 0.05$). This effect was sustained for 336 h (2 weeks) in the 1.0 mg/kg cohort ($p \leq 0.05$; 47% reduction), with a trend to suppression in the 3.0 mg/kg cohort that was not statistically significant ($p > 0.05$). No significant inhibition of SOCS3 expression at 4 and 336 h was seen in either the placebo or 0.3 mg/kg cohort (figure 2).

Clinical activity

Subjects had mild to moderate disease activity at baseline, with a mean DAS28 of 3.79 ± 1.0 and 3.35 ± 0.9 in the placebo and mavrilimumab cohorts, respectively. The majority (63%) had normal acute phase reactants at baseline. No significant change

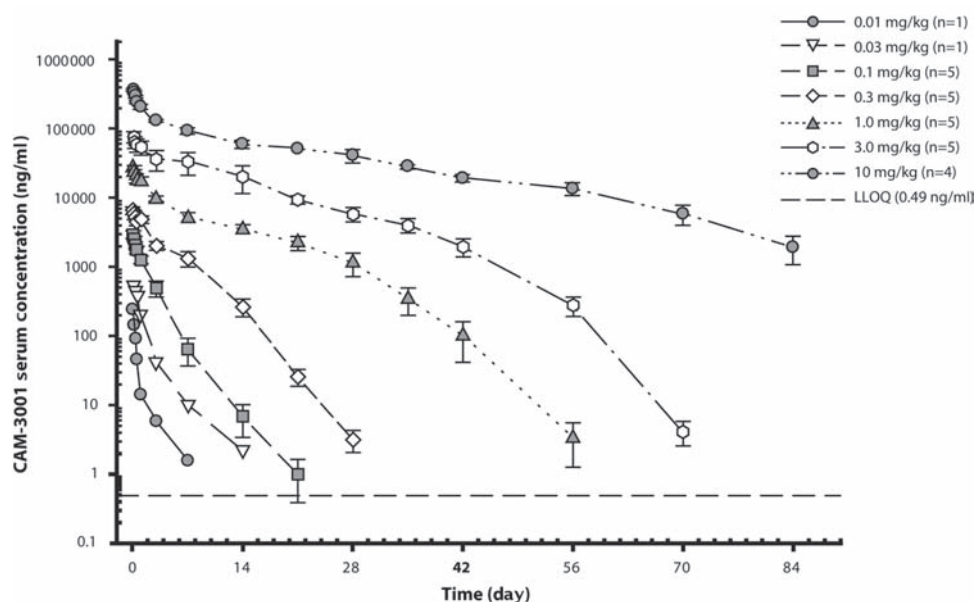


Figure 1 Mean pharmacokinetic profiles of mavrilimumab (formerly known as CAM-3001) after a single intravenous dose in subjects with mild to moderate rheumatoid arthritis. Error bars represent SEM. Pharmacokinetic observations from the subject in the 10.0 mg/kg cohort who received partial infusion were excluded from mean concentration calculations. LLOQ, lower limit of quantification.

Table 3 Non-compartmental pharmacokinetic parameters of mavrilimumab in subjects with mild to moderate rheumatoid arthritis

Pharmacokinetic parameter	Mavrilimumab dose (mg/kg)						
	0.01 (n = 1)	0.03 (n = 1)	0.1 (n = 5)	0.3 (n = 5)	1.0 (n = 5)	3.0 (n = 5)	10.0 (n = 4)
C_{max} ($\mu\text{g/ml}$)	0.241	0.550	2.95 (0.87)	6.72 (1.43)	26.8 (4.69)	81.4 (23.6)	373 (38)
AUC_{inf} ($\mu\text{g}\cdot\text{day/ml}$)	0.113	0.781	5.01 (1.72)	25.4 (9.1)	147 (42)	706 (429)	3200 (290)
CL (ml/kg/day)	88.8	38.4	21.6 (6.1)	13.1 (4.6)	7.23 (2.07)	5.19 (2.06)	3.15 (0.31)
$t_{1/2}$ (day)	1.51	2.13	1.81 (0.59)	2.55 (0.21)	4.78 (0.66)	7.59 (1.83)	15.1 (3.6)

Parameter values are shown as mean (SD) except for the 0.01 mg/kg and 0.03 mg/kg dose levels. Data from the subject who received partial infusion in the 10.0 mg/kg cohort were excluded from the analysis.

AUC_{inf} , area under the concentration–time curve extrapolated to infinity; CL, systemic clearance; C_{max} , maximum observed concentration; $t_{1/2}$, elimination half-life.

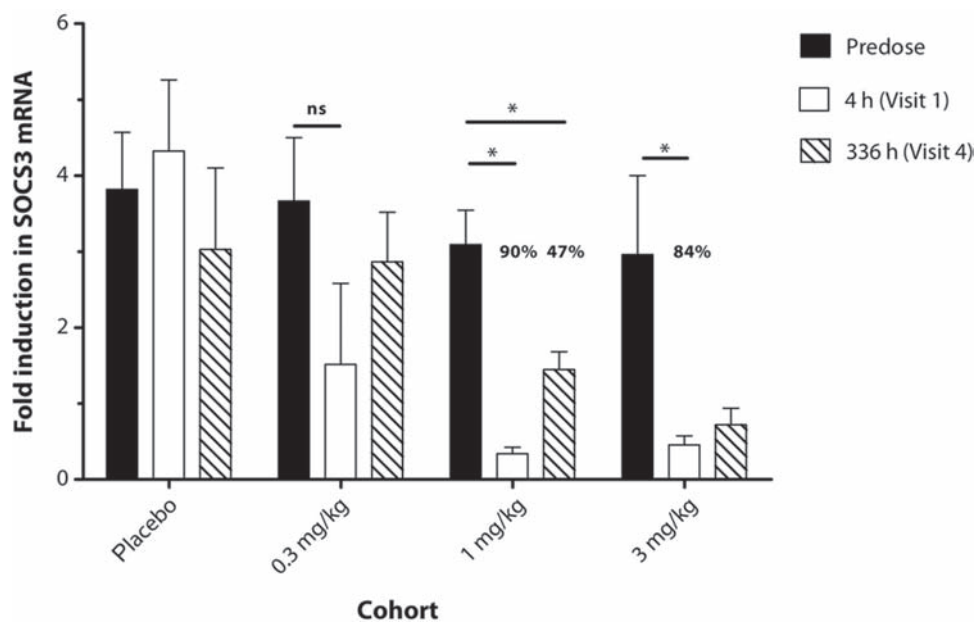


Figure 2 Effect of mavrilimumab on suppressor of cytokine signalling 3 (SOCS3) mRNA transcript levels induced by granulocyte-macrophage colony-stimulating factor ex vivo from peripheral blood leucocytes of subjects with mild to moderate rheumatoid arthritis. Data are presented as mean (SE). Asterisks indicate a significant change ($*p < 0.05$) in comparison with predose samples within the same cohort; ns, not significant.

in DAS28 score between baseline, week 4 and week 12 was observed in the mavrilimumab cohorts (figure 3A). Exploratory subanalyses showed that, of subjects exposed to mavrilimumab with DAS28 >2.6 at baseline, 33% (7/21) achieved a DAS28 remission (<2.6) at week 4. In addition, subanalysis of subjects receiving mavrilimumab with moderate disease activity (baseline DAS28 >3.2) demonstrated a statistically significant reduction in DAS28 score at week 4 compared with controls (figure 3B). Systemic inflammation was monitored by CRP levels and ESR. Consistent with clinical score, there was no significant change in CRP levels in response to mavrilimumab (figure 3C); however, a trend towards a reduction was seen with mavrilimumab 0.1, 0.3, 1.0 and 3.0 mg/kg. To investigate this, a post hoc analysis was conducted for all subjects with elevated baseline CRP levels (>5 mg/l). In mavrilimumab subjects with elevated CRP (>5 mg/l) at baseline, mean CRP levels were significantly reduced for 4 weeks when compared with baseline (figure 3D). CRP levels for these subjects returned to baseline by week 12. Furthermore, of the 10 mavrilimumab subjects with elevated (≥ 20 mm/h) ESR at baseline, 90% showed normalisation of ESR at least once during the first 4 weeks after dosing.

At study week 4, mean changes from baseline in subjects' global assessments of RA and fatigue (visual analogue scale) were reductions of 20% and 1%, respectively, in the mavrilimumab cohorts. Subjects' global assessment of pain and physicians' assessment of RA were only assessed at the screening visit, with no discernible differences in mean scores between cohorts.

DISCUSSION

There is increased awareness that aggressive treatment of RA should be started early to achieve remission and arrest radiographic progression.³² Furthermore, new biological treatments targeting B and T cells or soluble cytokines such as TNF α , IL-1 or IL-6 are available and have further advanced the treatment of RA. However, a substantial number of subjects do not respond (primary non-responders) or experience a loss of efficacy after a

primary response (secondary non-responders). While monitoring can help to identify non-responders early and allow switching to another treatment, the causes of non-response or loss of response remain, in most cases, elusive. Although it is possible that the clinical manifestations of RA may be driven by different pathways in different subjects, the multifactorial nature of the disease has made identification of robust biomarkers challenging, thus highlighting a significant unmet need.^{33–35} In this small phase I study, mavrilimumab demonstrated an adequate safety profile when administered as a single, escalating intravenous dose of 0.01–10.0 mg/kg in subjects with RA. Reported AEs were mostly mild and similar between the mavrilimumab and placebo cohorts. One treatment-related moderate event of urticaria was reported (10.0 mg/kg cohort), which led to early termination of the infusion. The event was treated symptomatically, resolved on the same day, and the subject remained in the study. This type of reaction has been observed as a common feature of monoclonal antibody infusion³⁶ and is typically related to the infusion rate and antibody concentration. No subject withdrew from the study owing to an AE or for any other reason.

Antibodies against cell membrane-associated antigens are usually subject to the target-mediated clearance, or the antigen sink effect.^{37–40} There are two major elimination pathways for mavrilimumab: intrinsic clearance by the reticuloendothelial system in the same way as that for an endogenous IgG, and elimination by the target antigen receptor (GM-CSFR- α -mediated clearance). At low serum concentrations, the antigen sink dominates and mavrilimumab had a short elimination half-life. When the antigen sink is saturated, the elimination of mavrilimumab approximates that of an endogenous IgG, with a more prolonged elimination half-life. Consistent with previously reported antireceptor antibodies,^{38–41–44} mavrilimumab pharmacokinetics was non-linear at low doses. From the non-compartmental analysis, the systemic clearance of mavrilimumab approached the intrinsic clearance of endogenous IgG by the reticuloendothelial system at doses >1.0 mg/kg, suggesting saturation of the antigen sink (full GM-CSFR- α occupancy) at higher dose levels. Once

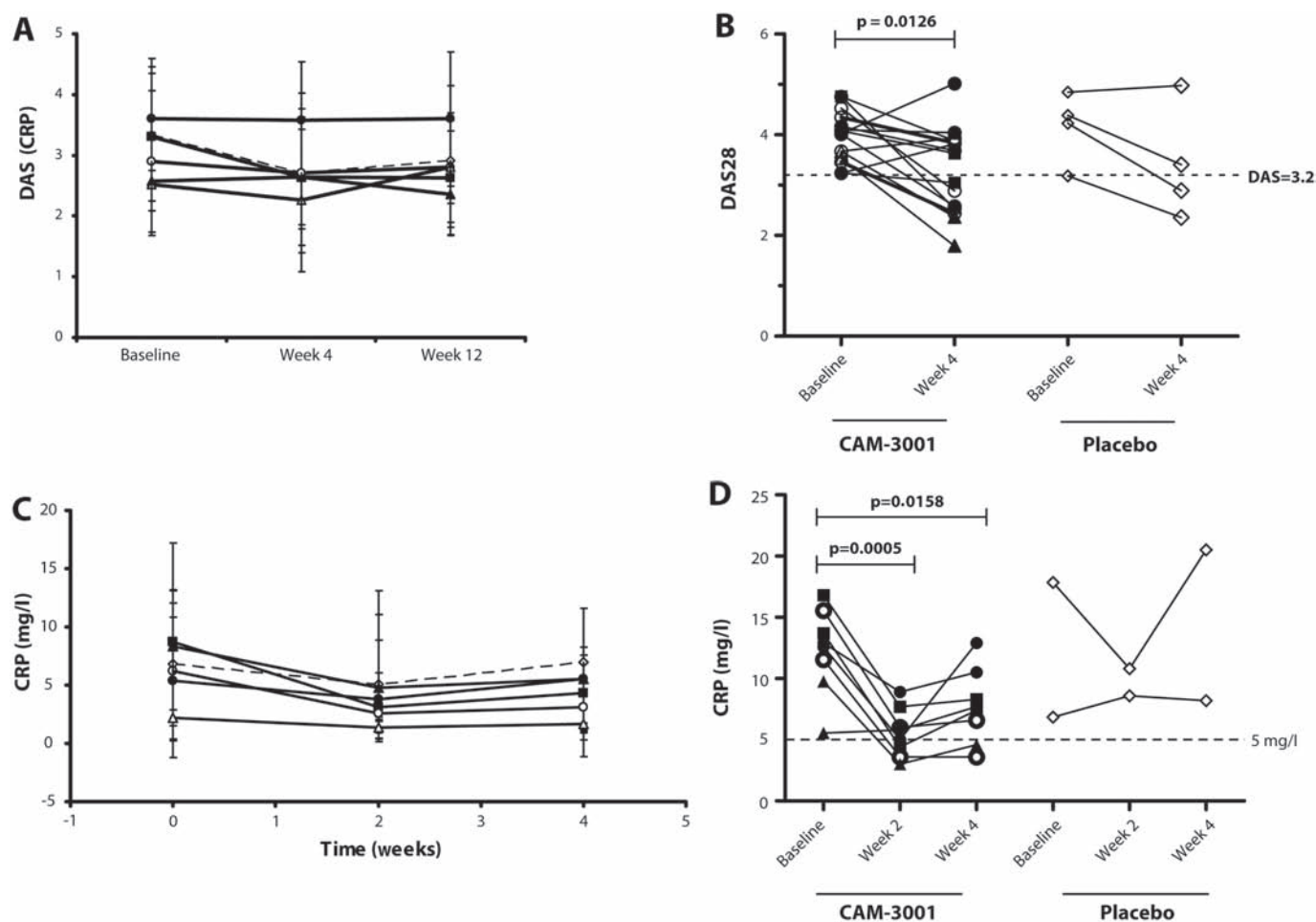


Figure 3 (A) Effect of mavrilimumab (formerly known as CAM-3001) on Disease Activity Score 28-joint assessment (DAS28) levels at baseline, week 4 and week 12. Data are presented as the mean (SD) for each visit. (B) Effect of mavrilimumab on DAS28 levels within the first 4 weeks after a single intravenous dose in subjects with moderate disease (DAS28 >3.2 at baseline). (C) Effect of mavrilimumab on C-reactive protein (CRP) level at baseline (week 0), week 2 and week 4. Data are presented as the mean (SD) for each visit. (D) Effect of mavrilimumab on CRP level within the first 4 weeks after a single intravenous dose in subjects with mild rheumatoid arthritis who had elevated (>5 mg/l) CRP levels at baseline. Legend: placebo (◇) and mavrilimumab 0.1 mg/kg (▲), 0.3 mg/kg (●), 1.0 mg/kg (■), 3.0 mg/kg (○) and 10.0 mg/kg (△).

saturated, the pharmacokinetics of mavrilimumab ranged from 4.78 to 15.1 days between 1.0 and 10.0 mg/kg, equivalent to the pharmacokinetics of currently approved antibody treatments for RA, such as adalimumab (0.25–5.0 mg/kg intravenous doses; apparent terminal half-life = 15–19 days)⁴⁵ and tocilizumab (8 mg/kg intravenous dose; half-life = 10 days).⁴⁶

The pharmacodynamics of mavrilimumab supports these pharmacokinetic observations. The *ex vivo* assay demonstrated a significant inhibition of GM-CSF-induced SOCS3 expression 4 h after dosing in peripheral white blood cells from subjects in the 1.0 and 3.0 mg/kg cohorts, but not the 0.3 mg/kg cohort, consistent with full receptor occupancy as predicted from non-compartmental analysis. Furthermore, this effect appeared to be sustained for 2 weeks after dosing even though the 3.0 mg/kg cohort did not achieve significance. Since no additional data were collected after 2 weeks of dosing, the duration of receptor occupancy is unknown.

Because this was a phase I study designed to evaluate the safety and tolerability profile of mavrilimumab, clinical activity was not formally determined. This was reflected in the fact that 63% of subjects had normal acute phase reactants at baseline; however, post hoc analyses of subjects with elevated baseline

CRP (>5 mg/l) and ESR (>20 mm/h) showed a reduction of these markers at least once within the first 4 weeks after mavrilimumab administration. Recombinant GM-CSF has been shown to increase both systemic IL-6 levels and circulating acute phase response proteins, such as CRP and serum amyloid A, and to exacerbate arthritis in neutropenic subjects.^{24,25} Conversely, the observation that this antibody was able to reduce CRP levels is consistent with the hypothesised mechanism of action of mavrilimumab. Moreover, exploratory subanalyses of pharmacological activity demonstrated positive trends of mavrilimumab on RA signs and symptoms up to 4 weeks after a single infusion for subjects who had moderate disease activity (DAS28 >3.2). Additionally, a subset of subjects in the study with moderate disease activity experienced remission as defined by a DAS28 <2.6. While these preliminary observations are encouraging, this study was not designed or powered to demonstrate efficacy; therefore, these results should be interpreted with caution.

This is the first-in-human study of a monoclonal antibody targeting the GM-CSF pathway in RA. In this study, mavrilimumab given as a single, escalating intravenous dose (0.01–10.0 mg/kg) had an adequate safety and tolerability profile in subjects with mild to moderate RA. The pharmacokinetics

was consistent for an antibody to a cell surface receptor and suggested full GM-CSFR- α occupancy at doses ≥ 1.0 mg/kg. Additionally, subjects with elevated baseline CRP and ESR showed a trend towards a reduction of circulating CRP levels or normalisation of ESR at least once within the first 4 weeks after administration.

Acknowledgements The authors thank Dr Athula Herath for his assistance with the exploratory efficacy analyses; Drs Ehsanollah Esfandiari, Mark Layton, Gerry Grove and Barry Oemar for their valuable comments; and Heba Costandy, MD, MS, at HH Consulting and Miriam Gitler, PhD, at MedImmune, for medical writing and editorial contributions.

Funding The study and manuscript preparation were funded by MedImmune, Gaithersburg, MD, USA. As the study sponsor, MedImmune was responsible for the study design; the collection, analysis and interpretation of data; the writing of the clinical study report; and the decision, along with the authors, to submit this manuscript for publication.

Competing interests GRB and EF received research funding from MedImmune to conduct this clinical study. MAS, B Wang and FM are employees of MedImmune. B White is a former employee of MedImmune.

Contributors MAS, B Wang and GRB were involved in the design of the study, acquisition and analysis of the data and interpretation of the results; FM, B White and EF were involved in the acquisition and analysis of the data and interpretation of the results; all authors critically reviewed and revised the manuscript and approved the final version.

Ethics approval This study was conducted with the approval of the State of Berlin ethics committee.

Provenance and peer review Not commissioned; externally peer reviewed.

B White, present address: UCB Biosciences, Raleigh, North Carolina, USA.

REFERENCES

- Klareskog L, van der Heijde D, de Jager JP, *et al.* Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004;**363**:675–81.
- Maini R, St Clair EW, Breedveld F, *et al.* Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999;**354**:1932–9.
- Breedveld FC, Weisman MH, Kavanaugh AF, *et al.* The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006;**54**:26–37.
- Felson DT, Anderson JJ, Boers M, *et al.* American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;**38**:727–35.
- Salmon-Ceron D, Tubach F, Lortholary O, *et al.* Drug-specific risk of non-tuberculosis opportunistic infections in patients receiving anti-TNF therapy reported to the 3-year prospective French RATIO registry. *Ann Rheum Dis* 2011;**70**:616–23.
- Listing J, Strangfeld A, Rau R, *et al.* Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low—results from RABBIT, the German biologics register. *Arthritis Res Ther* 2006;**8**:R66.
- Bresnihan B, Gerlag DM, Rooney T, *et al.* Synovial macrophages as a biomarker of response to therapeutic intervention in rheumatoid arthritis: standardization and consistency across centers. *J Rheumatol* 2007;**34**:620–2.
- Hamilton JA. Colony-stimulating factors in inflammation and autoimmunity. *Nat Rev Immunol* 2008;**8**:533–44.
- Gamble JR, Elliott MJ, Jaipargas E, *et al.* Regulation of human monocyte adherence by granulocyte-macrophage colony-stimulating factor. *Proc Natl Acad Sci USA* 1989;**86**:7169–73.
- Cheung DL, Hamilton JA. Regulation of human monocyte DNA synthesis by colony-stimulating factors, cytokines, and cyclic adenosine monophosphate. *Blood* 1992;**79**:1972–81.
- Hart PH, Vitti GF, Burgess DR, *et al.* Activation of human monocytes by granulocyte-macrophage colony-stimulating factor: increased urokinase-type plasminogen activator activity. *Blood* 1991;**77**:841–8.
- Shibata Y, Berclaz PY, Chronos ZC, *et al.* GM-CSF regulates alveolar macrophage differentiation and innate immunity in the lung through PU.1. *Immunity* 2001;**15**:557–67.
- Alsalameh S, Firestein GS, Oez S, *et al.* Regulation of granulocyte macrophage colony stimulating factor production by human articular chondrocytes. Induction by both tumor necrosis factor-alpha and interleukin 1, downregulation by transforming growth factor beta and upregulation by fibroblast growth factor. *J Rheumatol* 1994;**21**:993–1002.
- Fiehn C, Wermann M, Pezzutto A, *et al.* [Plasma GM-CSF concentrations in rheumatoid arthritis, systemic lupus erythematosus and spondyloarthritis]. *Z Rheumatol* 1992;**51**:121–6.
- Nakano K, Okada Y, Saito K, *et al.* Rheumatoid synovial endothelial cells produce macrophage colony-stimulating factor leading to osteoclastogenesis in rheumatoid arthritis. *Rheumatology (Oxford)* 2007;**46**:597–603.
- Berenbaum F, Rajzbaum G, Amor B, *et al.* Evidence for GM-CSF receptor expression in synovial tissue. An analysis by semi-quantitative polymerase chain reaction on rheumatoid arthritis and osteoarthritis synovial biopsies. *Eur Cytokine Netw* 1994;**5**:43–6.
- Lang RA, Metcalf D, Cuthbertson RA, *et al.* Transgenic mice expressing a hemopoietic growth factor gene (GM-CSF) develop accumulations of macrophages, blindness, and a fatal syndrome of tissue damage. *Cell* 1987;**51**:675–86.
- Campbell IK, Bendele A, Smith DA, *et al.* Granulocyte-macrophage colony stimulating factor exacerbates collagen induced arthritis in mice. *Ann Rheum Dis* 1997;**56**:364–8.
- Bischof RJ, Zafiroopoulos D, Hamilton JA, *et al.* Exacerbation of acute inflammatory arthritis by the colony-stimulating factors CSF-1 and granulocyte macrophage (GM)-CSF: evidence of macrophage infiltration and local proliferation. *Clin Exp Immunol* 2000;**119**:361–7.
- Campbell IK, Rich MJ, Bischof RJ, *et al.* Protection from collagen-induced arthritis in granulocyte-macrophage colony-stimulating factor-deficient mice. *J Immunol* 1998;**161**:3639–44.
- Cook AD, Braine EL, Campbell IK, *et al.* Blockade of collagen-induced arthritis post-onset by antibody to granulocyte-macrophage colony-stimulating factor (GM-CSF): requirement for GM-CSF in the effector phase of disease. *Arthritis Res* 2001;**3**:293–8.
- Yang YH, Hamilton JA. Dependence of interleukin-1-induced arthritis on granulocyte-macrophage colony-stimulating factor. *Arthritis Rheum* 2001;**44**:111–19.
- Plater-Zyberk C, Joosten LA, Helsen MM, *et al.* GM-CSF neutralisation suppresses inflammation and protects cartilage in acute streptococcal cell wall arthritis of mice. *Ann Rheum Dis* 2007;**66**:452–7.
- Hazenber BP, Van Leeuwen MA, Van Rijswijk MH, *et al.* Correction of granulocytopenia in Felty's syndrome by granulocyte-macrophage colony-stimulating factor. Simultaneous induction of interleukin-6 release and flare-up of the arthritis. *Blood* 1989;**74**:2769–70.
- de Vries EG, Willemse PH, Biesma B, *et al.* Flare-up of rheumatoid arthritis during GM-CSF treatment after chemotherapy. *Lancet* 1991;**338**:517–8.
- Hansen G, Hercus TR, McClure BJ, *et al.* The structure of the GM-CSF receptor complex reveals a distinct mode of cytokine receptor activation. *Cell* 2008;**134**:496–507.
- Fleetwood AJ, Cook AD, Hamilton JA. Functions of granulocyte-macrophage colony-stimulating factor. *Crit Rev Immunol* 2005;**25**:405–28.
- Gearing DP, King JA, Gough NM, *et al.* Expression cloning of a receptor for human granulocyte-macrophage colony-stimulating factor. *EMBO J* 1989;**8**:3667–76.
- Rajotte D, Sadowski HB, Haman A, *et al.* Contribution of both STAT and SRF/TCF to c-fos promoter activation by granulocyte-macrophage colony-stimulating factor. *Blood* 1996;**88**:2906–16.
- Arnett FC, Edworthy SM, Bloch DA, *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;**31**:315–24.
- Fries JF, Spitz P, Kraines RG, *et al.* Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;**23**:137–45.
- Smolen JS, Aletaha D. What should be our treatment goal in rheumatoid arthritis today? *Clin Exp Rheumatol* 2006;**24**(6 Suppl 43):S–7–13.
- Scherer HU, Dörner T, Burmester GR. Patient-tailored therapy in rheumatoid arthritis: an editorial review. *Curr Opin Rheumatol* 2010;**22**:237–45.
- Coenen MJ, Enevold C, Barrera P, *et al.* Genetic variants in toll-like receptors are not associated with rheumatoid arthritis susceptibility or anti-tumour necrosis factor treatment outcome. *PLoS ONE* 2010;**5**:e14326.
- Lindberg J, Wijbrandts CA, van Baarsen LG, *et al.* The gene expression profile in the synovium as a predictor of the clinical response to infliximab treatment in rheumatoid arthritis. *PLoS ONE* 2010;**5**:e11310.
- Caloguri G, Ventura MT, Mason L, *et al.* Hypersensitivity reactions to last generation chimeric, humanized [correction of umanized] and human recombinant monoclonal antibodies for therapeutic use. *Curr Pharm Des* 2008;**14**:2883–91.
- Levy G. Pharmacologic target-mediated drug disposition. *Clin Pharmacol Ther* 1994;**56**:248–52.
- Mager DE, Jusko WJ. General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. *J Pharmacokinetic Pharmacodyn* 2001;**28**:507–32.
- Hansen RJ, Balthasar JP. Pharmacokinetic/pharmacodynamic modeling of the effects of intravenous immunoglobulin on the disposition of antiplatelet antibodies in a rat model of immune thrombocytopenia. *J Pharm Sci* 2003;**92**:1206–15.

40. **Hayashi N**, Tsukamoto Y, Sallas WM, *et al*. A mechanism-based binding model for the population pharmacokinetics and pharmacodynamics of omalizumab. *Br J Clin Pharmacol* 2007;**63**:548–61.
41. **Tabrizi MA**, Tseng CM, Roskos LK. Elimination mechanisms of therapeutic monoclonal antibodies. *Drug Discov Today* 2006;**11**:81–8.
42. **Rowinsky EK**, Schwartz GH, Gollob JA, *et al*. Safety, pharmacokinetics, and activity of ABX-EGF, a fully human anti-epidermal growth factor receptor monoclonal antibody in patients with metastatic renal cell cancer. *J Clin Oncol* 2004;**22**:3003–15.
43. **Wang B**, Arends R, Roskos L, *et al*. A preliminary population pharmacokinetic analysis of panitumumab, a fully human IgG2 anti-EGFR monoclonal antibody. *AAPS J* 2004;**6**(Suppl 1):abstract 2375.
44. **Wang W**, Wang EQ, Balthasar JP. Monoclonal antibody pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther* 2008;**84**:548–58.
45. **Weisman MH**, Moreland LW, Furst DE, *et al*. Efficacy, pharmacokinetic, and safety assessment of adalimumab, a fully human anti-tumor necrosis factor-alpha monoclonal antibody, in adults with rheumatoid arthritis receiving concomitant methotrexate: a pilot study. *Clin Ther* 2003;**25**:1700–21.
46. **Nishimoto N**, Yoshizaki K, Maeda K, *et al*. Toxicity, pharmacokinetics, and dose-finding study of repetitive treatment with the humanized anti-interleukin 6 receptor antibody MRA in rheumatoid arthritis. Phase I/II clinical study. *J Rheumatol* 2003;**30**:1426–35.