EXTENDED REPORT

A phase 2 dose-ranging study of subcutaneous tabalumab for the treatment of patients with active rheumatoid arthritis and an inadequate response to methotrexate

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ABSTRACT

Objectives To assess the dose-response relationship, efficacy and safety of tabalumab, a human monoclonal antibody that neutralises membrane-bound and soluble B-cell activating factor (BAFF), in patients with rheumatoid arthritis (RA) with inadequate response to methotrexate (MTX).

Methods In this phase 2, 24-week, double-blind, placebo-controlled, dose-ranging study, patients with RA (N=158) on stable MTX were randomised by Bayesian-adaptive method to receive 1, 3, 10, 30, 60, or 120 mg tabalumab or placebo subcutaneously every 4 weeks for 24 weeks. The primary objective was to test for a significant dose-response relationship using a statistical model of the proportion of patients having ≥50% improvement in American College of Rheumatology (ACR) criteria (ACR50) at week 24 (prespecified α=0.10).

Results At week 24, a significant dose-response relationship was observed using ACR50 (p=0.059) and ACR20 (p=0.044) response rates. Using model-estimated data, only 120 mg had significantly higher ACR50 and ACR20 response rates versus placebo (p<0.05). Observed response rates were significantly higher for 120 mg versus placebo as measured by ACR50 at weeks 12 (p=0.039) and 20 (p=0.018), but not week 24, and by ACR20 at weeks 12 (p=0.011) and 24 (p=0.039). Mean DAS28-C reactive protein improved with 120 mg at week 24 (p=0.048). Frequency of TEAEs was similar across groups (range 50–69%, p=0.884). Ten (8.2%) tabalumab and 5 (13.9%) placebo patients reported a serious adverse event (SAE). Infections occurred more frequently in patients exposed to tabalumab (30.3% vs 19.4%). Serious infections were reported in 3 (2.5%) tabalumab-treated patients only.

Conclusions A dose-response relationship was detected with monthly subcutaneous tabalumab. A significant effect was detected with the 120 mg dose with no unexpected safety signals.

Clinical Trial # NCT00785928.

INTRODUCTION

Rheumatoid arthritis (RA) affects approximately 1% of the population1 and is characterised by joint inflammation that can lead to joint destruction and systemic complications.2 Currently available biologic therapies selectively target key molecules associated with joint inflammation, but approximately 30% of patients will remain unresponsive to these treatments.3

B-cell activating factor (BAFF) is a tumour necrosis factor (TNF) family ligand that is increased in the sera and synovial fluid of patients with RA,4–6 and is required for B-cell survival.7 BAFF has two biologically active forms, a soluble and membrane-bound form,8 and induces polyclonal maturation of immature and mature B cells involved in RA pathogenesis.9 10

Tabalumab is a human monoclonal antibody that neutralises soluble and membrane-bound BAFF.11 In a previous study, intravenous tabalumab (30, 60 and 160 mg) reduced RA signs and symptoms in patients with an inadequate response to methotrexate (MTX-IR); although all doses were effective, no dose-response relationship in American College of Rheumatology (ACR) scores was observed.12

The current trial, which used Bayesian-adaptive randomisation, explored the dose-response relationship of tabalumab given subcutaneously once every 4 weeks (Q4W) to patients with active RA receiving stable doses of MTX.

METHODS

Patients

Patients were recruited from 64 centres in 12 countries (Argentina, Australia, Chile, China, Hungary, India, Mexico, Poland, Romania, Slovakia, Ukraine and the USA). All patients provided voluntary written informed consent. The study was approved by local Institutional Review Boards in accordance with the Declaration of Helsinki and applicable laws and regulations.

Patients were aged between 18 and 75 years, were taking MTX (10–25 mg/week) for ≥16 weeks, and met ACR (1987 revised) criteria for RA.13 Major inclusion criteria included ≥5/28 swollen and ≥5/28 tender joints; ACR functional class I, II, or III; a history of, or a current, positive rheumatoid factor (RF+) test; a C-reactive protein (CRP) ≥1.2 times upper limit of normal (ULN; 1.0 mg/dl); and the absence of pregnancy or breast feeding.

Major exclusion criteria included use of any parenteral or oral corticosteroid at >10 mg/day of prednisone or its equivalent within 4 weeks of
baseline; use of any B-cell biotherapies at any time; insufficient response to a TNF inhibitor (TNF-IR; patients who stopped for reasons other than lack of efficacy were eligible); presence of other autoimmune disorders; a positive protein derivative test for tuberculosis; or serious bacterial infections within 6 months of enrolment. Study participants must have discontinued etanercept ≥28 days before baseline, and infliximab, adalimumab, or other biologic TNF inhibitors ≥56 days before baseline.

**Study design**

This was a phase 2, 24-week, double-blind, placebo-controlled, dose-ranging study. Following two screening visits, patients were randomised by Bayesian-adaptive method to receive placebo or tabalumab (1, 3, 10, 30, 60, or 120 mg) subcutaneously Q4W for 24 weeks (figure 1A). Patients maintained their prestudy stable dose of MTX and received their other usual medical treatments for RA or concomitant diseases as allowed by protocol.

Bayesian-adaptive randomisation used accumulating data from the ongoing trial to make progressive adjustments in dose-group assignments. Over time, these adjustments were expected to provide a more precise estimate of the dose-response relationship. Computer-generated random treatment assignments were made using an interactive voice-response system (IVRS). The first 35 patients were randomised to 1 of 7 treatment groups in equal number. Once 35 patients were randomised, there was a constant 20% chance of randomisation to placebo and an 80% chance of randomisation to one of the tabalumab doses. A contract research organisation periodically updated a non-informative, normal, dynamic linear model prior distribution, from which the posterior distribution of a 24-week, treatment-response model was derived. The posterior distribution was used to adjust the probability of randomisation to each tabalumab dose. As the study progressed, the probability of assignment to higher doses increased. Enrolment and randomisation ended when approximately 150 patients had been randomised. These 150 patients provided 80% power to detect a difference based on simulations using varying responses-to-dose assumptions as well as varying patient accrual and dropout rates.

![Figure 1](http://ard.bmj.com/)

**Figure 1**  Study design and patient disposition. (A) Patients were adaptively randomised by Bayesian method. Over time, the probability of randomisation to more effective doses increased, resulting in unequal distribution of patients across groups. Study drug was administered six times by SC injection for 24 weeks. (B) Disposition of 158 randomised and treated patients through week 24. The percentage of patients who withdrew from the study and reasons for discontinuation are also shown for each group. *One patient in the placebo group was discontinued due to elevated liver enzymes at the sponsor’s request. †Two patients in the 120 mg group were excluded from primary efficacy analyses due sponsor decision to withdraw a site for violation of good clinical practices. AEs, adverse events, SC, subcutaneous.
Endpoints
The primary endpoint was to test for a significant dose-response relationship based on a statistical model of the proportion of patients having ≥50% improvement in ACR criteria (ACR50) at week 24. Key secondary efficacy endpoints included the dose-response relationship based on modelled ACR20 response rates at week 24; ACR20 and ACR50 response rates, change in DAS28, and percent change in CRP at each visit (weeks 1, 4, 8, 12, 16, 20 and 24); and pharmacokinetic parameters. Safety endpoints included incidences of adverse events (AEs) and serious adverse events (SAEs), and clinical laboratory test and immunogenicity results. Pharmacodynamic endpoints included changes over time in serum immunoglobulins (IgM, IgG, IgA), total B cells (CD20), and B-cell subsets (mature naïve (CD19, IgD+, CD27–), memory (CD19, IgD–, CD27+)).

All efficacy measures used 28-joint counts and CRP for response calculations. Blood samples were collected at baseline and subsequent visits for determining serum tabalumab concentrations (weeks 1, 4, 8, 12, 16, 20 and 24), serum immunoglobulins (IgG, IgM and IgA) (weeks 1, 4, 16 and 24), and anti-tabalumab antibodies (weeks 4, 8 and 24). Serum tabalumab and immunoglobulin concentrations were assayed using validated methods. B cells were assayed by flow cytometry.15

Standard laboratory tests, including chemistry, haematology, urinalysis panels and ECGs were obtained at regular intervals. Vital signs were taken, and AEs and SAEs were recorded and summarised at each visit.

Clinical response
A significant (prespecified α=0.10) dose-response relationship was detected for ACR50 (p=0.059) and ACR20 (p=0.044) at week 24 using a regression model. The ED50 was 119.0 mg and 118.5 mg for ACR50 and ACR20, respectively. Modelled and observed results for ACR50 and ACR20 responders at week 24 are presented in table 2. Using model-estimated data at week 24, only the 120 mg dose had significantly higher ACR50 and ACR20 response rates versus placebo (table 2).

The observed ACR50 response rate (NRI) was significantly higher with only the 120 mg dose versus placebo at week 12 (53.3% (8/24) vs 11.1% (4/36); p=0.039) and week 20 (53.3% (8/24) vs 8.3% (3/36); p=0.018), but not at week 24 (table 2, figure 2A). The ACR20 response rate (NRI) was significantly higher with 120 mg versus placebo at week 12 (66.7% (16/24) vs 33.3% (12/36); p=0.011), and week 24 (table 2, figure 2B).

No other dose was significantly different from placebo at any timepoint for ACR20, except 60 mg at week 4 (58.5% (5/13) vs 11.1% (4/36); p=0.043) (figure 2B).

At baseline, DAS28 scores were similar across groups (table 1). DAS28 score significantly improved from baseline with 120 mg versus placebo at week 24 (table 2); this improvement was also observed at earlier timepoints (figure 2C). No other dose showed a significant DAS28 improvement.

RESULTS
Patient disposition and characteristics
A total of 142/158 patients (89.9%) completed: 34/36 (94.4%) in the placebo group and 108/122 (88.5%) in all tabalumab groups combined (figure 1B). The most common reasons for early withdrawal were AEs and patient decision (figure 1B).

Overall, baseline characteristics were similar across groups with a few exceptions (table 1). In the 60 mg group, a smaller percentage were Caucasian (39%; range 53–73%, p=0.049 vs placebo). The placebo group had shorter disease duration than the 30 mg group (p=0.001). Baseline disease activity parameters and average MTX and prednisone doses were comparable across groups. Eleven patients had prior TNF-inhibitor exposure: 7 placebo (infliximab, n=2; adalimumab, n=2; investigational drug, n=1; etanercept, n=2), one 1 mg (infliximab), one 30 mg (etanercept), one 60 mg (infliximab), and one 120 mg tabalumab (investigational drug).

Clinical and epidemiological research
Clinical and epidemiological research

Table 1 Baseline demographics and clinical parameters (ITT population)

<table>
<thead>
<tr>
<th>Placebo (N=36)</th>
<th>Tabalumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (16.7)</td>
</tr>
<tr>
<td>Female</td>
<td>30 (83.3)</td>
</tr>
<tr>
<td>Age, years</td>
<td>50.6±11.7</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>25 (69.4)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>8 (22.2)</td>
</tr>
<tr>
<td>East Asian</td>
<td>2 (5.6)</td>
</tr>
<tr>
<td>West Asian</td>
<td>0</td>
</tr>
<tr>
<td>African</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Disease duration, years</td>
<td>6.2±7.2</td>
</tr>
<tr>
<td>CRP above ULN at baseline, n (%)</td>
<td>28 (77.8)</td>
</tr>
<tr>
<td>MTX dose, mg/week</td>
<td>16.8±4.5</td>
</tr>
<tr>
<td>Prednisone dose, mg/day</td>
<td>6.6±2.2</td>
</tr>
<tr>
<td>CD20 B-cell counts, cells/μl</td>
<td>193.4±130.3</td>
</tr>
<tr>
<td>Tabalumab dose, mg/day</td>
<td>1 mg (N=30) 3 mg (N=20) 10 mg (N=15) 30 mg (N=18) 60 mg (N=13) 120 mg (N=26)</td>
</tr>
</tbody>
</table>
| Placebo (N=36) | 67.75 vs 14.64 cells/μl, p<0.001) and subsequently increased at week 1 (mean change in all doses combined vs placebo: 67.75 vs 14.64 cells/μl, p<0.001) and subsequently increased at week 1 (mean change in all doses combined vs placebo: 67.75 vs 14.64 cells/μl, p=0.008). Of the CD19 cell subsets, only mature, naïve cell counts showed a pattern similar to CD20 cells (week 1: 38.17 vs 15.70 cells/μl, p=0.028; week 24: 45.63 vs 18.06 cells/μl, p<0.001). Increases in memory cell counts from baseline were observed across groups over 24 weeks, with the largest increases in the higher dose groups. At week 24, only 30 mg (p=0.006), 60 mg (p=0.003) and 120 mg (p<0.001) demonstrated statistically significant increases in memory B cells versus placebo.

Mean IgM and IgA levels tended to be lower than baseline for all tabalumab groups at weeks 16 and 24. For IgM, this difference was statistically significant at week 16 with the 30 mg (−0.15±0.40 g/l, p=0.016), 60 mg (−0.24±0.27 g/l, p=0.028), and 120 mg (−0.17±0.32 g/l, p=0.005) versus placebo (0.02±0.39 g/l), and at week 24 with 30 mg (−0.08±0.53 g/l, p=0.023), 60 mg (−0.30±0.30 g/l, p=0.004), and 120 mg (−0.09±0.58 g/l, p=0.017) versus placebo (0.02±0.52 g/l). For

Table 2 Summary of efficacy endpoints at week 24

<table>
<thead>
<tr>
<th>Placebo (N=36)</th>
<th>1 mg (N=30)</th>
<th>3 mg (N=20)</th>
<th>10 mg (N=15)</th>
<th>30 mg (N=18)</th>
<th>60 mg (N=13)</th>
<th>120 mg (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACR50 obs, n (%)</td>
<td>8 (22.2)</td>
<td>3 (10.0) (0.896)</td>
<td>2 (10.0) (0.940)</td>
<td>5 (33.3) (0.311)</td>
<td>2 (11.1) (0.919)</td>
<td>1 (7.7) (0.954)</td>
</tr>
<tr>
<td>ACR50 model, % (p) *</td>
<td>18.1</td>
<td>17.7 (0.827)</td>
<td>17.0 (0.828)</td>
<td>15.0 (0.833)</td>
<td>11.8 (0.834)</td>
<td>11.8 (0.767)</td>
</tr>
<tr>
<td>ACR20 obs, n (%) (p) *</td>
<td>16 (44.4)</td>
<td>12 (40.0) (0.730)</td>
<td>9 (45.0) (0.594)</td>
<td>7 (46.7) (0.563)</td>
<td>11 (61.1) (0.193)</td>
<td>7 (53.8) (0.397)</td>
</tr>
<tr>
<td>ACR20 model, % (p) *</td>
<td>43.2</td>
<td>43.6 (0.171)</td>
<td>44.3 (0.170)</td>
<td>46.9 (0.162)</td>
<td>53.5 (0.132)</td>
<td>61.5 (0.070)</td>
</tr>
<tr>
<td>DAS28, mean±SD</td>
<td>−1.5±1.3</td>
<td>−1.5±1.3 (0.457)</td>
<td>−1.0±1.1 (0.874)</td>
<td>−1.7±1.0 (0.278)</td>
<td>−1.5±1.3 (0.357)</td>
<td>−1.6±1.2 (0.271)</td>
</tr>
</tbody>
</table>

*1-sided Fisher exact test that the tabalumab group has more responders than placebo.
†Imputed by non-responder imputation.
§Likelihood ratio test of quadratic logistic regression model, testing the existence of a dose-response with a prespecified 2-sided type 1 error rate of 0.10.
¶Imputed by last-observation-carried-forward.
**Dose-response relationship from 1-sided Spearman non-parametric correlation analysis.
AUC, American College of Rheumatology 50 responder index; ACR20, American College of Rheumatology 20 responder index; DAS28, Disease Activity Score based on 28-joint count; obs, actual observations; model, assessed using a statistical model; NA, not available; p, p Value.
IgA, this difference was statistically significant at week 16, with 120 mg versus placebo (−0.32±0.42 vs −0.12±0.50 g/l, p=0.040), and at week 24 with 60 mg (−0.42±0.45 g/l, p=0.025) and 120 mg (−0.25±0.63 g/l, p=0.030) versus placebo (−0.12±0.48 g/l). Mean IgG levels were not significantly different from placebo with any tabalumab dose at any timepoint. There was no association between changes in serum immunoglobulin levels and occurrence of infection or other AEs. There was no correlation between clinical response, B-cell counts, or serum immunoglobulin levels.

Safety
The frequency of treatment-emergent adverse events (TEAEs) was similar across tabalumab doses (range 50–69%, p=0.884) (table 4). The majority of TEAEs were mild or moderate in severity with no obvious trends in the nature or frequency by dose. The most frequently reported TEAEs were injection-site pain and upper respiratory tract infection (table 4). Five patients discontinued due to an AE, all of whom were treated with tabalumab 1 mg (hemiplegia), 3 mg (prolonged QT and RA worsening (exacerbation/flare)), or 120 mg (diverticulitis and RA worsening). The incidence of SAEs was 13.9% (5/36 patients) with placebo and ranged from 3.8% (1/26 patients) with 120 mg to 16.7% (3/18 patients) with 30 mg (table 4). RA worsening was the only SAE reported in >1 patient (n=2, placebo). No patients died during the study.

Infection was reported at a higher incidence with tabalumab (30.3% (37/122 patients)) than placebo (19.4% (7/36 patients)), but did not increase with higher doses. The lowest incidence of infection was observed with 120 mg (11.5%). Serious infections...
were reported in three (2.5%) tabalumab-treated patients. One patient discontinued due to a serious infectious event of H1N1 influenza pneumonia 24 days after a single 30 mg dose.

No clinically relevant differences or trends were identified in vital signs, ECG, or chemistry, haematology and urinalysis panels. The percentage of patients with abnormal laboratory values was comparable across groups, with no apparent trends.

Immunogenicity

At 24 weeks, two tabalumab-treated patients had treatment-emergent antitabalumab antibodies (TEAb (fourfold increase from baseline); 1 mg and 10 mg group). One patient seroconverted at week 4, the other at week 3, and TEAb persisted to week 24. None were neutralising. Two additional patients (1 mg and 10 mg group) and 2 placebo patients had transient TEAb detected at a single sampling. One placebo patient had neutralising antibodies at week 24. The presence of TEAb did not appear to have an effect on ACR response. None of the tabalumab-treated patients who tested positive for antibodies experienced an SAE or serious infection, nor did they discontinue due to lack of efficacy. There was no discernible reduction in tabalumab serum concentrations in the presence of antitabalumab antibodies and no dose-related trends.

### Table 3 Composite score components at baseline and at week 24 (LOCF)

<table>
<thead>
<tr>
<th>Tabalumab</th>
<th>Placebo (N=36)</th>
<th>1 mg (N=30)</th>
<th>3 mg (N=20)</th>
<th>10 mg (N=15)</th>
<th>30 mg (N=18)</th>
<th>60 mg (N=13)</th>
<th>120 mg (N=24)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Swollen joint count (28)</td>
<td>12.0±5.5</td>
<td>13.4±5.8</td>
<td>11.2±5.0</td>
<td>15.4±6.3</td>
<td>12.7±5.6</td>
<td>13.1±5.4</td>
<td>11.9±6.1</td>
</tr>
<tr>
<td>Week 24</td>
<td>6.3±4.7</td>
<td>6.5±5.5</td>
<td>5.5±5.8</td>
<td>6.5±5.3</td>
<td>7.3±7.6</td>
<td>6.9±4.8</td>
<td>4.3±3.5</td>
</tr>
<tr>
<td>Tender joint count (28)</td>
<td>16.0±6.5</td>
<td>17.8±7.2</td>
<td>16.5±6.3</td>
<td>16.5±8.3</td>
<td>15.4±5.8</td>
<td>15.2±6.3</td>
<td>13.7±6.3</td>
</tr>
<tr>
<td>Week 24</td>
<td>8.9±6.7</td>
<td>10.5±9.9</td>
<td>12.0±9.6</td>
<td>7.8±5.9</td>
<td>7.7±6.9</td>
<td>7.8±7.4</td>
<td>6.2±5.9</td>
</tr>
<tr>
<td>Physician’s global assessment of disease activity</td>
<td>61.8±16.6</td>
<td>61.5±20.2</td>
<td>57.9±16.5</td>
<td>67.2±14.6</td>
<td>59.9±16.8</td>
<td>53.0±13.7</td>
<td>61.6±14.8</td>
</tr>
<tr>
<td>Week 24</td>
<td>39.0±23.7</td>
<td>38.7±24.3</td>
<td>31.7±22.5</td>
<td>37.0±22.3</td>
<td>31.6±21.7</td>
<td>31.6±20.8</td>
<td>25.8±14.2*</td>
</tr>
<tr>
<td>Patient’s global assessment of disease activity</td>
<td>70.3±19.4</td>
<td>71.6±17.5</td>
<td>68.8±18.3</td>
<td>61.6±20.8</td>
<td>64.5±24.3</td>
<td>60.9±20.1</td>
<td>69.4±15.0</td>
</tr>
<tr>
<td>Week 24</td>
<td>46.1±26.2</td>
<td>50.9±27.5</td>
<td>50.8±21.2</td>
<td>39.1±28.4</td>
<td>45.9±23.7</td>
<td>45.5±17.3</td>
<td>35.6±20.2</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>66.3±23.7</td>
<td>66.4±20.2</td>
<td>63.1±18.4</td>
<td>61.5±23.4</td>
<td>59.5±23.7</td>
<td>64.4±16.1</td>
<td>66.2±15.3</td>
</tr>
<tr>
<td>CRP</td>
<td>48.6±25.6</td>
<td>48.6±26.1</td>
<td>50.4±20.8</td>
<td>40.3±28.6</td>
<td>46.4±25.3</td>
<td>46.8±16.9</td>
<td>36.4±21.0</td>
</tr>
</tbody>
</table>

All values are mean±SD. Analyses are 2-sided pairwise comparisons of tabalumab dose versus placebo were performed using contrast statements within ANCOVA.

*P<0.05 versus placebo.

CRP, C-reactive protein; LOCF, last-observation-carried-forward; p, p Value.

### Table 4 Overview of adverse events at week 24

<table>
<thead>
<tr>
<th>Tabalumab</th>
<th>Placebo (N=36)</th>
<th>1 mg (N=30)</th>
<th>3 mg (N=20)</th>
<th>10 mg (N=15)</th>
<th>30 mg (N=18)</th>
<th>60 mg (N=13)</th>
<th>120 mg (N=24)</th>
<th>All tabalumab doses combined (N=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SAEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patients who discontinued due to an AE</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TEAEs</td>
<td>22 (61.1)</td>
<td>20 (66.7)</td>
<td>12 (60)</td>
<td>9 (60)</td>
<td>12 (66.7)</td>
<td>9 (69.2)</td>
<td>13 (50)</td>
<td>75 (61.5)</td>
</tr>
</tbody>
</table>

AE, adverse event; RA, rheumatoid arthritis; SAEs, serious adverse events; TEAEs, treatment-emergent adverse events.

Percentages are based on the number of patients in each column.
DISCUSSION

In the current study, which used Bayesian-adaptive randomisation, a statistically significant dose-response relationship was detected using regression models of ACR50 and ACR20 response rates at 24 weeks for tabalumab, administered monthly by subcutaneous injection over a 1 mg to 120 mg dose range. Significant efficacy versus placebo was detected with the 120 mg dose for ACR50 (by regression analysis only), ACR20, and DAS28 at week 24.

The principles and potential utility of B-cell depletion in RA treatment have been recognised since 2001. Subsequent work at week 24.

The concept of effective RA treatment through B-cell inhibition (without profound depletion) has been explored with limited success. Belimumab, a monoclonal antibody that neutralises soluble BAFF was studied but not developed as an RA treatment after modest phase 2 results. Atacicept, a fusion protein targeting BAFF and APRIL (a proliferation–inducing ligand), failed to achieve clinical benefits in two RA trials.

Tabalumab neutralises membrane-bound and soluble BAFF and, thus, may have different biologic action and clinical outcomes than belimumab, atacicept and briobiocyte (a recombinant BAFF receptor immunoglobulin fusion protein). In an earlier study, intravenous tabalumab (30, 60 and 160 mg) administered every 5 weeks (Q5W) for 6 weeks demonstrated clinical efficacy in biologic-naive patients with RA. The present trial evaluated subcutaneous tabalumab across a wider range of doses given Q4W for 6 months. Adjusting for bioavailability and differences in dosing frequency, a subcutaneous Q4W 120 mg dose provides exposure equivalent to an intravenous Q5W 45 mg dose (data not shown).

Overall, no unexpected safety signal was detected in this relatively small study; tabalumab had a consistent safety profile across dose groups and placebo. Infectious events were more frequent with tabalumab than placebo, although the frequency did not increase with higher doses. Mean IgM and IgA levels tended to be lower than baseline in all tabalumab groups in the later weeks of the study; changes from baseline were not associated with increases in AEs or infectious AEs.

Within 1 week of the first injection, CD20 B cells and CD19 mature, naïve cells transiently increased with all tabalumab doses before decreasing back to baseline levels or below without profound reductions. Early increases in B cells with subsequent decreases have been observed with other BAFF-targeted therapies, such as briobiocyte and atacicept. No correlations were observed between B-cell changes and clinical efficacy or safety with tabalumab.

The following limitations of this study should be considered. Bayesian-adaptive randomisation was intended to estimate the dose-response relationship more precisely and to allocate patients to more effective dosing. However, patients were enrolled faster than planned, and updates to randomisation probabilities were not frequent enough. As a result, a higher percentage of patients were assigned to placebo or very low dose treatments. Despite this, a dose-response relationship was detected. Additionally, this was a short-term study with small treatment arms, and ACR50, rather than ACR20, was the primary endpoint. This study enrolled patients with active RA who were taking MTX, but not patients who previously failed TNF inhibitors or other biologic RA treatments, and only included RF+ patients. These findings cannot be generalised to patients on other background RA medications, with a history of exposure to a larger repertoire of agents, or who are seronegative. Despite these limitations, tabalumab demonstrated efficacy in MTX-IR patients.

In the present study, subcutaneous 120 mg tabalumab appeared to reduce RA signs and symptoms in patients taking concomitant MTX. Overall, based on a limited number of exposures in this phase 2 study, tabalumab had no unexpected safety signals. After this study was completed, phase 3 clinical trials were undertaken using tabalumab in patients with RA. These trials were recently discontinued after interim analyses provided results that did not meet efficacy expectations. No safety concerns were noted.

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A phase 2 dose-ranging study of subcutaneous tabalumab for the treatment of patients with active rheumatoid arthritis and an inadequate response to methotrexate

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