Synopsis

Identifier: GM2008/00100/00 **Study Number:** RA3103718

Title: A randomised, double blind, placebo controlled study to investigate the safety and tolerability and clinical activity of 28 days of repeat dosing with GW856553 at 7.5 mg BID in subjects with active rheumatoid arthritis (RA) on stable anti-rheumatic therapy.

Investigators: Multi-centre study.

Study centres: There were 2 centres in Romania, 7 centres in Russia and 10 centres in Spain.

Publication: None at the time of this report

Study period:

Initiation Date:	30 OCT 2006
Completion Date:	21 JAN 2008

Phase of development: IIa

Objectives:

Primary:

- To investigate the clinical activity of GW856553 after 27 days of oral dosing in RA subjects as measured by Disease Activity Score based on 28 joint count (DAS28) score (calculated using erythrocyte sedimentation rate [ESR]) compared with placebo.

Secondary:

- To investigate the safety and tolerability of GW856553 after 27 days of dosing in RA subjects.
- To investigate the clinical activity of GW856553 after 27 days of dosing in RA subjects as measured by DAS28 score (calculated using C-reactive protein [CRP]) compared with Placebo.
- To investigate the clinical activity of GW856553 after 27 days of dosing in RA subjects as measured by percent of subjects achieving American College of Rheumatology (ACR) 20/50/70 scores compared with Placebo.
- To investigate the activity of GW856553 after 27 days of dosing in RA subjects as measured by effects on biomarkers compared with Placebo.
- To investigate differences in pain, fatigue and quality of life after 27 days of GW856553 dosing in RA subjects compared with Placebo.

- To characterise population pharmacokinetics (PK) of GW856553 in RA subjects.
- To explore the potential correlation between plasma exposure to GW856553 and disease surrogates (e.g. CRP and serum amyloid A (A-SAA)) and clinical endpoints (e.g. ACR20 and DAS28).
- To investigate the effect of GW856553 on the joints after 28 days of dosing in RA subjects compared with Placebo.
- Optional objective (depending on safety checkpoint): To explore the safety and tolerability and the effect on biomarkers and synovial inflammation of
  - 56 days dosing with 7.5 mg BID GW856553 compared with Placebo
  - 28 days dosing with 10 mg BID GW856553 (after at least 28 days of dosing with 7.5 mg BID) compared with Placebo

Methodology:

The purpose of this study was to investigate the safety, tolerability and clinical activity of 28 days of repeat dosing with GW856553 at 7.5 mg BID in subjects with active rheumatoid arthritis on stable anti-rheumatic therapy.

GW856553 is a potent and selective inhibitor of p38α mitogen-activated protein kinase (MAPK). In healthy volunteers administered single (7 mg to 60 mg) and repeat doses (5 mg once daily to 7.5 mg BID) of GW856553 significant inhibition (50-70%) of lipopolysaccharide (LPS)-induced tumour necrosis factor alpha (TNFα) production in a whole blood *ex vivo* assay was observed. P38 MAPK was involved in the signalling through the LPS receptor and the pharmacodynamic (PD) assay was therefore sensitive to p38 MAPK inhibitors.

This was a randomised, double blind, placebo controlled study, designed to provide preliminary information that GW856553 had clinical activity in subjects with RA who were receiving standard anti-rheumatic therapies (excluding biological therapies).

Subjects attended a Screening visit within 21 days prior to randomisation. Eligible subjects were then randomised to one of the 3 treatment sequences in a 1:1:1 ratio as follows and dosed for a total of 56 days (although duration of active dosing was limited to 28 days). Subjects were required to attend the clinic/unit for assessments on study Day 1, Day 15, Day 28, Day 43, Day 56, Day 70 and Day 84. The schedule is detailed in the Attachment 1: Time and Events Table.

Sequence 1: Oral GW856553 (7.5 mg BID) for 28 days followed by Placebo for 28 days (AP).

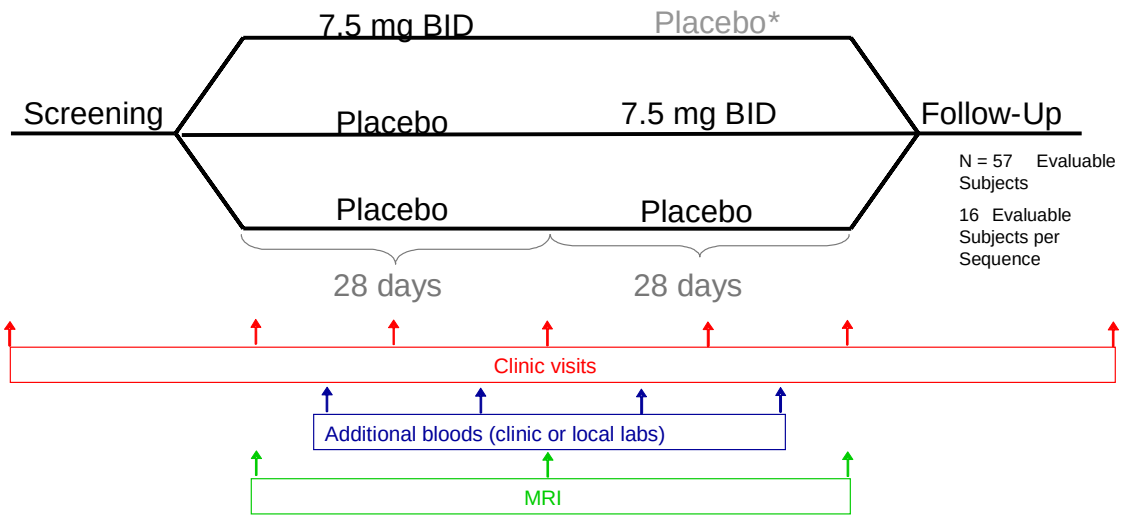
Sequence 2: Placebo for 28 days followed by oral GW856553 (7.5 mg BID) for 28 days (PA).

Sequence 3: Placebo for 56 days (PP).

Follow-up visit occurred between 7 and 14 days after the last dosing day. Therefore, the subjects were enrolled in the study for a maximum of 13 weeks (Screening to Follow-up inclusive).

The study design is illustrated in the figure below.

Study Schematic Figure



*Note: The primary efficacy comparison is not using the placebo data from sequence 1

A blinded safety checkpoint occurred when additional long term pre-clinical toxicology data became available and after 20 subjects had completed 56 days of dosing (of which a maximum of 28 days were on active). The process for undertaking this safety checkpoint was compliant with GSK SOPs.

After the safety check point, subjects were re-allocated to receive 7.5 mg BID of GW856553 for 56 days (Sequence 1a) instead of 7.5 mg BID of GW856553 for 28 days followed by placebo for 28 days. The other 2 treatment regimens remained unchanged. A further re-allocation of treatment regimen occurred at Day 56 and for newly recruited subjects. This additional dosing increased the dosing period to 84 days and increased the dose of GW856553 to 10 mg BID as follows:

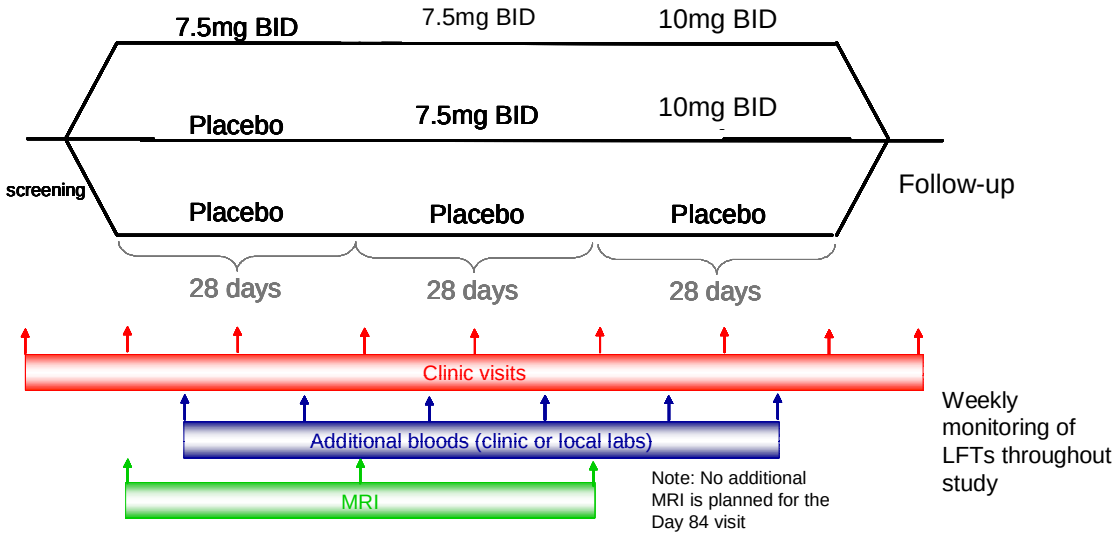
Sequence 4: Oral GW856553 (7.5 mg BID) for 56 days followed by GW856553 (10 mg BID) for 28 days;

Sequence 5: Placebo for 28 days followed by oral GW856553 (7.5 mg BID) for 28 days followed by GW856553 (10 mg BID) for 28 days or

Sequence 6: Placebo for 84 days.

The study design after the safety checkpoint is illustrated in the study schematic figure below.

Study Schematic Design After Safety Checkpoint



The 10 mg BID dose was only to be administered to subjects who have already tolerated 7.5 mg BID for at least 28 days. This strategy allowed the maximum number of subjects to extend the duration of dosing and to receive the higher dose. Thus all subjects newly recruited after the safety checkpoint and those who had not completed 56 days of dosing were eligible to participate in the extended duration of dosing and to receive a modest increase in dose.

Number of subjects:

Subject Disposition and Demographics:

Number of Subjects	Total
Number of subjects planned, N:	54
Number of subjects randomised, N:	57
Number of subjects included in All subjects (safety) population, n (%):	57 (100)
Number of subjects included in PK population, n (%):	34 (59)
Number of subjects completed as planned, n (%):	53 (93)
Number of subjects with missing data[1]	1 (2)
Number of subjects withdrawn (any reason), n (%):	3 (5)
Number of subjects withdrawn for AE, n (%):	2 (4)
Reasons for subject withdrawal, n (%)	
Adverse events	2 (4)
Protocol violation	1 (2)
Demographics	Total
Age in Years, Mean (Range)	56.5 (24 - 76)
Sex, n (%)	
Female:	52 (91)
Male:	5 (9)
BMI (kg/m^2), Mean (Range)	27.04 (18.59 – 34.97)
Height (cm), Mean (Range)	161.6 (144 – 190)
Weight (kg), Mean (Range)	70.62 (48.0 – 99.4)
Ethnicity, n (%)	
Hispanic or Latino:	8 (14)
Not Hispanic or Latino:	49 (86)
Race, n (%)	
White – White/Caucasian/European Heritage	57 (100)

Source Data Table 9.1, Table 9.18

1. [redacted]

Diagnosis and main criteria for inclusion: Male and female subjects aged ≥18 years, body weight ≥50 kg (110 lbs) for male and ≥45 kg (99 lbs) for female, body mass index (BMI) ranged from 18.5 – 35.0 kg/m^2 inclusive, diagnosed with RA according to the revised 1987 criteria of the ACR, having DAS28 ≥4.2 (calculated using ESR), LFT [alanine aminotransferase (ALT), aspartate aminotransferase (AST) and total bilirubin] <1.5 x upper limit of normal (ULN); alkaline phosphatase (ALP) <2 x ULN at screening, were included in this study.

The subjects who were on any biological anti-rheumatic therapy, oral prednisolone at doses >10 mg/day, methotrexate >25 mg/week or sulphasalazine >5 g/day and the subjects who had received rituximab, leflunomide for less than 6 months prior to randomisation; had changed Disease Modifying Anti-Rheumatic Drugs (DMARD), non steroidal anti-inflammatory drugs (NSAIDs), cycloxygenase-2 (COX-2) inhibitors or glucocorticoid dosing regimen 4 weeks prior to randomisation and statin dosing regimen during 3 months prior to randomisation were excluded from the study.

[redacted]

Treatment administration: GW856553X tablets were available as white, film-coated, round; tablets manufactured using GW856553X active substance. Tablets were available containing doses of 2.5 mg and 5 mg of GW856553X. Placebo tablets to match the active tablets were available. Investigational products used in this study are detailed in the table below.

Summary of Treatment Administration

Drug / strength	Dose/Form/Route	Frequency	Batch Numbers
GW856553 2.5 mg	7.5 mg (2.5 mg + 5 mg) tablet oral	Twice daily	061122843, 061115552, 061116106
GW856553 5 mg	10 mg (5 mg + 5 mg) tablet oral	Twice daily	061122849, 061115554, 061116109
Placebo	Tablet oral	Twice daily	061122712, 051092474

For the GW856553 7.5 mg BID dose, subjects had taken one 2.5 mg tablet (or placebo) plus one 5 mg tablet (or placebo) each morning and 12 hours (h) later (at bedtime). For the GW856553 10 mg BID dose, subjects had taken two 5 mg tablets (or placebo) each morning and 12 h later (at bedtime). The evening (12 h later) dose was not administered on Day 84. Subjects swallowed the tablets with water.

Criteria for evaluation:

Primary:

- DAS28 [swollen joint count (SJC), tender joint count (TJC), subject's global assessment of arthritis condition, ESR]

Secondary:

- Safety and tolerability [adverse events, vital signs, 12-lead electrocardiogram (ECG), clinical laboratory tests; ALT, AST, ALP, gamma glutamyl transpeptidase (γGT) and bilirubin, full blood count and urinalysis].
- DAS28 (SJC,TJC, subject's global assessment of arthritis condition, CRP) and ACR20/50/70
- The European League against Rheumatism (EULAR) response criteria
- Individual components of the rheumatological assessment:
    - Number of tender joints (TJC): 28 joint count
    - Number of swollen joints (SJC): 28 joint count
    - Duration of morning stiffness (minutes)

  - Physician global assessment of arthritis condition
  - Subject global assessment of arthritis condition
  - Acute phase reactants (ESR and CRP)
  - Subject assessment of pain (visual analogue score)
- Health outcomes
  - Functional Disability Index [Health assessment questionnaire –(HAQ)]
  - Multidimensional Assessment of Fatigue (MAF) [Belza, 1995]
- Biomarkers
  - Plasma levels of interleukin-6 (IL-6), A-SAA, matrix metalloproteinases (MMPs) (other markers associated with inflammation and the p38 MAPK-dependent signalling pathway may be measured using a multiplex assay and these may include but are not limited to soluble intracellular adhesion molecule (sICAM1), myeloid progenitor inhibitory factor (MPIF1), membrane-bound isoform of colony stimulating factor (MCSF1), B- lymphocyte chemoattractant (BLC), S100A8/A9 heterodimer, 41BB)
  - Samples would be stored for measurement of exploratory biomarkers of cartilage damage, bone formation and bone resorption.
  - Whole blood levels of messenger-ribonucleic acid (mRNA) for the following genes: inducible nitric oxide synthase (iNOS), COX-2, TNF-α, IL-8, IL-6 and IL-1β.
  - Exploratory whole blood transcriptional profiles
- Population PK parameters
- Model parameters for the correlation of plasma concentration of GW856553 and the clinical endpoints (DAS28 and ACR20)
- Gadolinium-enhanced Magnetic Resonance Imaging (MRI) of metacarpal-phalangeal (MCP) and wrist joints of one hand. Endpoints of interest:
  - Enhancing synovium vascular response
  - Total enhanced tissue volume
  - Enhanced synovium volume
  - Synovium volume (without enhancement)
  - Bone oedema volume
  - RAMRIS Score
- Subject structural damage at baseline, through X-ray of the hands and feet. Endpoint of interest
  - Sharp-van der Heijde scores of erosions, joint space narrowing and combined damage.

- Correlation of MRI endpoints and joint damage as measured by X-ray.

Statistical methods:

Sample size

This study was powered in order to detect a difference in modified DAS28 between GW856553 and placebo after 27 days of treatment. It was estimated that 16 subjects in each sequence would provide approximately 90% power to detect an 0.8 difference between GW856553 and placebo based on a test of significance at the two-sided 5% level. To allow for an estimated 10% of subjects withdrawing from treatment, it was intended that 18 subjects per arm would be enrolled into the study.

The sample size was re-estimated after 28 subjects had completed 56 days of dosing and used all available DAS28 data at that time to ensure that estimates of DAS28 variability are applicable in the countries participating in this study. The re-estimation was performed by an independent GSK statistician, and used unblinded data.

Interim analyses

No formal interim analysis was performed. However, a blinded safety review and an unblinded sample size re-estimation were performed.

Main analyses

The MITT population was used for figures, tables and listings for all endpoints excluding safety. The analysis of DAS28, CRP and ACR20 was repeated using the per protocol population. For all formal statistical analyses three treatment groups were used these are;

- 7.5 mg BID (A): Day 1 to Day 28 data from subjects randomised to Sequence 1 and Day 29 to Day 56 data from subjects randomised to Sequence 2.
- Placebo (P1): Day 1 to Day 28 data from subjects randomised to Sequence 2, Day 1 to Day 28 data from subjects randomised to Sequence 3 and Day 29 to Day 56 data from subjects randomised to Sequence 3.
- Placebo (P2): Day 29 to Day 56 data from subjects randomised to Sequence 1.

The main analysis was performed after all subjects had completed 56 days of dosing. At the main analysis Period 1 and Period 2 DAS28, CRP, ESR, TJC, SJC, Patients assessment of pain, IL6 and A-SAA data were listed and summarised.

Mean DAS28 and 95% confidence intervals (CIs) for each treatment group and visit were plotted. DAS28 scores were analysed using a repeated measures analysis. Adjusted means and treatment differences were presented along with their corresponding two-sided 95% CIs.

Geometric mean CRP and 95% CIs for each treatment group and visit were plotted. CRP and ESR were analysed using a repeated measures analysis following a $\log_e$-transformation. Adjusted geometric means and treatment ratios were presented along with their corresponding two-sided 95% CIs.

ACR20, ACR50 and ACR70 and EULAR responders were listed and the number and percentage of responders was summarised. The percentage of subjects achieving an ACR-defined 20% and the percentage of subjects meeting the EULAR criteria were analysed using conditional logistic regression models. Adjusted odds ratios and two-sided 95% CI were presented. Formal analyses of ACR50 and ACR70 were not performed due to the small number of responders.

Tender/painful joint count, swollen joint count and subject's pain assessment were analysed using a repeated measures mixed effects model.

Period 1 and 2 safety data were listed and summarised. Individual LFT data were plotted. Mean LFT data and 95% CIs for each treatment and treatment by laboratory were plotted.

Final Analyses

The final analysis was performed after all subjects had completed the entire study. At the final analysis Period 3 DAS28, CRP, ESR, TJC, SJC, patients' assessment of pain, IL6 and A-SAA were listed and summarised. Period 3 ACR20, ACR50 and ACR70 and EULAR responders were listed and the number and percentage of responders were summarised. All data for early morning stiffness, MAF, HAQ, patients and physician's global assessment of disease activity and other biomarkers were listed. MRI derived data was listed and summarised. The synovium volume and the total RAMRIS score, together with its erosion and synovium components, were analysed using a mixed effects model. The distribution of bone oedema volume and RAMRIS bone oedema scores were summarised within specific ranges. X-ray data were listed and summarised.

Period 3 safety data were listed and summarised. Individual LFT data was plotted for those subjects who completed 84 days of dosing. Mean LFT data and 95% CIs for each treatment were plotted using data from the subjects who completed 84 days of dosing only.

Changes in conduct of the study or planned analyses:

- In the Reporting and Analysis Plan (RAP) [Attachment 3] it was stated that the summaries for the study population information would use the same treatment groups as for safety and efficacy raw summaries; however at the time of reporting it was considered to be more appropriate and efficient to summarise that particular data type by sequence.
- Listings of liver events were inadvertently omitted from the RAP and were added to the final analysis.
- Due to there being only a small number of ACR50 and 70 responders the statistical analyses of these endpoints were not performed.
- The plot of mean LFTs and 95% CIs over 84 days of dosing by laboratory was not produced for the final analysis, due to there being too few subjects for each combination of treatment and laboratory.

- For A-SAA some data were received that were indicated as > upper limit of quantification (ULQ) for that subject. The team decided that these values would be replaced with the ULQ for that subject.
- The RAP stated that the subject level baseline would be the mean of the period level baselines for that subject. Further clarification was needed to indicate that the appropriate definition of the subject level baseline is the mean of the period level baselines for Period 1 and Period 2 only for each subject.
- Total Synovitis score was not derived as described in the RAP. As MRI gadolinium enhancement was not used for many of the subjects, an alternative total synovium score was derived from the images without Gadolinium. The total synovium score was calculated by summing the individual synovium scores for the distal Radioulnar, Radiocarpal and Intercarpal-carpometacarpal wrist joints, together with synovium scores for the MCP II, MCP III, MCP IV and MCP V knuckle joints.
- The statistical analyses of Total Bone Oedema and Total Bone Erosion score were not performed due to the number of zero values for these endpoints. A summary of the number and percentage of subjects whose values for these endpoints were within certain ranges was produced instead.
- A listing of the derived MRI endpoints was inadvertently omitted from the RAP and was added to the final analysis.
- All subjects received Period 2 drug on Day 28 morning instead of Period 1 drug. The subjects that completed 84 days of dosing also took Period 3 drug on Day 56 morning instead of Period 2 drug. This impacted on the MRI measurements as the MRI imaging was post dose on Day 28 and Day 56. The team took the decision to assign MRI measurements on Day 28 to Period 1 and on Day 56 to Period 2. This is because the team believed that MRI is not sensitive to pick up changes after one dose and that any change seen in the MRI on Day 28 would entirely be due to the repeat dosing of the Period 1 drug; similarly, on Day 56.

Summary:

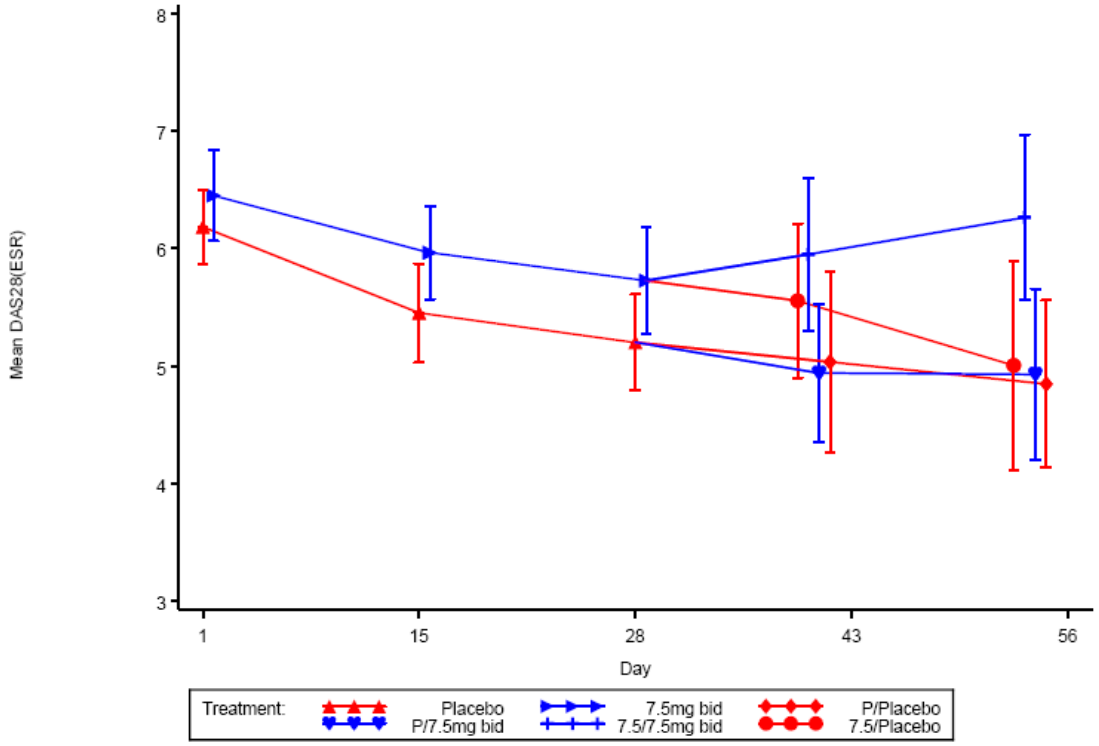
Efficacy:

The MITT was used for the efficacy listings, summaries and analyses. The per-protocol population was also used for additional DAS28, CRP and ACR20, 50 and 70 summaries and analyses.

DAS28

The DAS28 data for Day 1, Day 15, Day 28, Day 43 and Day 56 are summarised in Table 10.1 and for Day 70 and Day 84 are summarised in Table 10.26. Raw mean DAS28 and 95% CI by treatment for visits up to and including Day 56 are displayed in the figure below.

Plot of Mean DAS28 (ESR) Scores over 56 Days of Dosing with 95 percent CIs



Source Figure 10.1

The statistical analysis of DAS28 on the MITT population is displayed in the table below.

Summary of the Statistical Analysis of DAS28

Period	Adjusted Mean		Treatment Difference (7.5 mg BID (A) – Placebo (P1)) (95% CI)
	7.5 mg BID (A)	Placebo (P1)	
Day 15	5.486	5.318	0.167 (-0.236,0.571)
Day 28	5.334	5.089	0.245 (-0.169,0.659)

Source Data Table 10.2
Note: A clinically significant treatment difference would have been at least minus 0.6.

There was no evidence of a statistically significant difference in DAS28 between 7.5 mg BID (A) and placebo (P1) after 14 and 27 days of dosing.

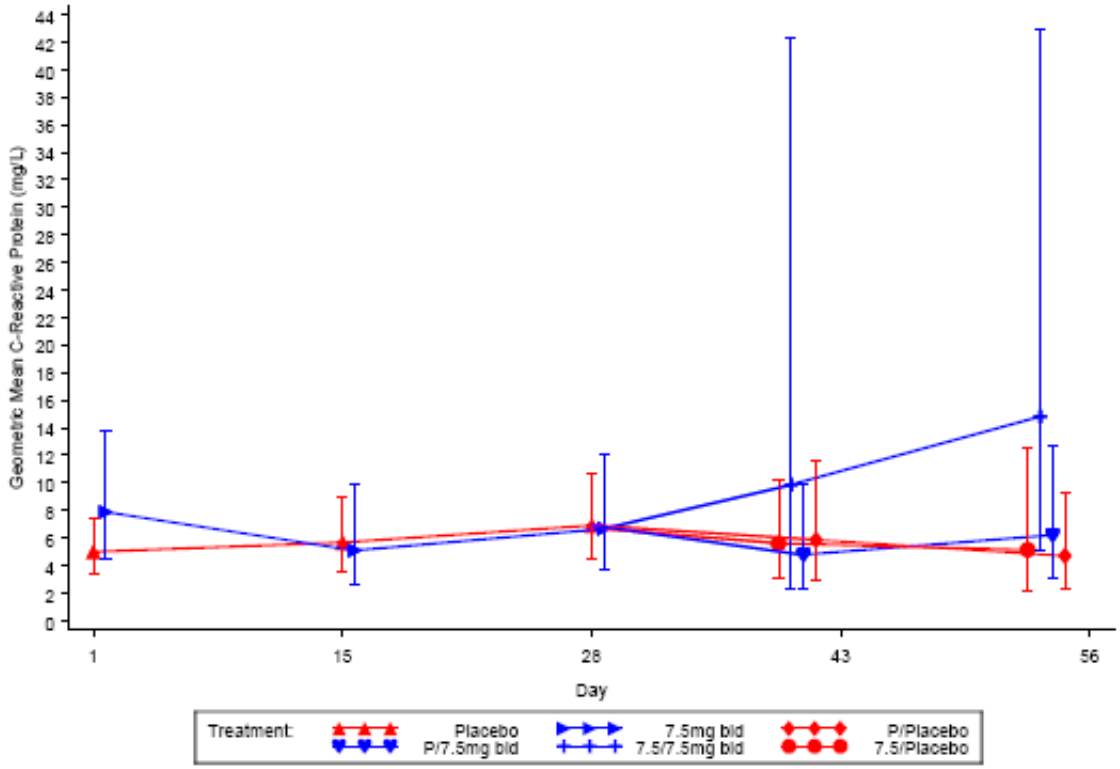
The summary and analysis of DAS28 were also reproduced using the per-protocol population (Table 10.3 and Table 10.4). This analysis produced similar conclusions to those described for the MITT population.

The mean DAS28 for each treatment in Period 3 were consistent with the Period 1 and Period 2 data. The mean DAS28 for the 7.5/7.5/10 mg BID group was high compared with the mean DAS28 score for the Placebo/7.5/10 mg BID and Placebo/Placebo/Placebo groups. However, the high mean DAS28 in the 7.5/7.5/10 mg BID group was due to three out of the 4 subjects having high DAS28. These three subjects had consistently high DAS28 values across all visits.

C - reactive protein (high sensitivity)

The high sensitivity CRP data for Day 1, Day 15, Day 28, Day 43 and Day 56 are summarised in Table 10.5 and Day 70 and Day 84 are summarised in Table 10.27. Raw mean CRP and 95% confidence by treatment for visits up to and including Day 56 are displayed in the figure below.

Plot of Geometric Mean CRP Over 56 Days of Dosing with 95 Percent CIs



Source Figure 10.3
Note: The large confidence intervals for Day 43 and Day 56 (sequence 7.5 mg BID/7.5 mg BID) are caused by the small number of subjects (n=9) of whom at least 3 had consistently high levels of CRP across the whole treatment period (Day 1- Day 84).

The statistical analysis of CRP is summarised in the table below.

Summary of the Statistical Analysis of CRP

Period	Adjusted Geometric Mean (mg/L)		Treatment Ratio
	7.5 mg BID (A)	Placebo (P1)	[7.5 mg BID (A) / Placebo (P1)] (95% CI)
Day 15	4.48	6.42	0.70 (0.46,1.07)
Day 28	5.72	6.83	0.84 (0.56,1.26)

Source Data Table 10.6

There was no evidence of a statistically significant difference in CRP between 7.5 mg BID and placebo after 14 and 27 days of dosing. However, there were slight decreases in CRP compared with Placebo for the 7.5 mg BID treatment group. After 14 days of treatment, there was a 30% reduction for 7.5 mg BID (A) compared with placebo (P1). This reduction decreased after 27 days of dosing where a 16% reduction in CRP was observed for 7.5 mg BID (A) compared with Placebo (P1).

The summary and analysis of CRP were also performed using the per-protocol population (Table 10.5 and Table 10.8). This analysis produced similar conclusions to those described for the MITT population.

The CRP geometric means for each treatment in Period 3 were consistent with the Period 1 and Period 2 data. The geometric mean CRP for the 7.5/7.5/10 mg BID group was high compared with the mean CRP score for the Placebo/7.5/10 mg BID and Placebo/Placebo/Placebo groups. However, in the 7.5/7.5/10 mg BID group 3 out of the 4 subjects had high CRP values consistently across all visits.

American College of Rheumatology-defined improvements of 20%, 50% and 70% (ACR20, ACR50 and ACR70)

The percentage of subjects who were classified as ACR20 responders in the MITT population is tabulated below. The ACR20 response was calculated using period level baseline.

Summary of the Number and Percentage of ACR20 Responders

Period	Treatment	N	Visit	n	ACR20 responders number (%)
1	Placebo	38	Day 28	37	11 (29.7%)
	7.5 mg BID	19	Day 28	19	4 (21.1%)
2	Placebo/Placebo	19	Day 56	18	3 (16.7%)
	Placebo/7.5 mg BID	18	Day 56	17	1 (5.9%)
	7.5 mg/ Placebo	10	Day 56	10	1 (10.0%)

Source Data Table 10.12

The statistical analyses of the ACR20 responder data are presented in Table 10.14. After 27 days of dosing, the estimated odds of being an 'ACR20 responder' in the 7.5 mg BID (A) group were 0.24 (95% CI 0.00 to 6.39) of the estimated odds of being a responder in the placebo group.

The summaries and analysis of ACR20 data were repeated using the per protocol population. These produced similar results to those described for the MITT population.

There was no evidence of a statistically significant difference in any other efficacy endpoints between 7.5 mg BID (A) and Placebo (P1) after 14 and 27 days of dosing.

Safety:

Up to Day 56

There were no deaths or pregnancies reported up to Day 56 of the study. Eighteen subjects (31%) experienced 28 adverse events (AEs) across the treatment groups. [redacted] The event, which required hospitalisation, was considered to be severe and unrelated to the study drug by the Investigator. The event was resolved on the same day it occurred (detailed in Attachment 2: Case Narrative). All other adverse events were mild to moderate in intensity.

[redacted] The clinically significant values are detailed in the Clinical Chemistry Values of Potential Clinical Concern. [redacted] These subjects were withdrawn from the study as they met liver function stopping criteria.

[redacted]

Summary of All Adverse Events (up to 56 Days - Main)

Adverse Events	Period1 P	Period1 A	Period 2 P/P	Period 2 P/A	Period 2 A/A	Period 2 A/P
	N=38	N=19	N=19	N=18	N=9	N=10
Any AE n (%)	7 (18)	6 (32)	3 (16)	4 (22)	2 (22)	0
Any AE related to investigational product n (%)	2 (5)	2 (11)	0	0	1 (11)	0
All AEs n (%)						
Nasopharyngitis	0	1(5)	0	1 (6)	0	0
Influenza	0	0	1 (5)	0	0	0
Laryngitis	1 (3)	0	0	0	0	0
Vaginal candidiasis	0	1 (5)	0	0	0	0
Abdominal pain	1 (3)	0	0	0	0	0
Abdominal pain upper	0	0	0	1 (6)	0	0
Constipation	1 (3)	0	0	0	0	0
Nausea	0	1 (5)	0	0	0	0
Rectal haemorrhage	0	0	0	0	1 (11)	0
Respiratory disorder	1 (3)	1 (5)	0	0	0	0
Pharyngolaryngeal pain	0	0	0	1 (6)	0	0
ALT	1 (3)	0	0	0	0	0
AST	1 (3)	0	0	0	0	0
GGT	1 (3)	0	0	0	0	0
Transaminase	0	0	0	1 (6)	0	0
Psoriasis	0	1 (5)	0	0	0	0
Urticaria	0	0	1 (5)	0	0	0
Atrial fibrillation[1]	0	0	1 (5)	0	0	0
Cardiac failure chronic	0	0	1 (5)	0	0	0
Myocardial ischaemia	0	0	1 (5)	0	0	0
Vertigo	0	1 (5)	0	0	0	0
Upper limb fracture	0	0	0	0	1 (11)	0
Osteochondrosis	1 (3)	0	0	0	0	0
Headache	1 (3)	0	0	0	0	0
Hypertension	1 (3)	0	0	0	0	0

Source Data Table 11.1 and Table 11.2
A= GW856553 7.5 mg BID, P= Placebo.
1. Serious Adverse Event

Eight out of 28 AEs were considered to be drug related by the Investigator (Source Data Table 11.2).

Day 56 to Day 84

There were no deaths or non fatal SAEs reported during Day 56 to Day 84 of study. [redacted] The event was mild in intensity and unrelated to the study drug.

Summary of All Adverse Events (Day 56 to Day 84 - Final)

Adverse Events	Period 3 P/P/P	Period 3 P/A/C	Period 3 A/A/C
Any AE n (%)	0	1 (33)	0
Respiratory tract infection viral	0	1 (33)	0

Source Data Table 11.16
A= GW856553 7.5 mg BID, P= Placebo, C = GW856553 10 mg BID

There were no drug-related AEs reported during Day 56 to Day 84.

ECG abnormalities:

[redacted]

Vital signs:

Vitals signs (heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP) of potential clinical importance are listed in the table below. These values were not considered to be clinically significant by the Investigator (Source Data Table 11.37).

Vital Signs of Potential Clinical Importance (PCI)

[redacted]

Source Data Table 11.37

Clinical Laboratory Tests:

Haematology values of a potential clinical concern (PCC) are listed in the table below. None of these values were considered to be clinically significant by the Investigator (Source Data Table 11.34).

Hematology Values of PCC

Source Data Table 11.34
A= GW856553 7.5 mg BID, P= Placebo.

Clinical chemistry values of a PCC are listed in the table below. These events were considered to be clinically significant and were reported as AEs by the Investigator. These subjects were withdrawn from the study. All other values were not considered to be clinically significant by Investigator (Source Data Table 11.35).

Clinical Chemistry Values of PCI

Source Data Table 11.35 and Table 11.33
1. Phosphorus normal range was considered 0.7 - 1.4 mmol/L.
A= GW856553 7.5 mg BID, P= Placebo.

Concomitant medication:

RA and non-RA concomitant medications taken during the study are summarised in Source Data Table 9.6 and Table 9.7, respectively.

Biomarkers:

IL-6 - The IL-6 data for Day 1, Day 15, Day 28, Day 43 and Day 56 are summarised in Table 13.1 and Day 70 and Day 84 are summarised in Table 13.3. The statistical analysis of IL-6 is summarised in the table below.

Summary of the Statistical Analysis of IL-6 Data

Period Day	Adjusted Geometric Mean (ng/L)		Treatment Ratio (7.5 mg BID (A) / Placebo (P1)) (95% CI)
	7.5 mg BID (A)	Placebo (P1)	
15	7.466	11.589	0.644 (0.395,1.049)
28	10.138	13.104	0.774 (0.504,1.187)

Source Data Table 13.2

There was no evidence of a statistically significant difference in IL-6 between 7.5 mg BID and Placebo after 14 and 27 days of dosing. However, there was a slight decrease in IL-6 compared with Placebo for the 7.5 mg BID treatment group. After 14 days of treatment, there was a 36% reduction for 7.5 mg BID (A) compared with placebo (P1). This reduction decreased after 27 days of dosing where a 23% reduction in IL-6 was observed for 7.5 mg BID (A) compared with Placebo (P1).

Period 3 data for these were consistent with data from Period 1 and Period 2. However, the geometric mean IL-6 for the 7.5/7.5/10 mg BID group was high but this was due to 3 out of the 4 subjects in that treatment group having high IL-6 values consistently across all visits.

S**erum Amyloid A (SAA) -** The serum amyloid A data for Day 1, Day 15, Day 28, Day 43 and Day 56 are summarised in Table 13.1. The statistical analysis of serum amyloid A is summarised in the table below.

Summary of the statistical analysis of Serum Amyloid A data

Period day	Adjusted Geometric Mean (ng/mL)		Treatment Ratio (7.5 mg BID (A) / Placebo (P1)) (95% CI)
	7.5 mg BID (A)	Placebo (P1)	
15	66570.0	70937.7	0.9 (0.6,1.5)
28	81990.3	84759.4	1.0 (0.6,1.5)

Source Data Table 13.2

There was no evidence of a statistically significant difference in serum amyloid A between 7.5 mg BID and Placebo after 14 and 27 days of dosing. After 14 days of treatment a 10% reduction for 7.5 mg BID (A) compared with Placebo (P1) was observed. After 27 days of dosing this reduction decreased where no reduction in serum amyloid A was observed for 7.5 mg BID (A) compared with Placebo (P1).

Imaging endpoints (X-ray and MRI):

The Sharp-van der Heijde X-ray scores indicate that these subjects had moderate damage for this disease duration cohort, mean score 29 (range 0-133).

The MRI data for Day 1, Day 28 and Day 56 are recorded in Table 10.35. MRI erosion scores correlate to baseline X-ray erosion scores, $R^2 = 0.58$. The statistical analysis of MRI synovium volume and RAMRIS total, erosion and synovium scores is summarised in the table below. Bone oedema scores and volume measurements were assessed separately.

Summary of the statistical analysis of MRI data

Endpoint	7.5 mg BID (A) (N=37)		Placebo (P1) (N=38)		7.5 mg BID(A)/Placebo (P1)
	n	Adjusted Geometric. mean	n*	Adjusted Geometric. mean	Ratio (95% CI)
Total RAMRIS Score	23	58.39	40	58.80	0.99 (0.96,1.03)
Total Bone Erosion Score	23	34.77	40	35.41	0.98 (0.95,1.02)
Total Synovium Score	23	16.02	40	15.70	1.02 (0.97,1.08)
Total Synovium Volume (mm^3)	23	9009.51	40	8285.97	1.09 (0.92,1.28)

Source Data Table 10.35

Note: Total RAMRIS score is the sum of the bone erosion, synovium and bone oedema scores. Synovium volume is the sum of synovium in the hands and wrists in mm^3. Whilst n* is larger than N for Placebo (P1) as subjects whom received Placebo/Placebo are counted twice in the Placebo (P1) treatment group (i.e. Period 1 and then Period 2).

There was no evidence of a statistically significant difference in any of the MRI endpoints between 7.5 mg BID and Placebo after 27 days of dosing.

Pharmacokinetics:

Pharmacokinetic Analyses

Sparse blood samples for pharmacokinetic analysis of GW856553 were taken on Visits Day 1, Day 15, Day 28, Day 43, Day 56, Day 70 and Day 84 from all subjects. The Day 70 and Day 84 samples were only available from subjects who went on to the extension period of this study. The sampling windows for PK samples at each visit were selected based on the preliminary population PK model developed using healthy subjects data and the optimal sampling design technique. The sampling windows applied for this study were: pre-dose, 0.25 to 2 h, 4 to 7 h, 8 to 12 h on scheduled Day 1, Day 28, Day 56 and Day 84 visit. Only pre-dose data were obtained on Day 15, Day 43 and Day 70.

Description of PK data

Out of the total 37 subjects who were randomised and received at least one dose of GW856553, 34 subjects had at least one valid plasma concentration data for PK analysis of GW856553. [redacted]

[redacted] All the plasma PK samples from these two subjects were re-assayed. [redacted] These two subjects were excluded from the following analysis. A summary of the available data by visit and sampling window for the Period 1 and Period 2 is summarised in the table below.

Number of Plasma Concentration Sample Available For PK Analysis by Visit and Sampling Windows (Period 1 and Period 2)

Visit	Sampling window			
	0.25 - 2 h	4 – 7 h	8 - 12 h	Pre-dose
Day 1	31	31	23	0
Day 15	0	0	0	33
Day 28	18	18	14	19
Day 43	0	0	0	6
Day 56	2	2	2	5

Source Data Table 12.1

There were 23 out of the 34 subjects on methotrexate while taking GW856553. Data from these subjects were used to explore the influence of methotrexate on GW856553 systemic exposure.

Figure 12.1 and Figure 12.2 show the scatter plots of plasma drug concentration verses actual sampling time for subjects who had provided valid plasma concentration data during Period 1 and Period 2 (after 7.5 mg BID). Overlaid with the observed data is the model predicted median and 95% predictive interval of the GW856553 PK profiles by time following first dose and at a steady state.

Figure 12.3 presents the trough plasma concentration data by time. Also shown in Figure 12.3 is the 95% predictive interval of the model predicted plasma concentration at trough [GlaxoSmithKline Document Number GM2006/00607/00]. The observed trough concentration levels ranged from 2.676 ng/mL to maximum of 37.84 ng/mL, with median of 10 ng/mL, and lay within the 95% predictive intervals.

Ten subjects were dose escalated to 10 mg BID GW856553 or Placebo (Period 3). Out of the 10 subjects, seven subjects were dosed 10 mg BID GW856553 for further 28 days. A total of 45 valid observations were obtained from these seven subjects after 10 mg BID GW856553 dosing. Figure 12.4 presents the scatter plot of plasma drug concentration verses actual sampling time overlaid with the model predicted median and 95% predictive intervals of GW856553 PK profile following 10 mg BID dosing.

All these results indicate that the plasma concentration data obtained in RA patients from this study were predictable based on the historical data.

Population PK Analysis

Population PK modelling investigations below were based on the PK data obtained from Period 1 and Period 2 where subjects were given 7.5 mg BID GW856553.

Base Model: A non-linear mixed effect model has been developed using PK data available from healthy subjects, RA and chronic obstructive pulmonary disease (COPD) patients [GlaxoSmithKline Document Number GM2005/00545/00]. Model simulated concentration-time data and associated median and 95% prediction interval using the base model developed in the previous report, based on the dosing strategy in this study (7.5 mg BID GW856553) were retained on Day 1 and at steady state. The predicted results and overlaid with the observed concentration time data from this study are presented in Figure 12.1-Figure 12.4.

These results indicated that the PK model already available for RA patient population can be used to describe the data from this study and no further model updating was needed.

Covariates Selection: The correlations of demographical variables, age, gender, body weight had been incorporated into the model to explain some of the variability in the data. These covariates were retained in the model for further application of the population PK model. Figure 12.5 showed that scatter plots of individual and population predictions versus the observed plasma concentration data. Overall, both models gave similar predictions.

The post-hoc estimates of primary PK parameters area under the concentration time curve over the dosing interval [AUC(0-τ)], where τ=12 h for BID dosing regimen, and KA (absorption rate constant) were obtained. The impact of the common co-medication (methotrexate) on the PK parameters of GW856553 was explored. The boxplot of AUC(0-τ), KA by methotrexate usage are shown in Figure 12.6 and Figure 12.7. Note: τ=12 h for BID regimen. These results indicate no evidence of impact of methotrexate on GW856553 systemic exposure. Thus this covariate was not added into the population PK model. Additionally, exploration of correlation between the demographic variables on the PK parameters of GW856553 was conducted but no clear trend was observed.

Estimation of Daily GW856553 Systemic Exposure AUC(0-24) at Steady State:

Steady state area under the concentration time curve from zero to 24 h [AUC(0-24)] of GW856553 for each patient in this study was estimated from the PK model with their corresponding covariates, using formula AUC(0-24)=Total Daily Dose/Apparent clearance following oral dosing (CL/F), where Total Daily Dose = 2*7.5 mg =15 mg, given for each subject in this study and CL/F is the individual estimation of oral clearance of GW856553.

The summary of the estimated AUC(0-24) is presented in Table 12.2, and its distribution is shown in Figure 12.8. The estimated AUC (0-24) was used to explore the possible correlation between exposure and efficacy and biomarker endpoints below.

Relationship between PK and PD parameters

The purpose of the pharmacokinetic and pharmacodynamic analysis was to: investigate the possible relationship of plasma GW856553 exposure with patients DAS28, ACR20 responses on Day 28 and biomarkers (CRP and IL-6) on Day 15 and Day 28 in RA patients.

For these analyses, the daily exposure of GW856553 in RA patients who were allocated to receive GW856553 7.5 mg BID were estimated using the population PK model, as described in the population PK analysis [Table 12.2 and Figure 12.8 for summary and distribution of AUC (0-24)]. For subjects who received Placebo, the AUC (0-24) was set as 0 for all the following analyses.

DAS28 on Day 28 versus GW856553 Exposure

Figure 12.9 shows the relationship between the observed change from period baseline (measured at the beginning of each period) of DAS28 (ESR) on Day 28 versus the predicted GW856553 daily exposure at a steady state. The relationship between the observed change from study baseline (measured on Day 1 pre-dose) of DAS28 (ESR) on Day 28 versus the predicted GW856553 daily exposure at a steady state using data obtained from Period 1 only is shown in Figure 12.10.

The visual inspection of these results indicated that there was no clear trend or correlation between the change from baseline (either measured at beginning of each period or on Day 1) of DAS28 (ESR) on Day 28 and the GW856553 daily exposure at a steady state. No formal statistical modelling was conducted.

ACR20 response on Day 28 versus GW856553 Exposure

Figure 12.11 shows the distribution of GW856553 daily exposure at steady state by ACR20 response status. The result indicated no clear evidence of dependency of ACR20 response on the GW856553 exposure. No formal statistical modelling was conducted.

IL-6 inhibition on Day 15 and Day 28 versus GW856553 Exposure

Figure 12.12-Figure 12.15 show the scatter plots of observed inhibition of IL-6 on Day 15 or Day 28 (calculated based on period baseline or study baseline (Day 1 pre-dose)) versus GW856553 predicted daily exposure AUC (0-24). The results indicated no clear evidence of correlation between IL-6 inhibition and GW856553 exposure. No formal statistical modelling was conducted.

CRP inhibition on Day 15 and Day 28 versus GW856553 Exposure

The observed CRP change from baseline (obtained at the beginning of each period) on Day 15 or Day 28 versus GW856553 predicted daily exposure AUC(0-24) is presented in Figure 12.16. Visual exploration indicates no evidence of correlation between CRP change from baseline and GW856553 exposure. No formal statistical modelling was conducted.

Other Measures:

Pharmacogenetics

Fifty-four subjects consented to participate in pharmacogenetic research and provided 10 ml of blood sample for analysis (Source Data Table 14.1). Analysis of the samples may be conducted at any time there is a potential unexpected or unexplained variation in response to handling GW856553 attributable to genetic variation. Results of any such analysis will be presented in a separate report.

Discussion:

Study RA3103718 in patients with RA was designed to investigate the effect of GW856553 on DAS28 following 27 days of dosing. However, GW856553 did not show any evidence of an effect when dosed for up to 56 days at 7.5 mg BID on clinical scores (DAS28, ACR20, EULAR responders), individual components of the rheumatological assessments, serum biomarkers, or MRI endpoints (RAMRIS, Bone oedema volume, or Synovial volume). Extending the dosing period to 84 days and up-titrating the dose to 10 mg BID (in a small cohort of subjects) did not provide any evidence of efficacy.

GW856553 was generally safe and well-tolerated in this study. There were no deaths or pregnancies reported during the study. Two subjects, were withdrawn due to elevated transaminase (ALT>3xULN). One of these subjects received Placebo and the other received GW856553 concomitantly with isoniazid. In the latter case, this concomitant medication may have contributed to the observed elevated liver function tests, and was also subsequently withdrawn. Investigational product was discontinued, subjects were withdrawn from the study, and liver function returned to within normal limits. There was one serious AE of atrial fibrillation. This occurred during the Follow-up period in a subject who had received Placebo for 56 days. There were no clinically significant effects on clinical laboratory parameters (apart from the two subjects with elevated ALT), ECG (apart from the SAE on Placebo) or vital signs.

A population PK model of GW856553 has been developed using data from healthy subjects after single and repeated doses, RA patients after single dose and COPD patients after repeated doses. The model has incorporated a number of demographic covariates, e.g. age, gender and body weight, to explain some of the variabilities in the data. However, the impact of the covariates was relatively small; the predictions of data from this study (Period 1 and Period 2 only) from the models with or without covariates were similar.

The individual daily exposure following 7.5 mg BID GW856553 at steady state was predicted using the model with covariates. The visual inspection of the data indicated no clear trend of dependency of efficacy and biomarker endpoints on the total daily exposure of GW856553. It should be noted that because the study was not designed to investigate the exposure response correlation, these analyses were studied on an exploratory basis. Due to the smaller number of subjects in the study, and the narrow range of exposure observed, the findings should be interpreted with caution. Based on the visual exploration of these relationships between exposure and response on various endpoints, there was no further formal statistical modelling was conducted.

The study was robust and the outcome reliable. Patients had sufficiently active disease to allow the observation of improvement. They had elevated CRP levels at baseline and the mean DAS28 was 6.18 in the group that received Placebo in Period 1 and 6.45 in the group that received 7.5 mg BID in Period 1. A DAS28 greater than 5.1 indicates that a patient has severe active RA. A DAS28 score between 5.1 and 3.2 indicates moderate active RA. Baseline characteristics (including disease activity and anti-rheumatic therapy) were well matched between the treatment groups. GW856553 plasma levels indicated that patients received study medication and achieved expected levels of exposure. The observed variability of CRP and DAS28 were as expected from historic data; the study had the required power to detect a 0.80 change in DAS28 compared to Placebo. The Placebo effect was reasonable and similar to other published studies.

Conclusions:

- GW856553 did not show any evidence of an effect when dosed for up to 56 days at 7.5 mg BID on clinical scores (DAS28, ACR20, EULAR responders), individual components of the rheumatological assessments, serum biomarkers, or MRI endpoints (RAMRIS, Bone oedema volume, or Synovial volume).
- GW856553 was generally safe and well-tolerated by RA patients with active disease taking concomitant medications including methotrexate.
    - There was one non-fatal SAE of atrial fibrillation /paroxysmal atrial fibrillation during the Follow-up period in a subject who received placebo for 56 days.
    - Two subjects were withdrawn for ALT > 3xULN. One subject was receiving Placebo and the other was receiving GW856553 7.5 mg BID. However, the latter subject was also receiving concomitant isoniazid (protocol violation).
- The available GW856553 plasma concentration data obtained from this study indicated that the exposure achieved in the RA patients in this study was as expected and consistent with that observed from previous studies.
- The population PK model developed and reported using data from healthy subjects, RA (single dose) and COPD patients, was valid to describe the data in RA patients from this study. No further update is required for this model.
- The data from subjects who were exposed to both GW856553 and methotrexate indicated that there was no evidence of impact of methotrexate on GW856553 plasma concentration.
- There was no evidence of correlation in change from baseline (either period baseline or study baseline) of DAS28 on Day 28, ACR20 response on Day 28, CRP inhibition, IL-6 inhibition (measured based on period baseline or study baseline), with GW856553 daily exposure at steady state.

Date of Report:

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