Rheumatoid arthritis (RA) is a chronic systemic autoimmune inflammatory disease that affects all ethnic groups, with a prevalence of 0.5–1% worldwide. It predominates in women and peak incidence occurs within the fourth and fifth decades of life. Twin studies have demonstrated that the disease has a heritability of 60% and genes encoding HLA molecules have an important contribution to this genetic risk. Hormonal factors contribute to the female excess, and obesity, smoking and a number of specific dietary exposures have been identified as potential risk factors.

The primary target organ in RA is the synovial membrane, where increases in cellularity and vascularity are associated with infiltration of immune inflammatory cells. Participation of the humoral immunity is evidenced by a number of autoantibodies, including rheumatoid factor and anticyclic citrullinated peptide antibodies. T cells are also involved in the tissue damage found in RA. They can be found in the synovium; there is an association with HLA and there is evidence of the presence of T-cell cytokines. These are critical for the pathogenesis of RA. Proinflammatory cytokines, such as TNF-α, IL-1 and IL-6, have proved to be particularly important, although many others also play important roles in these mechanisms.

In tissue damage that is characteristic of RA, there is a complex interplay of cytokines, autoantibodies, immune complexes and a cellular milieu including macrophages, neutrophils, synoviocytes, B cells, T cells, osteoclasts and mast cells. Mast cells have been observed in the synovial membrane of patients with arthritis and, along with neutrophils and macrophages, express activating Fc receptors (FcεRI [mast cells] and Fcγ receptor type 1 [FcγRI], FcγRIIA and FcγRIII). These cells play a key role in inflammation by releasing lipid mediators of inflammation, cytokines, nitric oxide, reactive oxygen intermediates, matrix metalloproteinases (MMPs) and proinflammatory cytokines.

In most cases, RA is a chronic and progressive disease that, if left untreated, causes joint damage, deformity and disability, with a significant burden to both the patient and society. Radiographic joint damage of some degree develops in as many as 75% of patients within the first 2 years of disease. For this reason, current RA treatment approaches have focused on early and intensive therapy with multiple disease-modifying antirheumatic drugs (DMARDs) aiming to control inflammation and to preserve both structure and function of the musculoskeletal system, as well as to limit the systemic impact of the disease. The approval of new drugs for this indication has expanded the number of therapeutic options that can potentially allow for tight control of the inflammatory process. Methotrexate (MTX) remains the first-choice DMARD for the treatment of moderate-to-severe RA as it reduces the signs and symptoms and slows the radiologic progression of the disease. It is often the anchor drug for combination regimens. However, as 20–40% of patients do not respond satisfactorily, an increasing proportion of patients are receiving newer treatments.

R788 (fostamatinib disodium) is a prodrug rapidly converted to R406 upon oral administration. R406 is a potent inhibitor of spleen tyrosine kinase, required for the expression of a number of proinflammatory cytokines. R788 has shown efficacy in the control of patients with rheumatoid arthritis not responding to methotrexate, and some degree of response in those failing to respond to biologic agents with a reasonable safety pattern. It shows linear pharmacokinetics at the studied doses and it is not affected by the administration of methotrexate. The clinical applicability of R788 may have an impact in patients with rheumatoid arthritis failing to respond to conventional therapy. Once the Phase III studies are completed, R788 may find a place in the evolving treatment algorithm for rheumatoid arthritis.

**KEYWORDS:** fostamatinib disodium, kinase inhibitors, R788, rheumatoid arthritis, Syk kinase
agents, including leflunomide and ‘biologicals’, such as the TNF-α antagonists (etanercept, infliximab, adalimumab, golimumab and certolizumab) and molecules with different specific targets, such as abatacept, anakinra, rituximab and tocilizumab [7,8].

Current therapeutic options offer considerable advantages in the management of RA in most patients. Nevertheless, the risk of infection (and other complications), the inconvenient dosing regimens and the high cost of the biologic agents may limit access to treatments for many patients whose care depends on health systems with less resources. Patients with MTX-resistant RA benefit considerably from the newer treatments, but the response rates still show that most agents produce an American College of Rheumatology (ACR) response rate of 70% (ACR70); 70% improvement in tender joint count, swollen joint count plus 70% improvement of three of the following: patient pain assessment; patient global assessment; physician global assessment; patient self-assessed disability and an acute-phase reactant) in less than a fifth of the patients and the remission rate remains very low [8]. Therefore, the considerable activity in the pipeline of developing products for RA is understandable given the unmet therapeutic needs.

Chronic inflammatory processes are based on a sustained and tightly regulated communication network among different cell types. This network comprises extracellular mediators, such as cytokines, chemokines and matrix-degrading proteases, which orchestrate the participation of cells in the chronic inflammatory process. The mirrors of this outside communication world are intracellular transcription factor pathways, which shuttle information about inflammatory stimuli to the cell nucleus. The interest in small-molecule inhibitors has increased after evidence linking some of these products with modification in joint inflammation and tissue damage in RA [7,8].

Over the past years there has been increased insight into the expression, regulation and pathophysiological function of the components of the p38MAP kinase signaling cascade in inflammatory joint disease [9]. Current data suggest that stress kinases govern a variety of processes in the synovial tissue of the inflamed joint. These new insights are important in judging the rational selection of therapeutic targets in order to inhibit inflammation and tissue destruction in rheumatic diseases [9,10]. Nevertheless, clinical trials with two discrete p38MAP kinases in RA had discouraging results. Neither pamapimod as single therapy [11] nor VX-702 combined with MTX [12] resulted in significant improvement of the disease process. We review here the current status of an inhibitor of a member of a different family of cytoplasmic kinases, known as spleen tyrosine kinase (Syk kinase).

**Chemistry, pharmacodynamics & pharmacokinetics**

R788 or fostamatinib disodium (phosphoric acid mono-[6-(5-fluoro-2-(3,4,5-trimethoxy-phenylamino)-pyrimidin-4-ylamino)-2,2-dimethyl-3-oxo-2,3-dihydro-pyrido[3,2-b]-1,4-oxazin-4-ylmethyl] ester-disodium salt, hexahydrate) has the formula C_{23}H_{24}FN_{6}O_{9}P_{2}Na_{6}H_{2}O and molecular weight of 732.51. It is a prodrug that, following oral administration, is rapidly converted to a metabolite referred to as R406 by the action of phosphatases of the intestinal mucosa. R406 is a potent selective inhibitor of Syk.

Syk kinase is an important proximal signaling cytoplasmic tyrosine kinase related to activation of Fc receptors, which are expressed on various hematopoietic cells, including mast cells, neutrophils, macrophages, natural killer cells, B cells and dendritic cells [13]. The activated Fc receptors contain internal tyrosine activation motifs, which are phosphorylated following receptor engagement, thereby activating Syk, which in turn phosphorylates a variety of downstream targets. Distal to Syk in the inflammatory pathway are a series of mitogen-activated protein kinases including ERK, JNK and p38 [13]. Syk expression has been detected in RA synovium and increased levels of phosphorylated Syk have been observed in RA synovial tissue as compared with tissue from patients with osteoarthritis [14]. A link between Syk activation in human RA synoviocytes and activation of JNK has been reported and inhibition of Syk blocks TNF-α activation of JNK, the downstream effect of which is reduced expression of JNK-regulated genes such as IL-6 and MMP-3 [15-16]. These observations, and results of studies in standard animal models where the treatment with R788 and R406 in rodent collagen-induced arthritis models demonstrated a significant reduction in inflammation and bone erosion [16], support the concept of a role for Syk inhibition in the control of clinical manifestations of RA.

Phase I studies in healthy volunteers determined the pharmacokinetics, pharmacodynamics and safety of orally administered single doses (80–400 mg) and multiple doses (160 mg, twice daily [b.i.d.] for 7 days and 250 mg b.i.d.
for 20 days) of R788. Following single doses, R788 was rapidly and extensively converted to R406 (peak exposure of R788 in plasma was less than 7 ng/ml). At multiple doses of 160 mg the t<sub>max</sub> ranged from 1.08 to 1.25 h. A dose-related increase in R406 exposure, by area under the curve (AUC) estimates, was observed at doses of 80–250 mg of R788. Average terminal half-life ranged between 13 and 21 h, with a steady state achieved in 3–4 days. A high fat/high calorie meal increased the t<sub>max</sub> and lowered the c<sub>max</sub>, but did not affect the AUC. R406 is metabolized in the liver. Plasma protein binding is 98.2% and the primary route of elimination of R406 and its metabolites is through biliary excretion [101].

A study conducted in volunteer subjects used a biomarker for Syk activation and inhibition, and showed a 50% maximum response concentration (EC<sub>50</sub>; for R406 inhibition of Syk) of approximately 500 ng/ml [101]. The plasma concentration data from several pharmacokinetic and safety studies of a range of doses up to 250 mg b.i.d. given by mouth to human volunteers suggested that a dose-ranging study using twice-daily oral doses of 50–150 mg would be appropriate to test whether Syk inhibitory concentrations of R406 would have a clinical effect in RA. Another study explored the interactions of R788 and MTX in 16 patients with RA. There were no significant alterations in the plasmatic levels of R788 or R406 and the concentrations of MTX and its metabolites remained unchanged, suggesting that there are no significant adverse pharmacokinetic interactions between MTX and R788 [17].

**Clinical efficacy**

A Phase IIa study enrolled 189 patients with active RA despite MTX therapy in a 3-month, multicenter, ascending-dose, double-blind, placebo-controlled trial. The primary end point was the ACR 20% improvement criteria (ACR20) response rate at week 12. Patients were maintained with their own stable doses of MTX, nonsteroidal anti-inflammatory agents; prednisone up to 10 mg/day and other nonbiological DMARDs, such as hydrochloroquine and sulfasalazine.

Twice-daily oral doses of 100 and 150 mg of R788 were significantly superior to placebo or twice-daily oral doses of 50 mg at week 12 (ACR20 achieved in 65 and 72% vs 38 and 32% of patients, respectively [p < 0.01]). ACR50 (achieved in 49 and 57% vs 19 and 17% of patients, respectively) and ACR70 (achieved in 33 and 40% vs 4 and 2% of patients, respectively) scores showed a similar pattern. Clinical effect was noted as early as 1 week after initiation of therapy. Reductions in serum IL-6 and MMP-3 levels also occurred as early as week 1 in the groups receiving 100 and 150 mg R788 [18]. In this study, mean AUCs of approximately 8000, 20,000 and 35,000 ng × h/ml, respectively, were achieved across the three dosage groups of 50, 100 and 150 mg b.i.d. These ranges resulted in approximate steady-state concentrations of 300, 850 and 1500 ng/ml, the latter two well beyond the EC<sub>50</sub> for Syk inhibition described above [101], indicating a correlation between a pharmacodynamic effect and a clinical response, albeit in separate studies.

Another very recent Phase IIb study had the objective of confirming the efficacy and safety of R788 in patients with active disease despite chronic MTX therapy. It included 457 patients with active RA on stable doses of MTX and their usual therapy, enrolled in a 6-month, double-blind, placebo-controlled (two R788 doses: 100 b.i.d., 150 mg every day [q.d.]), multicenter, international trial. The principal end point was the ACR20 response rate at month 6. Demographics and baseline clinical characteristics were similar among groups. A total of 85% in the R788 and 79% in the placebo group completed the study. The most common reasons for withdrawal were adverse events in the R788 100 mg b.i.d. and 150 mg q.d. (5%) groups and lack of efficacy in the placebo group (12%). Both R788 dosing regimens were significantly superior to placebo at month 6 (response rates are shown in Table I). Clinical effects were noted as early as week 1 and maximum effect, which was sustained throughout the remainder of the study, by week 6. Significant improvement in Health Assessment Questionnaire Disability Index (HAQ-DI), Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue and short form (SF-36) was also noted in the R788 groups [19].

Another trial, designed with the objective to assess the efficacy, radiologic response and safety of R788 in patients with active disease who had failed biologic agents, included 219 patients with active RA who had a poor response to one or more biologic agents. They were enrolled in a 3-month, randomized, double-blind study where they were allocated to receive either 100 mg b.i.d. of R788 or placebo. The principal end point was the ACR20 response rate at month 3. R788 was also compared with placebo using MRI. Patients were studied using a modified Rheumatoid Arthritis MRI Scoring System for...
Table 1. 6-month response rates with two dosing regimens of R788 and placebo.

<table>
<thead>
<tr>
<th>Response rate at month 6</th>
<th>Placebo (n = 153)</th>
<th>R788, 150 mg q.d. (n = 152)</th>
<th>R788, 100 mg b.i.d. (n = 152)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>ACR20</td>
<td>53</td>
<td>35</td>
<td>87*</td>
</tr>
<tr>
<td>ACR50</td>
<td>29</td>
<td>19</td>
<td>49†</td>
</tr>
<tr>
<td>ACR70</td>
<td>16</td>
<td>10</td>
<td>21</td>
</tr>
<tr>
<td>DAS remission (&lt;2.6)*</td>
<td>9</td>
<td>7</td>
<td>26*</td>
</tr>
</tbody>
</table>

* p < 0.001; † p < 0.01; ‡ Percentage based on points with available DAS data; * p < 0.05 (compared with placebo).

ACR: American College of Rheumatology improvement criteria; b.i.d.: Twice daily; DAS: Disease activity score; q.d.: Every day.

Data from [19].

(RAMRIS) of hand and wrist at baseline and month 3. Demographic and baseline clinical characteristics were similar between groups with the exception of 21% of the R788 patients having failed three or more biologics versus 12% of the patients on placebo. At month 3, no significant difference in ACR responses was achieved between the R788 and placebo groups. Although differences in ACR responses were noted at week 6 (p = 0.003), this response difference was not observed at months 2 or 3, primarily owing to an increasing placebo response. Significant changes from baseline in C-reactive protein and erythrocyte sedimentation rate at all time points were achieved in the R788 group versus the placebo group. Interestingly, at the end of the study, significant differences in change from baseline between the R788 and placebo groups were observed in the RAMRIS osteitis scores (-0.19 in R788 vs +1.17 in placebo [p = 0.058]) and synovitis scores (-0.52 in R788 vs +0.35 in placebo [p = 0.038]), but the overall clinical response did not meet the defined end point [20].

Safety

During the 12-week study, there were a similar proportion of patients who experienced at least one adverse event in the placebo group and the R788 50, 100 and 150 mg groups. Overall, 80% of the patients experienced at least one adverse event.

The two most common adverse events in the overall safety population were diarrhea and neutropenia. Diarrhea occurred in six (13%), five (11%), eight (16%) and 21 (45%) of the patients in the placebo and R788 50, 100 and 150 mg groups, respectively. Other gastrointestinal adverse events included nausea and gastritis, again occurring more commonly in the active drug group as compared with placebo. Dose reduction due to gastrointestinal toxicities was instituted for one patient in the 150-mg group. Other adverse events that were observed in the trial included dizziness in 11% of the patients in the 150-mg group and in 2% of the patients in the placebo group. Hypertension occurred in 5% of the patients in the higher R788 dose groups and none in the placebo group. The mean increase in systolic/diastolic blood pressure in the 100- and 150-mg dose groups, relative to their baseline, was approximately 4/4 and 7/6 mmHg, respectively. The most common laboratory toxicity observed was neutropenia, which occurred overall in 15% of the patients treated with R788 (1, 5 and 14 patients in the 50-, 100- and 150-mg groups, respectively; the confirmed nadir in this group was 850 cells/mm³) as compared with none of the patients in the placebo group. A total of 10% of the patients in the R788 100-mg group and 21% of the patients in the 150-mg group had an adjustment in the study dose, as mandated by the study protocol, when the absolute neutrophil count decreased to less than 1500 cells/mm³. The leukocyte count subsequently recovered in all patients, and the absolute neutrophil count did not drop below 1500 cells/mm³ in any patient after restarting on the lower dose. An elevation in alanine aminotransferase (ALT) level requiring dose reduction was observed in three patients (6%) in the 150-mg group and one patient (2%) in the placebo group (a second patient in the placebo group had ALT levels of over three-times the upper limits of normal [ULN], but this occurred at week 12, the last visit at which the study drug was received, so there was no dose reduction). An elevation (>1.2-times the ULN) in either serum ALT or aspartate aminotransferase levels observed on more than three visits while receiving the study drug occurred in five patients in the 100-mg group, four patients in the 150-mg group, and none of the patients in the placebo group or the 50-mg group. One patient in the 50-mg group was withdrawn from the study due to neutropenia. Two patients in the 150-mg group were withdrawn due to laboratory abnormalities (one patient had neutropenia at week 1, which was also present at baseline, and one had an elevated aspartate aminotransferase level, which was also present at baseline).
Overall, 12 patients withdrew from the study due to adverse events: two in the placebo group (due to anorexia, nausea and dizziness in one, and RA flare that required a steroid injection in one) and ten in the R788 groups, including one in the 50-mg group (due to neutropenia), three in the 100-mg group (due to RA flare, varicella and hypertension) and six in the 150-mg group (due to pneumonitis, dizziness, fever and urinary tract infection, dehydration, gastritis and low-grade fever with vaginal bleeding). A total of five patients in the study experienced at least one serious adverse event, including two in the 50-mg group (cholecystitis and bladder cancer, both believed to be unrelated to study drug) and three in the 150-mg group (gastritis, pneumonia and dehydration secondary to diarrhea) [18].

In the 6-month study, the most common adverse event was diarrhea, which was reversible and dose-related (see Table 2 for details). Transient neutropenia (<1500/mm^3) occurred overall in 3% of patients treated with R788. Elevation of ALT of over three-times the ULN occurred more commonly in the R788 groups. Mean change from baseline in systolic blood pressure at month 6 was +0.2 mm and +0.6 mm for the 150 mg q.d. and 100 mg b.i.d. groups, respectively, and −1.8 mm for the placebo. An increase in blood pressure was observed most frequently in patients with a history of hypertension with blood pressure easily managed with adjustments of conventional antihypertensive medications [19]. Information of the safety of dosing R788 in patients with hepatic or renal diseases is not currently available.

### Clinical applicability

The ultimate goal for the treatment of every patient with RA is the complete remission of the disease activity. Early and aggressive control of the inflammatory process in the synovial tissue is required to have the greatest impact in preventing joint damage and disability [7,8]. Current therapy offers considerable benefits to most patients, particularly those treated since the early stages of the disease. Patients who do not respond to MTX alone or combined with other DMARDs frequently benefit from therapy with TNF-α inhibitors or another biologic agent [7,8]. However, the complex processes required to produce these therapies, the difficulties involved in current dosing regimens and their high cost may limit their availability to vast numbers of patients. Therapeutic failures with these agents and long-term side effects still indicate the need to look for more options for difficult cases of RA.

### Table 2. 6-month treatment emergent adverse events (≥3% in any treatment group).

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Placebo (n = 153)</th>
<th>R788, 150 mg/q.d. (n = 152)</th>
<th>R788, 100 mg/b.i.d. (n = 152)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5</td>
<td>3</td>
<td>18</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7</td>
<td>5</td>
<td>18</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>7</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>5</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Influenza</td>
<td>6</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Nausea</td>
<td>7</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Upper abdominal pain</td>
<td>3</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Transaminases increased</td>
<td>5</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td>1</td>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>Headache</td>
<td>8</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>5</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Cough</td>
<td>4</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Rash</td>
<td>5</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>4</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

b.i.d.: Twice daily; q.d.: Every day.

Data from [19].
Small-molecule inhibitors of enzymes in the inflammatory pathways constitute an attractive approach for the control of RA. Advances in clinical research of these agents, particularly R788, a Syk kinase inhibitor, will establish where these agents fit in the evolving treatment algorithms for RA. It has not been licensed in any country yet and it will take some time to complete the Phase III studies to confirm its long-term efficacy and safety in a broader range of RA patients.

**Conclusion**
Currently available (Phase I and II) studies show the efficacy of R788 up to 6 months of therapy in patients with insufficient response to MTX and some degree of benefit in 3-month treatment of patients failing to respond to one or more biologic agents, with a reasonable tolerability in both instances. It is ready to enter the Phase III studies that will define its future role in RA treatment.

**Future perspective**
Treatment of RA remains challenging in every patient. A broader range of therapeutic options is desirable for every rheumatologist. If Phase III and long-term extension studies confirm the efficacy and the safety of R788 it may be considered for treatment in cases with a poor or limited response to MTX and conventional DMARDs. It has the advantage of oral administration and it is possible to speculate that its cost may end at a smaller range than that of the currently existing biologics. Should it be used before or after biologic agents? Or, should it be considered as a single, first-line therapy? These and other questions may obtain response from the future trials that will probably be completed in the near future. The most probable dose for these trials will be 100 mg b.i.d. Some authors have expressed concerns related to the safety of kinase inhibitors, particularly with reference to selectivity and interactions with cytochrome P450 [10,13]. In the Phase II trials of R788, diarrhea, neutropenia and ‘transaminitis’ have been mild-to-moderate and manageable in most cases. Although only minor elevations of blood pressure were observed in a few patients in Phase II studies, this, and the other adverse events, will require close monitoring when a larger number of patients are exposed.

Besides, inhibition of Syk clinically might be expected to lead to significant immunomodulatory activity in a variety of clinical conditions related to Fc signaling or immune complex-based activation. It has recently been reported that R788 elicited significant improvements in platelet counts in patients with chronic refractory idiopathic thrombocytopenic purpura, a condition linked to Fc receptor activity [21,22], and Syk has recently gained attention as a target for intervention in systemic lupus erythematosus (SLE), as its inhibition prevented the onset of lupus nephritis and improved renal function, prolonging survival in those affected in a murine model of SLE [23]. This study, as well as the experiences in RA trials, opens the possibility to initiate studies in human patients with SLE.

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**Executive summary**

**Mechanism of action**
- R788 (fostamatinib disodium) is a prodrug of R406, a relatively selective inhibitor of Syk kinase.
- Inhibition of Syk blocks TNF-α activation of JNK, reducing expression of JNK-regulated genes, such as IL-6 and metalloproteinase-3.
- R788 blocks activating Fc receptor signal transduction.

**Pharmacokinetic properties**
- R788 is rapidly and extensively converted to R406, its active form, by intestinal phosphatases.
- R406 is metabolized in the liver and excreted predominantly by the biliary tract.
- Exposure to R406 is dose dependent and its terminal half-life is 13–21 h, and it is not significantly affected by food.
- It has no clinically relevant interactions with methotrexate.

**Clinical efficacy**
- Twice-daily oral doses of 100 mg R788 were significantly better than placebo in obtaining a significant improvement in rheumatoid arthritis failing to respond to methotrexate in 12 weeks and 6 months.

**Safety & tolerability**
- R788 was usually well tolerated.
- Diarrhea (mild-to-moderate) was the more common clinical side effect.
- Neutropenia and mild elevations of transaminases were observed in a few patients.
- Minor elevations – rarely hypertension – of blood pressure were observed in some cases.

**Drug interactions**
- Methotrexate, NSAID and prednisone do not appear to have negative interactions with R788.

**Dosage & administration**
- Studied doses in rheumatoid arthritis range from 50 to 150 mg twice daily or 150 mg every day. The most likely dose for the upcoming Phase III trials may be 100 mg twice daily.
R788 (fostamatinib disodium): a novel approach for the treatment of RA

Financial & competing interests disclosure
The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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