Efficacy and Safety of Mesalamine 1 g HS Versus 500 mg BID Suppositories in Mild to Moderate Ulcerative Proctitis: A Multicenter Randomized Study

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Background: Ulcerative proctitis (UP) usually presents as fresh rectal bleeding. Successful treatment using topical mesalamine 5-aminosalicyclic acid (5-ASA) 500 mg BID suppository led to developing a once-a-day formulation that could contribute to better acceptability and ease of use by patients. The objective of this randomized trial, conducted in 18 centers, was to compare efficacy of 2 modes of treatment with 5-ASA suppositories.

Methods: Ninety-nine patients with mild or moderate UP limited to 15 cm of the anal margin, evidenced by a disease activity index (DAI) between 4 and 11, were randomized to 5-ASA 500 mg suppository (Canasa; Axcan Pharma) BID or 1 g at bedtime (HS) for 6 weeks. The study used a noninferiority hypothesis based on the mean difference in DAI values after 6 weeks of treatment on an intent-to-treat basis using analysis of covariance. DAI was derived from a composite of the measures of stool frequency, rectal bleeding, mucosal visualization at endoscopy, and general well being.

Results: There was no difference between groups at baseline for demographic and clinical parameters. Mean DAIIs fell from 6.6 ± 1.5 (SD) to 1.6 ± 2.3 in the 500 mg BID group (n = 48) and from 6.1 ± 1.5 to 1.3 ± 2.2 in the 1 g HS group (n = 39). There was no significant difference (P = 0.74) in mean DAI at week 6 between the 2 groups. Both groups showed a significant reduction (P < 0.0001) in DAI over the course of the 6 weeks. Both formulations showed effectiveness in reducing each individual component of the DAI. There was no significant difference between treatments in adverse events, and both groups had an overall drug compliance of greater than 95%.

Conclusion: This study showed that 1 g HS and 500 mg BID mesalamine suppository treatments of UP patients were equivalent in all facets of efficacy, safety, and compliance in a 6-week trial.

Key Words: disease activity index, mesalamine trial, ulcerative proctitis

Ulcerative proctitis (UP) is a subset of idiopathic ulcerative colitis (UC) where involvement of the distal colon is limited, being confined to the rectum in 25% of patients. It usually presents as fresh rectal bleeding, which is often intractable to conventional treatment with oral sulfasalazine, oral prednisone, or steroids applied topically to the rectum. This localized disease is considered suitable for topical treatment with mesalamine in suppository form applied to the area involved.1-4

Colonic mucosa of patients with UC and Crohn’s disease synthesizes significantly more prostaglandins (PGs) compared with noninflamed colonic mucosa. Because PGs are potent proinflammatory mediators, they stimulate intestinal secretion, thus inducing diarrhea, increased mucus production, and contraction of the intestinal smooth muscle. Increased PG formation may contribute to mucosal inflammation and symptoms in patients with chronic inflammatory bowel disease (IBD). This hypothesis was supported by results showing inhibition of colonic mucosal PG formation by 5-ASA. More recently, mesalamine has been shown to impact on lymphocyte function, antibody secretion, and mononuclear cell chemotaxis,5 including inhibition of tumor necrosis factor6 and induction of nuclear factor-κB.5

Mesalamine 500-mg suppositories have been approved for treatment of UP for almost 2 decades, and the 1 g version does not differ except in size. The majority of patients respond to a BID dosage (i.e., 1 suppository in the morning and 1 at bedtime). In a clinical trial with active cryptogenic UP, there was no significant difference in clinical efficacy after 14 or 21 days of treatment between 1-g suppository HS versus 500-mg suppository BID. However, patient acceptability was much greater for HS than BID mode.3 These results were also confirmed by a trial in 50 UP patients after a 28-day treatment.4 Patients again confirmed that acceptability of HS mode was superior to BID.

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Knowing that both mesalamine 500-mg suppositories taken BID and 1-g suppositories taken HS are a safe and effective treatment for 3 weeks in UP patients, this study was undertaken to compare 500 mg BID and 1 g HS mesalamine suppositories for efficacy and safety after 6 weeks of treatment.

**MATERIALS AND METHODS**

The primary endpoint of this trial was to compare the clinical efficacy of 2 mesalamine therapeutic regimens after 6 weeks of treatment in patients with active mild to moderate UP in a multicenter randomized equivalency study. Secondary objectives were to assess whether compliance was maintained in both treatments for 6 weeks, whether both treatments continued to maintain efficacy from 3 to 6 weeks of treatment, and to assess safety of these therapeutic regimens. The protocol and consent form received ethics approval in each center. This trial was designed as an equivalence study because both treatments had previously been established as safe and effective for treatment up to 3 weeks. The focus of this suppository trial was to determine the effectiveness of both mesalamine dosage forms and compliance of patients during a longer period of treatment.

**Treatment**

Patients received Canasa/Salofalk, 500 mg BID or Canasa/Salofalk (Axcan Pharma, Quebec, Canada), 1 g HS, equivalent to daily doses of 1 g of mesalamine, for a 6-week treatment duration. Patients assigned to the 500 mg BID group took their first dose in the morning, whereas patients assigned to the 1 g HS group took their first dose in the evening.

**Criteria**

Inclusion criteria consisted of male or nonpregnant female 18 to 70 years of age, positive for UP confirmed by endoscopy, graded by a disease activity index (DAI) value between 4 and 11, UP not extending beyond the rectum, no change in smoking habits during the study, and ability to give written informed consent.

Exclusion criteria consisted of other confirmed diseases interfering with measurement of DAI, UC extending beyond the rectum as evidenced by flexible sigmoidoscopy or colonoscopy, chronic use of oral 5-ASA at a dose greater than 4 g daily or any form of rectal 5-ASA or use of any other medication for UP in the month preceding baseline, contraindication to use of mesalamine or other related products, significant impairment of renal or hepatic function, significant urinary tract obstruction, history of idiopathic pancreatitis, coagulation disorders or use of anticoagulant drugs (except acetylsalicylic acid at a daily dose of 325 mg or less for prevention of cardiovascular disease), pregnancy or lactation or women of child-bearing potential not using reliable contraception, other serious medical conditions, and use of any experimental drug within 30 days before enrollment.

Patients were eligible for the study if no pathogens, ova, or parasites were isolated from stool culture. Presence of *Clostridium difficile* sp. in conjunction with the associated produced toxins A and B was considered an exclusion criterion. The presence of toxins A and B produced by *C. difficile* sp. alone was an exclusion factor. Isolation of *C. difficile* sp. alone (commensal pathogen) did not exclude a patient.

**Screening**

Within 7 days before the start of medication, the patient had to be found positive for mild to moderate UP. Presence of proctitis was documented by baseline endoscopy and biopsies from inflamed and normal tissues. Pretreatment cultures from stools were done to exclude the presence of pathogens, ova, parasites, and toxins A and B produced by *C. difficile* sp.

**Clinical Procedures**

After signing the consent form at the first visit, medical history, complete physical examination (excluding genital/gynecologic, unless indicated), routine hematology, clinical chemistry, urinalysis, and pregnancy test (if indicated) were done.

The investigator performed an endoscopy and collected 2 biopsies: a rectum biopsy from the most severe diseased area and a biopsy from the normal tissue area located above the diseased area. Both histology and/or stool cultures had to confirm admissibility. A patient was considered for safety analysis only if medication was started on the basis of a positive diagnosis of UP and was later found negative by histology and/or culture.

If needed, all screening procedures could be done on the same day. In that case, results of the stool culture and biopsies were not available when the patient was randomized. Patients were allowed to start the trial but were withdrawn on confirmation of infectious conditions.

At each of the 2 follow-up visits, an endoscopy was done, and the DAI was evaluated and calculated by the physician based on a review of the patient diary and by asking about clinical symptoms from the last 3 days preceding the visit. The physical examination, clinical laboratories, and pregnancy tests done at prestudy were repeated.

**Visits**

The study involved a baseline visit, where the patients were screened for participation in the study and given their drug supplies (days −7 to 0). The second study visit was completed after 3 weeks of treatment and occurred during the fourth week (between days 22 and 28). The visit was scheduled as early as possible (day 22/23), and treatment continued until the visit. A third and final visit was completed after 6 weeks of treatment (between days 43 and 49). The visit was scheduled as early as possible (day 43/44), and treatment continued until the visit. This visit was classified as end of treatment visit.
for a patient not completing the trial (dropout, randomized screening failure, etc.).

**Patient Procedures**
Patients were given symptom and treatment diaries to complete each day. Day 1 was the day the patient took their first dose of study medication. The patient returned to the clinic for physical and endoscopic evaluations after 3 and 6 weeks of treatment. Number of stools, relative amount of blood in stools, urgency, severity of abdominal pain, general well being, time of retention of study medication (if < 6 h), other symptoms or possible side effects, and change in concomitant medication were recorded daily by the patient.

**Laboratory Procedures**
All clinical laboratory determinations (with the exception of erythrocyte sedimentation rate [ESR] and international normalized ratio [INR] done at local laboratories) were performed at a central laboratory. In the 7 days preceding baseline and at the last study visit, safety laboratory tests were conducted. Stool cultures for detection of pathogens, ova, and parasites, as well as *C. difficile* sp. and toxins A and B produced by *C. difficile* sp. were done during those periods. At time of baseline endoscopy, 2 separate biopsies were collected. Endoscopy was done when the patient was either conscious or under light general sedation. Pictures of the mucosa at its worst location were taken whenever possible.

The 2 mucosal biopsy specimens were evaluated based on degree of inflammation: grade 0, no abnormality; grade 1, mild chronic inflammatory infiltrate with architectural distortion; grade 2, mild to moderate chronic inflammatory infiltrate with architectural distortion (presence of neutrophils in epithelium); grade 3, marked chronic inflammatory infiltrate with architectural distortion (crypt destruction, erosion, or ulceration of mucosa). For histology, the appearance of IBD was identified by cellular morphology, and a final conclusion was derived from the results.

**Randomization and Blinding**
Patients were assigned to 1 of 2 treatment groups by a randomization list generated by an automated number program. Listings for a block of 5 patients were sent to each site along with 5 sets of study medications. For those sites enrolling more than 5 patients, an additional list of 5 patients and corresponding study medication were sent. Neither patients or physicians were blinded to the treatment, but the pathologist, laboratory, and statistical analyses were blinded.

**Outcomes**
The primary outcome variable was DAI at week 6 using the sum of 4 subscales, stool frequency, rectal bleeding, mucosal appearance at endoscopy, and disease global assessment, with each subscale having 4 subdivisions of severity from 0 to 3. DAI was computed using average values for each scale during the 3 days preceding a visit. Special attention was given to distinguishing between formed and liquid stools. Degree of incontinence and urgency experienced by the patient contributed to the physician’s overall rating.

Compliance was measured by counting the total number of suppositories dispensed minus the total number of suppositories returned divided by the total number of suppositories dispensed. The mean daily mesalamine dose in grams was determined as the total number of suppositories dispensed minus the total number of suppositories returned times the number of milligrams divided by the total extent of exposure.

Other outcomes were remission rate in each therapeutic regimen assessed by comparing DAI from week 3 with DAI from week 6. A safety profile for each regimen was developed from the adverse effects (AEs) reported.

**Statistical Analyses**
Descriptive statistics were determined at baseline and compared between groups. Analysis of covariance (ANCOVA) was applied to compare DAI treatments at 6 weeks to adjust for the covariate of baseline DAI. Missing DAI data were estimated by the last-observation-carried-forward method for the intent-to-treat (ITT) analysis. Remission rates were compared using a Fisher exact test. Complete response to the study drug was assessed by comparing DAI changes from week 3 to week 6 using a 2-sided paired *t* test. All subjects exposed to at least 1 dose of treatment were included in the safety analysis. All patients with confirmed UP at screening without any exclusion criteria were included in the ITT analysis. All patients found to have confirmed UP at screening and meeting the inclusion/exclusion criteria were included in the per protocol analysis.

**Sample Size Estimate**
The primary endpoint of this trial was to compare 500 mg BID to 1 g HS mesalamine doses on the DAI at 6 weeks through the conduct of an equivalence study using a noninferiority hypothesis. The sample size estimate was based on detection of a difference between DAIIs at week 6 for administration of 1 g HS versus 500 mg BID. Assuming a 5% significance level and a power of 80%, 37 patients per group were required to detect a difference of 1 DAI (95% confidence interval) unit (defined as the clinically significant threshold and based on a previous study) with a mean DAI of 2.5 units and an SD of 1.5 units using a 2-sided test. To account for dropouts and withdrawals in this study, 50 patients were required to be assigned to each treatment.

**RESULTS**
There were 99 patients recruited for the study from 3 countries and 18 sites, with 2 patients not receiving study medication (abnormal laboratory result and a withdrawn consent), leaving 97 in the safety population and 87 in the ITT
groups because 10 patients did not meet inclusion/exclusion criteria. Only ITT analyses are presented because the per protocol analyses gave similar findings.

There were 8 patients in the 500 mg BID group (2 adverse events, and 1 each lost to follow-up, protocol violation, positive *C. difficile*, and *Giardia lambia*) and 6 patients in the 1 g HS group (2 withdrew consent, 2 lost to protocol violation, 1 baseline stool culture, and 1 exclusion criteria) that did not complete the study. This left 48 patients in the 500 mg BID group and 39 patients in the 1 g HS group for the ITT analyses.

There were no significant differences between suppository treatment groups in demographic and clinical factors (Table 1). Both groups averaged slightly less than 40 years of age, and 1 g HS had more males (64%) than the 500 mg BID group (54%). Although the 2 groups had different percentages for both nonsmokers and exsmokers, collectively the 2 categories were identical for each group. DAI ranged from 4 to 9, with the majority of both groups having values in the middle of that range. Two thirds of each group had a previous history of UP, with both averaging slightly more than 4 years since onset.

**Efficacy Evaluation**

Primary outcome measure for this equivalency trial was to compare suppository treatments at week 6 on DAI values adjusted for baseline DAI (ANCOVA). There was no significant difference (*P* = 0.73) in DAI at 6 weeks between treatments (Table 2). Although the 500 mg BID group (1.6 [2.3]) had a higher DAI value than the 1 g HS group (1.3 [2.2]) at 6 weeks, there was also a higher DAI value at baseline for 500 mg BID (6.6 [1.5]) than for 1 g HS (6.1 [1.5]), so the percentage change over time in each group was similar. There was also no significant difference (*P* = 0.87) in DAI between treatments at week 3 adjusted for baseline DAI value. There was a significant improvement (*P* < 0.001) in DAI scores after both 3 and 6 weeks of treatments within both groups.

There was no significant difference between groups in mean daily mesalamine dose in grams for 500 mg BID (n = 49, 0.92 g) and 1 g HS (n = 42, 0.98 g). The overall compliance for the safety population after 6 weeks of treatment was 96% for 500 mg BID and 97% for 1 g HS, with compliance at 3 weeks being almost identical. There was 1 patient in each group that had compliance of less than 75%.

Other outcome measures were also compared between suppository treatments for each DAI component at 3 and 6 weeks, and there were no significant differences (Table 3). The patterns of DAI change for each component (stool frequency, rectal bleeding, visualization at endoscopy, and general well being) were similar, with marked decreases from baseline to week 3 and lesser percentage decreases, but still pronounced, from week 3 to week 6.

**Safety Evaluation**

There were 53 patients in the 500 mg BID group and 44 patients in the 1 g HS group who took at least 1 dose of the study drug and constituted the safety population. AEs were found in 57% (30/53) of patients in the 500 mg BID group and 55% (24/44) of the 1 g HS group. There were 71 AEs in the 500 mg BID group and 46 AEs in the 1 g HS group.

The organ classes that were reported as having AEs most frequently were the gastrointestinal system (10 in 500 mg BID...
and 7 in 1 g HS) and nervous system (9 in 500 mg BID and 8 in 1 g HS; Table 4), with flatulence, diarrhea, abdominal pain, and headaches cited most often. There was 1 AE reported as severe (abdominal distension) in the 500 mg BID group and 7 severe AEs in the 1 g HS group (2 abdominal pain, and 1 each of frequent bowel movement, rectal hemorrhage, diarrhea, headache, and bronchospasm). AEs considered to be related to study drug were found in 9 of 53 (17%) patients (11 events) in the 500 mg BID group and 9 of 44 (20%) patients (18 events) in the 1 g HS group. For both treatments, the most frequently reported AE related to study drug was headaches, with 3 events in each group. There were no serious AEs or deaths reported. There were 5 AEs rated as severe and related to study drug that occurred in 2 patients from the 1 g HS group (bloating, abdominal pain, diarrhea, increase in stool frequency, and rectal hemorrhage). All but the bloating AE were resolved at study conclusion.

**DISCUSSION**

Mesalamine is used as a treatment for UP, with 500-mg suppositories twice a day being the standard application. Given the fact that suppository use is more awkward and uncomfortable to accomplish than taking medication orally, the compliance rate for suppositories may be lower, making treatment less effective. With suppository studies showing that 1 g HS is as effective as 500 mg BID after 14 and 21 days of therapy, patients would likely prefer a once a day treatment compared with a twice a day treatment. As a consequence of the success of previous studies for safety and clinical effectiveness, a similar but longer-term equivalence study of 6 weeks instead of the usual 3 weeks was conducted. This was designed to assess whether extended suppository use could continue to be safe and effective for a longer-term period and to see whether compliance would still be reasonable in a UP population.

The majority of patients in both groups reached a DAI status showing a complete response, which demonstrated that mesalamine was effective in either formulation. The individual components of the DAI (stool frequency, rectal bleeding, visualization at endoscopy, and general well being) mirrored the results of the overall index and were consistent in their patterns of improvement.

An examination of results at 3 weeks was similar to those found in an earlier study at the same time period.

Comparisons of the DAI index between 3 and 6 weeks in this study showed significant improvement, establishing that more patients with UP reached complete response with an additional 3-week treatment.

Although there were more AEs found in the 500 mg BID group than the 1 g HS group, the percentage of patients having AEs were virtually the same. The safety profiles of both treatments showing specific categories of AEs were similar, with headaches being the most common event in both groups.

Of interest was the compliance profile, a factor usually of more concern with suppositories than oral drugs. There was no difference in compliance between groups at greater than 95% and with only 1 patient in each group having a compliance of less than 75%. The pattern of compliance was high for the

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**TABLE 3. Secondary DAI Components by Suppository Treatment**

<table>
<thead>
<tr>
<th>DAI Components*</th>
<th>Groups</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>500 mg BID [mean (SD)]</td>
<td>1 g HS [mean (SD)]</td>
<td></td>
</tr>
<tr>
<td>Stool frequency</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.5 (0.9)</td>
<td>1.2 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>0.8 (0.9)</td>
<td>0.5 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Week 6</td>
<td>0.5 (0.8)</td>
<td>0.4 (0.7)</td>
<td></td>
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<tr>
<td>Rectal bleeding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>1.7 (0.6)</td>
<td>1.2 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>0.4 (0.6)</td>
<td>0.5 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Week 6</td>
<td>0.3 (0.5)</td>
<td>0.4 (0.7)</td>
<td></td>
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<tr>
<td>Visualization at endoscopy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 0</td>
<td>1.8 (0.5)</td>
<td>1.7 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>0.8 (0.7)</td>
<td>0.3 (0.5)</td>
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</tr>
<tr>
<td>Week 6</td>
<td>0.5 (0.7)</td>
<td>0.4 (0.6)</td>
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<tr>
<td>General well being</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Week 0</td>
<td>1.6 (0.5)</td>
<td>1.5 (0.5)</td>
<td></td>
</tr>
<tr>
<td>Week 3</td>
<td>0.7 (0.7)</td>
<td>0.8 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Week 6</td>
<td>0.3 (0.6)</td>
<td>0.4 (0.7)</td>
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</tbody>
</table>

*No significant difference at any time period for any component.

**TABLE 4. Adverse Events† by Suppository Treatment [n (%)]**

<table>
<thead>
<tr>
<th>System Organ Class*</th>
<th>Groups</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>500 mg BID [n = 53] 57%</td>
<td>1 g HS [n = 44] 55%</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections/infestations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General/administration site</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive breast disorder</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Musculoskeletal connective tissue</td>
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</tbody>
</table>

*No significant difference in system AEs between treatments.

†Only includes AEs of 2 or greater.

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first 3 weeks of treatment and slightly greater during the last 3 weeks of the study. Given the nature of UP and the clinical experience of most patients, this compliance is not surprising. However, the fact that both treatments had a similar compliance at both 3 and 6 weeks was surprising given results from earlier studies.

There were limitations in the design of the study. The presence of a placebo run-in phase would have been beneficial to exclude a placebo response in patients with unstable UP. However delaying the beginning of active treatment of patients already symptomatic raised ethical concerns. The study was open label except for the measurement of the primary outcome measure because patients and clinicians were aware of the group assignment. It was not possible to double-blind, even using a double dummy method. If two suppositories of different size were inserted at bedtime (one active and one placebo) it likely would trigger expulsion of only 1 suppository. The extra amount of excipient (diluent) carried by the placebo suppository could interfere with the local action of mesalamine from the active suppository. Both those actions could be detrimental to the efficacy and could have created a bias in the trial.

Future studies could examine the merit of extending the treatment period of mesalamine in UP beyond 6 weeks. Given that the rate of patients reaching remission in the 3- to 6-week period (43% for 500 mg BID and 58% for 1 g HS) was not much different than from baseline to 3 weeks (56% for 500 mg BID and 54% for 1 g HS), there is reason to believe that patients still not in remission after 6 weeks of treatment could be given further treatment. Consideration could also be given to conducting mesalamine suppository studies in patients with more severe UP. Certain types of patients with UC might receive benefit with mesalamine treatment.

This equivalence mesalamine study shows that 1 g HS treatment is similar in efficacy and safety to 500 mg BID after 6 weeks. The compliance of both suppository groups was positive, and the similar compliance of both treatments was encouraging, given the results of shorter trials.3,4 The results clearly show that both mesalamine suppository formulations, when used in mild to moderate UP, are effective and safe treatments with very good compliance.

ACKNOWLEDGMENTS

The study coordinators from each clinical site contributed greatly to the success of the trial. The work of the study monitors L. Aber, D. Esquivel, and M. F. Goyer is appreciated. Our thanks also to L. Regnau, M. Laganiere, M. Desgagne, and M. Asselin for assistance in validating the data and to R. Gaudet and J. Fredette of Quintiles Canada for the statistical analysis.

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