Articles

Efficacy and safety of alosetron in women with irritable bowel syndrome: a randomised, placebo-controlled trial

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Summary

Background Irritable bowl syndrome (IBS) is a common gastrointestinal disorder with symptoms of abdominal pain, discomfort, and altered bowel function. Antagonists of the type 3 serotonin receptor (5-HT_3) have shown promising results in the relief of IBS-associated symptoms. We aimed to confirm these findings by doing a randomised, placebo-controlled trial.

Methods We studied 647 female IBS patients with diarrhoea-predominant or alternating bowel patterns (diarrhoea and constipation). 324 patients were assigned 1 mg alosetron and 323 placebo orally twice daily for 12 weeks, followed by a 4-week post-treatment period. Adequate relief of abdominal pain and discomfort was the primary endpoint; secondary endpoints included improvements in urgency, stool frequency, and stool consistency. Analysis was by intention to treat.

Findings 79 (24%) of patients in the alosetron group and 53 (16%) in the placebo group dropped out. The difference in the drop-out rate between groups was mainly due to a greater occurrence of constipation in the alosetron group. A greater proportion of alosetron-treated patients than placebo-treated patients (133 [41%] *vs* 94 [29%], respectively) reported adequate relief for all 3 months of treatment (difference 12% [4·7–19·2]). Alosetron also significantly decreased urgency and stool frequency, and increased stool firmness. Constipation occurred in 30% and 3% of patients in the alosetron and placebo groups, respectively.

Interpretation Alosetron was well tolerated and clinically effective in alleviating pain and bowel-related symptoms in this population of women with IBS.

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See Commentary page

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Introduction

Irritable bowel syndrome (IBS) is one of the most common gastrointestinal disorders seen in primary care and specialist practices.[1,2] The primary symptoms of IBS are chronic recurrent abdominal pain and alterations in bowel function. Such alterations can present as diarrhoea or constipation, or can alternate between the two (referred to as "alternating IBS" in this paper). IBS has a negative impact on patients' daily activities and quality of life,[3–5] and incurs substantial health-care costs.[3,6]

Previous studies have indicated that antagonists of the type 3 serotonin receptor (5-HT_3) represent potentially valuable therapeutic compounds for the treatment of IBS. In patients with this disorder, 5-HT_3 receptor antagonists increase thresholds for sensation and discomfort during distension of the rectum, increase colonic compliance, slow colonic transit, and improve stool consistency.[7–12] The 5-HT_3 receptor antagonist alosetron has been assessed in patients with IBS, and dose-ranging studies showed that, in women, 1 mg alosetron twice daily was the most effective dose for improving IBS abdominal pain and discomfort, urgency, stool frequency, and stool consistency.[13,14]

We assessed alosetron efficacy and tolerability in female IBS patients with diarrhoea-predominant or alternating bowel patterns. Since there is no single treatment for multiple IBS symptoms, alosetron was assessed against placebo only.

Methods

Screening of patients

At 119 sites in the USA, we screened women with IBS aged 18 years or older who had a normal colonic anatomy (as assessed by flexible sigmoidoscopy, colonoscopy, or double-contrast barium enema plus flexible sigmoidoscopy within the previous 5 years). Patients were required to have had symptoms that fulfilled the Rome criteria for IBS[15] for at least 6 months.

Although no objective criteria exist for subgrouping of IBS patients, physicians assessed patients according to predominant bowel-function pattern on the basis of the patient's disease history. If diarrhoea or constipation were present for at least 75% of the time during which a patient's IBS was active, the disease was classified as diarrhoea-predominant or constipation-predominant, respectively; otherwise the patient was classified as having alternating IBS. Constipation-predominant IBS patients were excluded because 5-HT_3 receptor antagonists slow colonic transit.[12,16]

During the 2-week screening phase, severity of pain and discomfort was assessed daily on a 5-point scale (0=none, 1=mild, 2=moderate, 3=intense, 4=severe). We enrolled patients with average daily baseline pain and discomfort scores

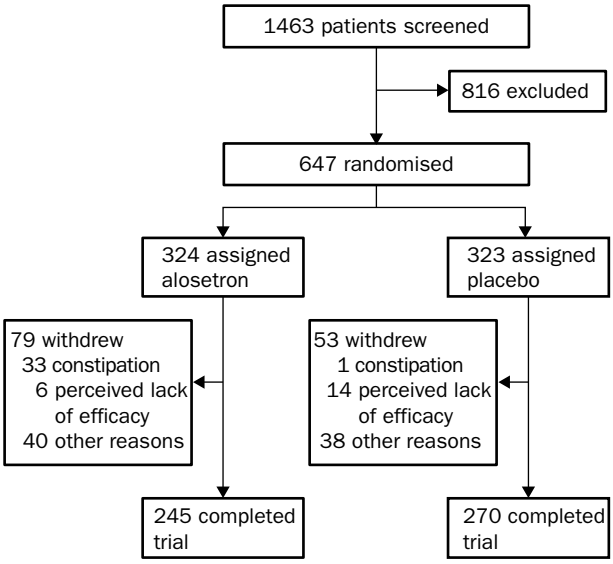

Figure 1: **Trial profile**

between 1·0 and 3·3, inclusive. Data on stool consistency were also recorded daily (1=very hard, 2=hard, 3=formed, 4=loose, and 5=watery). An average daily stool consistency score of at least 2·5 was required for entry into the study.

Patients were excluded if they were pregnant, breast-feeding, or not using approved methods of contraception (if of child-bearing potential); if an unstable medical disorder or other gastrointestinal disorder existed; if the patient had a history of a major psychiatric disorder or substance abuse within the previous 2 years; if aspartate aminotransferase or alanine aminotransferase concentrations were greater than 2·5 times the upper limit of normal, or if serum creatinine concentrations were greater than 152·4 mmol/L; if they had hyperthyroidism or hypothyroidism; if they had a non-skin malignancy within the previous 5 years; if an investigational drug was used within 30 days of the screening phase. Patients were also excluded if they used antibiotics, anticholinergics, cholestyramine, narcotics, colchicine, docusate, enema preparations, iron supplements, laxatives, non-steroidal anti-inflammatory drugs or other analgesics if used more than 3 days per week, treatments for Parkinson's disease, antipsychotics, isoniazid, rifampicin, anticonvulsants, peppermint oil, leuprolide, stimulants, and amphetamine-like drugs. Institutional review boards at all sites approved the protocol, and all patients provided written informed consent.

Study design

Patients were randomly assigned 12 weeks of twice-daily treatment with either placebo or 1 mg alosetron taken before meals, followed by a 4-week post-treatment period. Patients had monthly visits with the enrolling physicians to assess drug compliance and occurrence of adverse events. Constipation was coded as an adverse event after either the patient's subjective report of constipation, or if there was a 4-day continuous period with no bowel movement. The randomisation schedule was generated by a computer-generated random codes system. Treatment assignments were not revealed until the study was completed.

During the screening, treatment, and follow-up periods, data on daily and weekly symptoms were collected by means of an electronic touch-tone telephone system connected to a central database.[17] Patients telephoned daily and were asked a series of questions by the computer; they responded by pressing appropriate keys on the telephone pad. Each day during the treatment and follow-up phases, patients recorded their IBS symptoms (pain, severity, urgency, stool consistency, and stool frequency).

The primary endpoint in the study was adequate relief of IBS pain and discomfort for at least 2 weeks per month. A patient experiencing such relief was termed a "monthly responder".

Characteristic	Alosetron (n=324)	Placebo (n=323)
Mean (SD) age (years)	46·5 (13·7)	45·6 (13·6)
Ethnic origin		
White	299 (92%)	302 (93%)
Black	8 (2%)	14 (4%)
Hispanic	13 (4%)	4 (1%)
Other	4 (1%))	3 (1%)
Childbearing potential		
Sterile	162 (50%)	147 (46%)
Postmenopausal	62 (19%)	66 (20%)
Potentially able to conceive	100 (31%)	110 (34%)
Menstruation		
Yes	133 (41%)	129 (40%)
No	191 (59%)	194 (60%)
Use of female sex hormones		
Contraceptives	57 (18%)	64 (20%)
Replacement therapy	104 (32%)	120 (37%)
None	163 (50%)	139 (43%)
IBS subtype		
Diarrhoea-predominant	221 (68·4%)	237 (73·1%)
Alternating	95 (29·4%)	85 (26·2%)
Constipation-predominant	7 (0·02%)	2 (0·01%)
IBS symptoms (mean [SD])		
Pain severity	1·95 (0·60)	1·90 (0·63)
Sense of urgency*	67·0 (25·6)	69·3 (25·5)
Stool consistency score	3·42 (0·54)	3·40 (0·57)
Stools per day	2·71 (1·22)	2·77 (1·28)
Bloating*	77·8 (26·3)	76·3 (27·3)

Pain severity scale: 0=none, 1=mild, 2=moderate, 3=intense, 4=severe; stool consistency scale: 1=very hard, 2=hard, 3=formed, 4=loose, 5=watery.
*Proportion of days (%) during which symptom occurred.

Table 1: **Baseline characteristics**

The adequate relief question ("in the past seven days have you had adequate relief of your irritable bowel syndrome pain and discomfort?") was asked of patients once every 7 days. The threshold for clinical relevance (ie, adequate relief during more than half of the weeks in a month) was prospectively defined after consultation with a panel of IBS experts. In addition, the proportion of patients who reported adequate relief each week was assessed to identify the onset and duration of the therapeutic effect.

Secondary endpoints included the bowel functions of stool consistency, sense of urgency, and stool frequency. The main interval of interest for the bowel functions was the change from baseline each week for the first 4 weeks. Further analyses were also done on the weekly change from baseline for weeks 5–12. Descriptive analysis of changes from baseline was also done for pain scores.

Statistical analysis

We assumed that there would be a 40% response to placebo and a 55% response to alosetron. 244 patients were needed to detect a 15% difference in the proportion of monthly responders with 90% power at the α=0·05 significance level. 600 patients were needed to allow for a 20% dropout rate.

Efficacy analyses were by intention to treat, and included all patients randomly assigned alosetron or placebo; safety analyses included all patients randomised except for those who did not take at least one dose of alosetron or placebo. The handling of missing data was by the principle of last observation carried forward (LOCF), whereby missing values were replaced with the last previous non-missing value. To assess the robustness of the adequate relief results with respect to the LOCF method, an alternative analysis was done whereby missing values were regarded as "no relief".

The proportion of monthly responders, and the proportion of patients reporting adequate relief each week, were compared between treatment groups by means of a Mantel-Haenszel test stratified by clusters of centres.

Centres were prospectively grouped into five geographic clusters to avoid the loss of centres with small numbers of patients in tests stratified by centre, or in tests of treatment-by-

Month	Alosetron (n=324)	Placebo (n=323)	Difference (95% CI)	p
1	169 (52%)	137 (42%)	10% (2·1–17·4%)	0·019
2	176 (54%)	152 (47%)	7% (–0·4–14·9%)	0·080
3	183 (56%)	151 (47%)	9% (2·1–17·4%)	0·015

Table 2: **Monthly responders**

centre interaction. Treatment-by-centre interaction was assessed by ordinal logistic regression; the total number of months in which a patient was a monthly responder was used as the dependent variable, and treatment, cluster, and treatment-by-cluster interaction terms were used as independent predictors.

Daily stool-consistency scores, pain scores, and daily number of bowel movements were averaged at baseline (for the 2-week screening period), at each week of the treatment and follow-up periods, and at each month of the treatment period. In addition, the proportion of days during which patients experienced a sense of urgency was calculated for the same weekly and monthly intervals. Changes from baseline for each month and week were compared between treatment groups by means of van Elteren's test stratified by clusters of centres.

Multiple significance testing was addressed by prespecification of the order for testing endpoints, and then by provision of evidence of significance before testing of the next endpoint in the sequence. The primary endpoint was tested first: we calculated the total number of months for which a patient was a monthly responder, and if significant, the number of responders at each month, followed by analyses at each week. Secondary endpoints were then assessed in the following sequence for the change from baseline during the first 4 weeks: stool consistency, urgency, and stool frequency. If significant, analyses were then done on the change from baseline for weeks 5–12.

Results

Patients

Of 1463 patients screened, 647 were randomised: 324 were assigned alosetron and 323 placebo. Of those who were excluded, 686 did not meet the inclusion criteria, 81 withdrew consent, 13 did not complete daily assessments, 11 had adverse events, and 25 were excluded for other reasons (figure 1). Although physicians were asked to enrol only patients with diarrhoea-predominant or alternating IBS, nine patients with constipation-predominant IBS were mistakenly

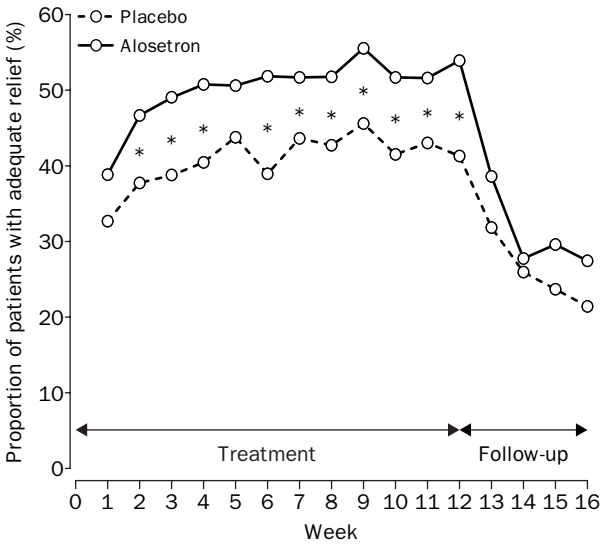

Figure 2: **Proportion of patients with adequate relief of pain and discomfort per week**
*p<0·05.

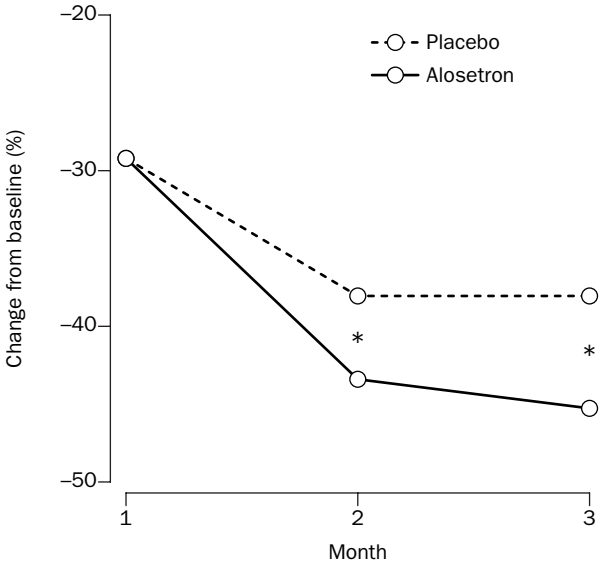

Figure 3: **Change in pain severity scores from baseline by month**
*p<0·05.

enrolled. These patients were included in the intention-to-treat analysis. Enrolment ranged from one to 21 patients per site, and averaged five patients per site. 132 (20%) patients withdrew from the study prematurely: 79 of 342 (24%) in the alosetron group and 53 of 323 (16%) in the placebo group. More alosetron-treated patients than placebo patients withdrew because of constipation (33 *vs* 1; p<0·001). One patient in the alosetron group and two in the placebo group withdrew from the study before receiving the first dose and were not included in the safety analysis. The patients' characteristics were similar between treatment groups (table 1).

Adequate relief of pain and discomfort

A greater proportion of alosetron-treated patients than placebo-treated patients reported adequate relief for all 3 months of treatment (133 [41%] *vs* 94 [29%]; difference 12% [4·7–19·2]); the treatment difference was homogeneous across clusters of centres.

The proportion of monthly responders is shown in table 2). Figure 2 shows the proportion of patients in each group with adequate weekly relief. Analysis with missing values coded as "no relief" showed similar results. Analysis by IBS subtype showed that alosetron-treated patients who were classified as diarrhoea-predominant received significant improvement compared with placebo-treated patients, whereas those classified as having alternating IBS received no benefit compared with placebo. Change in pain scores from baseline are shown in figure 3.

Bowel function

Alosetron significantly decreased urgency, stool frequency, and stool consistency, compared with placebo (where a decrease in stool consistency corresponds to an increase in stool firmness; figure 4). Significant changes were seen both in patients with alternating and diarrhoea-predominant IBS.

Safety

233 (72%) of 323 patients in the alosetron group and 210 (65%) of 321 patients in the placebo group reported

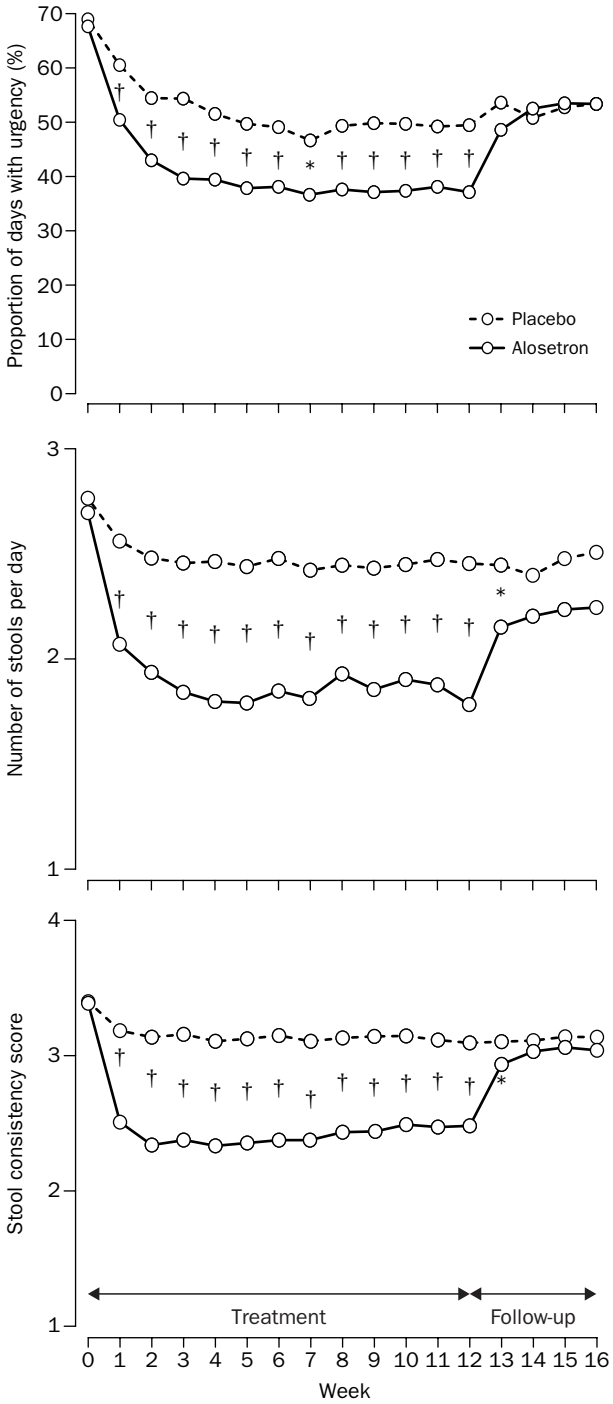

Figure 4: **Characteristics of bowel function by week**
*p≤0·05; †p<0·001.

Adverse event	Alosetron (n=321)	Placebo (n=323)	p
Gastrointestinal*	156 (48%)	97 (30%)	<0·001
Ear, nose, and throat	66 (20%)	58 (18%)	0·485
Neurological	45 (14%)	62 (19%)	0·072
Lower respiratory	33 (10%)	35 (11%)	0·799
Musculoskeletal	26 (8%)	34 (11%)	0·281
Skin	12 (4%)	15 (5%)	0·562
Cardiovascular	8 (2%)	15 (5%)	0·143
Psychiatric	9 (3%)	12 (4%)	0·515
Urological	7 (2%)	12 (4%)	0·255
Reproductive	10 (3%)	8 (2%)	0·812
Endocrine and metabolic	7 (2%)	11 (3%)	0·351
Ocular	7 (2%)	5 (2%)	0·772
Hepatobiliary and pancreatic	0	5 (2%)	0·030
Haematological and lymphatic	1 (<1%)	3 (<1%)	0·372
Non-site-specific	20 (6%)	45 (14%)	0·001
Drug interaction, overdose, and trauma	13 (4%)	15 (5%)	0·704

*Including one case of colitis.

Table 3: **Summary of all adverse events**

at least one adverse event during the course of the study (table 3). Constipation was the most commonly reported adverse event in the alosetron-treated group (96 patients [30%] *vs* 10 [3%] in the placebo-treated group). However, the proportion of alosetron-treated patients with adequate relief was similar to that of patients not reporting constipation (data not shown). Of the 53 patients with diarrhoea-predominant IBS who reported constipation as a drug-related adverse event, 37 (70%) remained in the study despite the fact that laxative use was not routinely permitted.

No serious drug-related adverse events or deaths were reported during the study. Ischaemic colitis was reported in one alosetron-treated patient. However, a review of the histopathology of the patient's biopsy suggested an infectious, rather than an ischaemic, aetiology. Immunohistochemical staining for *Escherichia coli* O157:H7 confirmed this hypothesis. Laboratory values were unchanged by alosetron therapy. Specifically, alosetron had no effect on liver-function tests compared with placebo.

Discussion

Alosetron significantly improved pain, urgency, stool frequency, and stool consistency after 1–2 weeks of therapy in women with IBS. Benefit persisted throughout all 12 weeks of treatment, and symptoms rapidly returned after cessation of therapy. Alosetron showed benefits over placebo for multiple endpoints. These results are important, since IBS pharmacotherapy has been difficult to assess, partly because of the variety of symptoms, and the substantial placebo effect in IBS patients.[18] Improvements in the symptoms of abdominal pain, urgency, and stool frequency are particularly notable since women with diarrhoea-predominant or alternating IBS report that these are the three most bothersome symptoms.[19]

The endpoint (adequate relief of abdominal pain and discomfort) was developed to provide a meaningful, patient-assessed measurement of clinical improvement in the symptoms of IBS. After consultation with a panel of IBS experts, we concluded that for a new IBS therapeutic agent to be judged effective, it should provide adequate relief of IBS pain and discomfort for at least half of the assessments. In clinical trials, IBS patients who reported adequate relief had significantly greater improvement in IBS abdominal pain and abnormal bowel functions than patients who did not report adequate relief.[20,21] Adequate relief is in direct correlation with improved pain-severity scores, a greater percentage of pain-free days, fewer days with urgency, and fewer and firmer stools, and is therefore an endpoint that reflects improvement in multiple IBS-relevant dimensions.

On the basis of observed increases in colonic transit time seen after treatment with 5-HT_3 receptor antagonists,[12,16,22] constipation was an anticipated consequence of alosetron treatment, especially since laxative use was not permitted in the study. IBS patients with constipation-predominant IBS were excluded from the study for these reasons. However, constipation did not seem to be perceived as a negative consequence of

alosetron treatment when it occurred in the patients in our study, since most patients who reported constipation remained in the study. We assume that in clinical practice, IBS patients receiving alosetron would obtain customary care for constipation if needed.

We studied only women, since the beneficial effects of alosetron have been shown more consistently in women than in men.[13,14] About 70% of IBS patients who present to physicians in western countries are women, although the reason for this predominance is not know.[23] Blood-brain perfusion patterns during colorectal distension differs between men and women with IBS,[24] and differences between men and women in motility and sensitivity to luminal distension have been observed in healthy volunteers.[25–27] Thus, there may be a physiological basis for the sex-specific efficacy of alosetron.[13,14]

IBS symptoms have previously been recorded in clinical trials by use of paper diary-cards on which patients enter daily data. However, diary cards are limited by a lack of assurance that the data are entered at the prescribed time. Since these data are central to the calculation of the efficacy of therapeutic agents, we developed a touch-tone telephone diary system, which ensured the reliability and security of data entry.[17] The system was programmed to accept data only once in a 24-h period. By this system, patients' responses to daily questions about abdominal pain and bowel function, and weekly questions about adequate relief of IBS pain and discomfort were immediately captured in a secure central database. Failure to enter data daily resulted in the system notifying the investigators that the patient had not recorded symptoms over the past 24 h. This notification signalled the investigators to remind the patient to enter data on a daily basis, or to ascertain whether the patient was experiencing a problem. This system helped to keep patient's difficulties with maintaining daily and weekly assessments to a minimum, and to improve the consistency and reliability of the data.

Contributors

M Camilleri, A Northcutt, S Kong, G Dukes, D McSorley, and A Mangel planned the study, designed the protocol, and contributed to the writing of the paper. A Northcutt and G Dukes supervised the study. D McSorley and S Kong did statistical analyses.

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