A dose finding study with 0.1%, 0.2%, and 0.4% glyceryl trinitrate ointment in patients with chronic anal fissures

J H Scholefield, J U Bock, B Marla, H J Richter, S Athanasiadis, M Pröls, A Herold

Background: Anal fissure is a common painful condition affecting the anal canal. The majority of acute fissures heal spontaneously. However, some of these acute fissures do not resolve but become chronic. Chronic anal fissures were traditionally treated by anal dilation or by lateral sphincterotomy. However, both of these surgical treatments may cause a degree of incontinence in up to 30% of patients. Several recent trials have shown that nitric oxide donors such as glyceryl trinitrate (GTN) can reduce sphincter pressure and heal up to 70% of chronic fissures.

Aim: This study addressed the dose-response to three different concentrations of GTN ointment compared with placebo in a double blind randomised controlled trial.

Method: A double blind, multicentre, randomised controlled trial was set up to compare placebo ointment against three active treatment arms (0.1%, 0.2%, and 0.4% GTN ointment applied at a dose of 220 mg twice daily) in chronic anal fissures. The primary end point was complete healing of the fissure.

Results: Two hundred patients were recruited over an eight month period from 18 centres. After eight weeks of treatment the healing rate in the placebo group was 37.5% compared with 46.9% for 0.1%, 40.4% for 0.2%, and 54.1% for 0.4% GTN. None was significantly better than the placebo response. A secondary analysis excluded fissures without secondary criteria for chronicity. Healing rates were then found to be 24% in the placebo group compared with 50% in the 0.1% GTN group, 36% in the 0.2% group, and 75% in the 0.4% GTN group. These values were statistically significantly different for the placebo group compared with 0.1% GTN, 0.4% GTN, and for the GTN treated group as a whole.

Conclusions: The results of this study have demonstrated the significant benefit of topical GTN when applied to patients suffering from chronic anal fissures but acute fissures showed a tendency to resolve spontaneously. The high proportion of fissures which healed in the placebo group suggests that the definition of “chronicity” needs to be reassessed. Further studies are required to confirm the optimal therapeutic strategy.

Anal fissure is a common painful condition affecting the anal canal. The majority of acute fissures heal spontaneously. However, some of these acute fissures do not resolve but become chronic. Chronic anal fissures were traditionally treated by anal dilation or by lateral sphincterotomy. However, both of these surgical treatments may cause a degree of incontinence in up to 30% of patients. Several recent trials have shown that nitric oxide donors such as glyceryl trinitrate (GTN) can reduce sphincter pressure and heal up to 70% of chronic fissures.

These agents cause transient relaxation of the internal anal sphincter (sometimes termed “chemical sphincterotomy”) by provision of exogenous nitrous oxide to the muscle tissue, without symptoms of irreversible incontinence. Relaxation of the internal anal sphincter can be measured during GTN therapy by measurement of the patient’s maximal anal resting pressure (MARP). The major side effect of topical GTN therapy for anal fissure is that up to 40% of patients using this treatment experience headaches. These headaches may reduce compliance and in some cases are severe enough to lead to discontinuation of treatment.

The purpose of the present study was to obtain accurate information on the efficacy and safety of topical GTN when used to treat chronic anal fissures. To this end, three dosage groups (0.1%, 0.2%, and 0.4% GTN ointment) and a placebo group were compared in the treatment of chronic anal fissure.

Patients and methods

The study was performed as a parallel group, double blinded, randomised, placebo controlled, multicentre trial. Local ethics approval for each centre was obtained through the respective hospital or independent ethics committees in Germany and the UK.

Patients were eligible for entry into the study if they were aged 18-70 years, had clinical features of a fissure for at least

Abbreviations: GTN, glyceryl trinitrate; MARP, maximal anal resting pressure; ITT, intention to treat; PP, per protocol.
GTN ointment in patients with chronic anal fissures

Randomised (n = 200)
(placebo (n = 51), 0.1% GTN (n = 52), 0.2% GTN (n = 51), 0.4% GTN (n = 48)
Excluded as inappropriately randomised (n = 3)

Patients commenced treatment (n = 197)

Allocated to placebo (n = 51)
Received allocated intervention (n = 51)
Not available for assessment (n = 3)
(thus effectively withdrew consent)

Allocated to GTN treatment (n = 146)
Received allocated GTN (n = 146)
Not available for healing assessment (n = 13)
(thus effectively withdrew consent)

ITT analysis: 48 received placebo
133 received GTN
Total ITT population = 181

Healing: placebo 18/48
0.1% GTN 23/49; 0.2% GTN 29/47; 0.4% GTN 20/37

Per protocol (PP) analysis—further exclusions

Excluded from analysis (n = 7)
Poor compliance with dose (n = 4)
Adverse events (n = 3)

Excluded from analysis (n = 19)
Poor compliance with dose (n = 9)
Adverse events (n = 7)
Non compliance with protocol (n = 3)

PP analysis: 41 received placebo
114 received GTN
Total PP population = 155

Healing: placebo 14/41
0.1% GTN 23/45; 0.2% GTN 14/37; 0.4% GTN 18/32

Figure 1 Consort flow chart of the progress of subjects through the phases of the study. GTN, glyceryl trinitrate; ITT, intention to treat; PP, per protocol.

the previous six weeks before enrolment into the study, and additionally, for female patients, provided they had a negative pregnancy test and were using appropriate contraception. Patients were excluded if they had previously been diagnosed as having an inflammatory condition of the anus, including anal sepsis, grade 3 or 4 haemorrhoids, or inflammatory bowel disease. Patients were also excluded if they were pregnant or breast feeding, or had taken non-steroidal anti-inflammatory drugs, calcium antagonists, nitrates, or sildenafil in the 14 days prior to commencing the study.

Fully informed written consent was obtained from each patient prior to entry into the trial. Patients with a confirmed diagnosis of chronic anal fissure (duration of symptoms in excess of six weeks) were randomised to treatment with either 0.1%, 0.2%, or 0.4% GTN ointment or placebo for eight weeks. The presence of secondary features (see fig 1) was noted at trial entry.

All medications were prepared by Dr Falk Pharma GmbH, Freiburg, Germany, and all medications were packaged in identical tubes. Dispensing was undertaken by the individual hospital pharmacies. Allocation of treatment was performed according to a computer generated randomisation method. Progress was assessed at three interim visits, once a fortnight, and at one final visit. Patients were withdrawn at the second interim visit if there was clear lack of efficacy (only a poor response was expected for placebo patients) or if there was complete resolution of symptoms. These patients were withdrawn at the discretion of the investigator in each centre on clinical grounds and without breaking the randomisation code for any patient.

Patients withdrawn without resolution were given the options for other therapy, including surgery or botulinum toxin injection. In addition to assessment of fissure healing (by visual inspection and measurement of the length and width of the fissure), patients were asked to describe the intensity of their pain using a visual analogue score. Patients and investigators recorded their global assessments of efficacy and safety, including adverse events. The amount of ointment used per patient was assessed at each visit by weighing the residual amount in the 20 g tube provided. The expected weight of the tube at each visit was calculated and the actual weight difference compared with this. Acceptable compliance was recorded if the quotient of the actual weight decrease divided by the expected weight decreased in the range 1.6–0.6 inclusive. Deviation greater than this was regarded as a protocol violation.

Patients were instructed to apply 1 cm (approximately 220 mg) of the ointment prescribed for them and to administer this with the tip of the index finger to a site just inside the anus at the junction of the perianal skin and the anal canal itself. Patients were instructed to apply the ointment twice daily at approximately 12 hourly intervals and were given a diary card to enter the time of day at which the ointment was applied. A dosing regimen of twice daily was chosen as this was used successfully in several other GTN trials; it was felt unwise to design a trial in which both GTN concentration and frequency of dosing were variables. Such a design would also have required a major increase in recruitment to power the trial.

All patients entering the trial were given standardised advice to follow a high fibre diet and advice on perianal hygiene at initial assessment.

At each follow up visit healing of the fissure was assessed visually, as were the presence or absence of associated secondary features. Intensity of pain on defecation was also assessed from a visual analogue score, as was overall intensity of pain. MARP was assessed before and during treatment in patients entered into the study in one centre. MARP was measured
using a solid state manometer (Gaeltec, Skye, UK) and PC based software (Synectic, London, UK).

Power calculations were based on an expected healing rate in the treated groups of 50% and 10% healing rate in the placebo group. Accordingly, it was suggested that recruitment of 40 patients to each group should give an 80% chance of detecting a significant result at p=0.05.

Statistical analysis was based on an intention to treat (ITT) analysis. The ITT population was defined as those individuals who had applied their assigned treatment at least once and had returned for assessment of the primary endpoint (healing of the fissure). Patients who failed to present for assessment and who would not reattend for assessment to determine an outcome were deemed to have withdrawn their consent to participate and were excluded from the analysis. A per protocol (PP) analysis was also undertaken. This population was defined as patients for whom no major protocol violations had occurred and for whom an assessment of the primary outcome measure had been undertaken. Patients who withdrew from treatment owing to lack of efficacy were included as treatment failures.

Pain scores were analysed against placebo using ANCOVA. The ANCOVA model comprised the baseline value for “overall” pain intensity and pain on “defecation” at trial entry as covariates, treatment, time point, treatment by time interaction as fixed factors, and subject as the random factor in the model. The interaction term was intended to reveal possible differences in the treatment effect over the time course of the study. The difference between each dose level and placebo was estimated together with 95% confidence intervals.

RESULTS

Two hundred patients were recruited to the study over eight months. There were no significant differences in age, sex, or ethnicity distribution in the placebo or GTN treated groups (table 1). Patients recruited to both the placebo and GTN groups had no significant differences in their previous medical histories. Mean (SD) age of the study population was 43 (13) years. Fissures were in the posterior position in 73% while 23% had an anterior fissure; 3.5% of patients had a fissure which had returned for assessment of the primary end point (healing of the fissure). Patients who failed to present for assessment and who would not reattend for assessment to determine an outcome were deemed to have withdrawn their consent to participate and were excluded from the analysis. A per protocol analysis was also undertaken. This population was defined as patients for whom no major protocol violations had occurred and for whom an assessment of the primary outcome measure had been undertaken. Patients who withdrew from treatment owing to lack of efficacy were included as treatment failures.

Table 1 Demographic data in the glyceryl trinitrate (GTN) and placebo groups

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Placebo 0.1% GTN</th>
<th>0.2% GTN</th>
<th>0.4% GTN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian</td>
<td>50 (98)</td>
<td>46 (88.5)</td>
<td>49 (96.1)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (2)</td>
<td>6 (11.5)</td>
<td>2 (3.9)</td>
</tr>
<tr>
<td>Male</td>
<td>23 (45.1)</td>
<td>25 (48.1)</td>
<td>25 (48.1)</td>
</tr>
<tr>
<td>Female</td>
<td>28 (54.9)</td>
<td>27 (51.9)</td>
<td>26 (51.0)</td>
</tr>
<tr>
<td>Site</td>
<td>12 (23.5)</td>
<td>5 (11.5)</td>
<td>16 (32.4)</td>
</tr>
<tr>
<td>Anterior</td>
<td>38 (74.5)</td>
<td>43 (82.7)</td>
<td>33 (64.7)</td>
</tr>
<tr>
<td>Posterior</td>
<td>1 (2)</td>
<td>3 (5.7)</td>
<td>2 (4.0)</td>
</tr>
<tr>
<td>Lateral</td>
<td>1 (2)</td>
<td>3 (5.7)</td>
<td>2 (4.0)</td>
</tr>
</tbody>
</table>

Thus the ITT analysis included 181 patients who had used some of the study medication and were assessed for healing at the end of the study. In the PP analysis, a further 26 patients were excluded from the analysis due to poor compliance with dosage (n=13), adverse events (headaches n=10), or use of prohibited co-medication (n=3). Thus for the per PP analysis, 155 patients were available for analysis (see consort flow chart in fig 1). The results of the PP and ITT analyses were very similar and thus the subsequent analysis and discussions are based on the ITT data.

Patient compliance was assessed by weighing the tubes of ointment at each visit. Acceptable compliance was set at 60–160% of expected consumption. A wide range of acceptable dosing was chosen as experience in earlier studies had shown that measurement of a 1 cm strip of ointment is very variable from person to person. Dosing was also likely to vary due to the need to reapply ointment if defecation occurred soon after application of the ointment. Compliance with dosing instruction and duration of treatment were found to be similar across all four treatment groups.

The primary criterion for efficacy of treatment was the proportion of patients who showed complete healing of their fissure after eight weeks of treatment. Overall, 62/133 (46.6%) patients receiving GTN had complete healing at the end of the treatment period compared with 18/48 (37.5%) patients in the placebo group (χ² test for trend, p=0.3). When individual doses of GTN were evaluated against placebo, complete healing rates for any given GTN dose were not significantly different from placebo (table 2). Using the ITT population, a global test for trend of GTN versus placebo was performed (χ² test, p=0.4), and for the PP population (χ² test, p=0.1).

The major side effect observed in the treatment groups was headache. In the ITT population, 57/181 (31%) patients in this
study complained of headaches. In the placebo group headaches were reported by 6/48 (12.5%) patients. This probably reflects the fact that the informed consent process warned all participants that headaches are a common side effect in the topical use of GTN. There was a gradual increase in the frequency of reported headaches with increasing GTN dose ($\chi^2$ test for trend, $p<0.01$) (table 3). When asked about the severity of side effects, 9/46 (19.6%) patients receiving 0.4% GTN classed their side effects as severe compared with less than 4% (placebo), 2% (0.1% GTN), and 5.9% (0.2% GTN) in the other three groups of patients. This was clearly correlated with the incidence of headaches (table 3). There were no other consistent side effects noted throughout the study whose severity might have been correlated with the dosage of GTN.

MARP was assessed in one centre using solid state anal manometry catheters (n=38). The reduction in anal resting pressure increased with increasing dose of GTN. However, there was wide scatter in the reduction in anal pressures, probably reflecting the relatively small numbers of patients in whom MARP measurements were made (table 4). Six patients failed to attend for their final manometry assessment (n=32). Analysis of the reduction in anal pressures achieved using GTN or placebo did not reach statistical significance for increasing dose or for pooled GTN groups versus placebo (Fisher's exact test with Bonferroni modification, $p=0.77$).

Analysis of pain scores for the three active treatments were compared in turn with placebo, both to assess pain on defecation and overall pain scores, using ANCOVA on the ITT population. The $p$ values obtained for the differences between baseline scores and assessments at two, four, six, and eight weeks for pain on defecation using increasing GTN doses were 0.87, 0.71, and 0.40 (all NS). A similar analysis for “overall” pain scores also failed to show any significant dose dependant effect ($p$ values 0.40, 0.34, and 0.64 for increasing doses of GTN).

### Results of secondary analysis

The high incidence of healing observed in patients receiving placebo in this trial led the investigators to believe that many of the fissures included in the trial were more typical of acute rather than chronic fissures.

Chronicity of an anal fissure may be characterised by the presence of secondary features, as listed in table 5.

Therefore, a secondary analysis of patients reported to have at least two (or more than one) of five features of chronicity were analysed for the end point of complete healing after eight weeks by GTN therapy versus placebo. A subset of patients eligible for the ITT analysis (36/181 (19.8%)) showed only one secondary criterion for chronicity (sentinal skin tag or hypertrophied anal papillae). By excluding patients with only one feature of chronicity, a comparison of the complete healing rates between active and placebo treatments yielded a significant result for 0.1% GTN and for 0.4% GTN ($p=0.05$), as did the test for trend for all GTN treatments versus placebo ($\chi^2$ test, $p=0.03$) (table 6). In the primary analysis, the proportion of fissures which healed using 0.4% (56.7%) was slightly greater than the proportion of healing on 0.1% (50.0%) and greater than on 0.2% (36.1%). The placebo response in the secondary analysis decreased to 24.3% compared with the placebo response in the primary analysis (37.5%) which might indicate that many of these fissures were “acute” rather than “chronic”.

### DISCUSSION

This was a large multicentre randomised trial investigating the efficacy of topical GTN in the treatment of anal fissures and demonstrated a similar healing rate to that reported in our original randomised trial using eight weeks of treatment with topical 0.2% GTN. We have demonstrated that in truly chronic anal fissures, topical GTN ointment will heal over 50% of fissures without surgical intervention. However, the unexpectedly high healing rate in the placebo group (37%) has precluded any conclusions from the dose ranging part of the trial.

The major side effect with topical GTN therapy is headache; no other significant side effects were seen. The severity of the headache with topical GTN therapy appears to be dose dependent; patients using 0.4% GTN had a higher dropout rate which adversely affected compliance in this group. Although it

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Frequency of adverse events by treatment group (intention to treat population)</th>
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<tbody>
<tr>
<td>Adverse event</td>
<td>Placebo (n=48)</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>Headache (n [%])</td>
<td>6 (12.5%)</td>
</tr>
<tr>
<td>Severe headache (n [%])</td>
<td>2 (4.2%)</td>
</tr>
</tbody>
</table>

$\chi^2$ test for trend, glyceryl trinitrate (GTN) versus placebo ($\chi^2=50.5$, $p<0.0001$).

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Reduction in anal pressure with dose-response to glyceryl trinitrate (GTN)</th>
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<tbody>
<tr>
<td>Treatment group</td>
<td>Baseline anal resting pressure</td>
</tr>
<tr>
<td>----------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>Placebo</td>
<td>110.9 (49.2) [n=9]</td>
</tr>
<tr>
<td>0.1% GTN</td>
<td>110.3 (61.3) [n=11]</td>
</tr>
<tr>
<td>0.2% GTN</td>
<td>88.2 (46.5) [n=11]</td>
</tr>
<tr>
<td>0.4% GTN</td>
<td>101.7 (56.2) [n=7]</td>
</tr>
</tbody>
</table>

Values are mean (SD) cm H$_2$O.
is postulated that such headaches diminish with persistent use and that an increasing dosing regimen can negate the worst of these side effects, experience in this study would suggest that the difference in healing rates between 0.1% and 0.4% would not merit using the higher strength ointment. Pharmacological studies of the dose-response curve for topical GTN are difficult to determine as GTN is broken down into mono- and dinitrates, which are also pharmacologically active and are also relatively unstable, making serum assays difficult (M Jonas, personal communication).

For fissures with two or more of the accepted features of chronicity, the present study has demonstrated a significant benefit of GTN. The results of the secondary analysis might indicate that formulations containing 0.1% GTN could be effectively used in chronic anal fissure.

The primary aim of this study was to demonstrate the efficacy of GTN treatment against placebo with the secondary aim of defining an optimal dose for efficacy. These aims were not achieved, largely due to the high rate of fissure healing in the placebo group (37.5%). Other single centre studies have reported a healing rate of 3–10% in placebo treated groups. This provides an important lesson for future trials in this condition. The most likely explanation for the high rate of healing with placebo in this study is that some of the fissures included in the present study were more typically acute than chronic. While this effect might also be expected to lead to a higher healing rate in the GTN groups, the difference between active treatment and placebo is diminished, thereby reducing the power of the study (global comparison of GTN v placebo, p=0.3). The finding that 0.2% GTN had lower healing rates than either 0.4% or 0.1% GTN was also unexpected but pharmaceutical analysis has not revealed any error in manufacture, and in those patients undergoing manometric analysis (n=26) the PP pressure reduction was less than with 0.4% GTN is likely to be pharmacologically correct. This is also supported by the manometric data which showed that the 0.2% gel was pharmacologically active. On this basis we conclude that the most likely explanation for this anomalous healing rate is the relatively small difference in healing rates between the different GTN groups and it is our impression that with a larger sample size in each group this anomaly would probably disappear.

In the analysis of the ITT population, we believe that the loss of 16/197 (8%) patients from the ITT population due to failure to reattend for follow up (and therefore assessment of healing) after starting their randomised treatment makes the outcome in these patients uncertain and therefore they were excluded from the analysis. In a worst case scenario one might assume that all 16 were receiving GTN rather than placebo and that all had failed to heal. This would reduce the healing rate from 46.6% to 41.6% and the comparison of GTN versus placebo would remain non-significant (p=0.4). In this worst case scenario, one might conclude that the 0.4% GTN group is smaller than the other groups because more patients defaulted, but this is not the case. A quirk of the randomisation process resulted in the 0.4% GTN group containing 46 patients compared with 51 or 52 in the other groups; the default rate was equally spread across all four treatment groups, including the placebo group (see fig 1).

Two other published trials have reported a lower healing rate using topical GTN where a course of only four weeks of treatment led to healing in only 10–30% of chronic fissures. The experience from the present study might offer two explanations for the variable results obtained in other trials. We conclude that the cut off of chronicity at six weeks is probably inadequate and chronicity needs to be redefined in the design of future placebo controlled trials in this condition. Inclusion of fissures which do not have features of chronicity will inevitably increase the proportion of fissures which heal spontaneously and therefore increase the healing rate in both treatment and placebo groups, but this is likely to cause a reduction in the differential healing rate between active and placebo arms leading to under powering of the trial. It is our experience that less than eight weeks of treatment with topical GTN is likely to be unsuccessful in truly chronic fissures as it takes chronic fissures this period of time to heal, indeed some fissures may only partially heal within eight weeks but will fully heal if treated for longer. Some fissures which initially heal on GTN will recur within 12 months but respond to further courses of GTN.

In conclusion, topical GTN remains the most widely used non-surgical treatment for chronic anal fissure. It is generally regarded as being effective in the treatment of both acute and chronic fissures. However, its complex pharmacology is limiting the development of optimal therapeutic strategies.

A more stringent definition of “chronicity” in anal fissures is required for clinical trials in this condition. We suggest that this should probably be revised from six to 12 weeks’ duration of symptoms plus the presence of at least two of the recognised features of chronicity.

ACKNOWLEDGEMENTS

This study would not have been possible without the help of a number of individuals in the participating centres. We would therefore like to extend their thanks to all of the following: Marion Jonas, Bill Speake, Keith Neal, and Shiela Hodgson, University Hospital, Nottingham; W Brühl, Darmklinik, Vlotho-Exter; M Dunlop, Western General Hospital, Edinburgh; B Eichmann, Praxis, Hamburg; T Eisenbach, Praxis, Leverkusen; C Görlitz-Burmeister, Praxis, Hamburg; J-U Kirsch, Enddarmzentrum Mannheim; DW Lange, Praxis, Köln; R Miltz, Praxis, Saarbrücken; KP Nugent, Southampton General Hospital, Southampton; V Olivier, Praxis, Berlin; G Osterholzer, Praxis, München; W Pfeiffer, Praxis, Bietigheim-Bissingen; HH Rehm, Praxis, Lippstadt; and J Kind, project statistician, Parexel GmbH, Berlin.

Sponsored by Dr Falk Pharma GmbH, Freiburg, Germany.

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**Table 6** Secondary analysis (intention to treat population) after excluding fissures with one of five features of chronicity. Complete healing assessed after eight weeks of treatment with glyceryl trinitrate (GTN) or placebo

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Proportion healed (%)</th>
<th>95% CI</th>
<th>p value v placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>9/37 (24.3%)</td>
<td>0.12-0.41</td>
<td>0.05</td>
</tr>
<tr>
<td>0.1% GTN</td>
<td>21/42 (50.0%)</td>
<td>0.34-0.66</td>
<td>0.05</td>
</tr>
<tr>
<td>0.2% GTN</td>
<td>13/36 (36.1%)</td>
<td>0.21-0.54</td>
<td>0.05</td>
</tr>
<tr>
<td>0.4% GTN</td>
<td>17/30 (56.7%)</td>
<td>0.37-0.75</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Using the Bonferroni method, p values were adjusted for multiple testing: χ² test for trend, GTN versus placebo (χ²=4.5, p=0.03)

Only 145/181 ITT patients were available for this evaluation (in 36 patients “features of chronicity” were not completed by the investigator).
Conflict of interest: The authors wish to point out that this study was conducted in a double blind and randomised fashion and was sponsored by Dr Falk Pharma. The data monitoring and data collection was undertaken by an independent commercial group, paid by the sponsors. Tabulation and initial statistical tests were performed by the sponsors and have subsequently been verified and finalised by an independent statistician.

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A Harold, Enddarmzentrum Mannheim, Germany

On behalf of the GTN study group (see acknowledgements).

REFERENCES
8 Carapeti EA, Kamm MA, Phillips RK5. Glyceryl trinitrate heals anal fissures, high doses do it quicker, but there is a high recurrence rate. Gastroenterology 1998;114:A7, (poster G0026).