European Heart Journal (2014) **35**, 895–903
doi:10.1093/eurheartj/eht384



# Efficacy of the long-acting nitro vasodilator pentaerithrityl tetranitrate in patients with chronic stable angina pectoris receiving anti-anginal background therapy with beta-blockers: a 12-week, randomized, double-blind, placebo-controlled trial

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*Received 22 February 2013; revised 11 August 2013; accepted 26 August 2013; online publish-ahead-of-print 26 September 2013*

**Background** The organic nitrate pentaerithrityl tetranitrate (PETN) has been shown to have ancillary properties that prevent the development of tolerance and endothelial dysfunction. This randomized, double-blind, placebo-controlled, multicentre study ('CLEOPATRA' study) was designed to investigate the anti-ischaemic efficacy of PETN 80 mg b.i.d. (morning and mid-day) over placebo in patients with chronic stable angina pectoris.

**Methods and results** A total of 655 patients were evaluated in the intention-to-treat population, randomized to PETN (80 mg b.i.d., $n = 328$) or placebo ($n = 327$) and completed the study. Patients underwent treadmill exercise tests at randomization, after 6 and 12 weeks of treatment. Treatment with PETN over 12 weeks did not modify the primary endpoint total exercise duration (TED, $P = 0.423$). In a pre-specified sub-analysis of patients with reduced exercise capacity (TED at baseline $\leq 9$ min, $n = 257$), PETN appeared more effective than placebo treatment ($P = 0.054$). Superiority of PETN over placebo was evident in patients who were symptomatic at low exercise levels ($n = 120$; $P = 0.017$). Pentaerithrityl tetranitrate 80 mg b.i.d. was well tolerated, and the overall safety profile was comparable with placebo.

**Conclusion** Although providing no additional benefit in unselected patients with known coronary artery disease, PETN therapy, administered in addition to modern anti-ischaemic therapy, could increase exercise tolerance in symptomatic patients with reduced exercise capacity.

**Keywords** Pentaerithrityl tetranitrate • Chronic stable angina • Total exercise duration • Organic nitrate

## Introduction

Coronary artery disease (CAD) is the predominant cause of death in most developed countries. The most common manifestation of this disease is chronic stable angina pectoris, a clinical syndrome characterized by discomfort in the chest, jaw, shoulder, back, or arm typically aggravated by exertion or emotional stress.

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With respect to treatment of patients with chronic stable angina, guidelines differentiate among drugs which relieve acute angina pectoris (such as short-acting nitrates), drugs that may improve prognosis (such as statins, ACE-inhibitors, and aspirin, or, in the secondary prevention, beta-receptor blockers), and drugs that can be added for patients who remain symptomatic despite therapy with the other classes of agents (such as calcium antagonists, beta-receptor blockers, and long-acting organic nitrates).[1]

Pentaerithrityl tetranitrate (PETN) is a long-acting nitrate vasodilator used in the treatment of angina pectoris. Similar to nitroglycerin (GTN), it is the nitric acid ester of a polyalcohol, in this case pentaerithrityl instead of glycerine.

Recent pre-clinical and clinical studies have established that, rather than a homogeneous class, organic nitrates represent a heterogeneous group of substances that differ greatly with respect to side effects such as the induction of nitrate tolerance and endothelial dysfunction (for review see Munzel *et al.*[2]). Although ISDN, ISMN, and GTN have been documented to cause tolerance[3–5] and endothelial dysfunction[6–8] mainly due to the pro-oxidant effects of these compounds, the organic nitrate PETN was shown to be deprived of these side effects,[9] and it actually improved endothelial function in an animal model of diabetes mellitus.[10] This favourable profile may be due to the up-regulation of antioxidant enzymes such as the heme-oxygenase-1, thereby preventing the development of tolerance and endothelial dysfunction. Furthermore, PETN has been associated with increased numbers and improved function of circulating endothelial progenitor cells,[11] and it has been shown to have protective properties similar to those of ischaemic pre-conditioning.[12,13]

The current trial is the largest to date to investigate the effects of long-term therapy with an organic nitrate, PETN, when compared with placebo, in patients with stable angina pectoris undergoing therapy with beta-blockers and/or ivabradine.

# Methods

The trial (CLEOPATRA study) was designed as a phase III, randomized, double-blind, placebo-controlled, multicentre trial. A total of 127 centres were initiated in Belarus, Bulgaria, Georgia, Germany, Hungary, Iceland, India, Poland, Romania, Russia, and Serbia (only 95 centres recruited at least one patient). The study was approved by all relevant competent authorities and received a favourable opinion from all responsible independent ethics committees. All patients gave voluntary written informed consent.

## Patient selection

Patients were included in the study if all the following criteria were satisfied: (i) voluntary informed consent in writing; (ii) age $>18$ years; (iii) history of stable effort angina for $>3$ months prior to study entry; (iv) clinical stability; (v) CAD documented by at least one of the following: history of myocardial infarction (Q-wave and/or cardiac enzyme elevation) at least 3 months before inclusion, coronary angioplasty at least 6 months before inclusion, bypass graft at least 3 months before inclusion, coronary angiography showing a significant stenosis (at least 50% relative diameter reduction in the proximal two-thirds of at least one of the major coronary arteries), exercise-induced reversible ischaemia in patients without left bundle branch block, a positive stress echocardiography showing regional wall motion abnormalities or no improvement in left ventricular ejection fraction under exercise; (vi) no ST-segment abnormality in a 12-lead electrocardiogram (ECG) at rest, *and* no bundle branch block or conditions precluding ST-segment interpretation at rest or during exercise, *and* sinus rhythm; (vii) at least four angina pectoris attacks in the 4-week period preceding randomization; (viii) compliance to treatment (calculated compliance $\geq$85%, with less than one full daily placebo dose missed during the placebo run-in period); (ix) a positive and repeatable exercise treadmill test (see definition below).

### Exclusion criteria

Exclusion criteria comprised: recent acute infarction or bypass surgery, unstable angina, significant valvular disease, hypersensitivity to nitrates, anticipated revascularization procedures, incapacity to perform an exercise test, significant left main stem stenosis, congestive heart failure NYHA III–IV, symptomatic hypotension, uncontrolled hypertension, atrial fibrillation, flutter, pacemaker or implantable defibrillator, ECG abnormalities confounding the interpretation of ST-changes, hepatic and electrolyte disorders, anaemia, thyroid disorders, treatment with amiodarone, use of digitalis, inability to suspend therapy with long-acting nitrates or calcium antagonist prior to inclusion, treatment with phosphodiesterase-5 inhibitors, hepatitis B, C, or HIV infection, psychiatric disorders, use of an investigational drug within 30 days of inclusion in the study, malignant disease, pregnancy or breast feeding, participation in another clinical trial, and poor compliance.

## Study protocol

The study design is depicted in *Figure 1*. Before randomization, patients were requested to return to the study centres on two occasions. During the 'inclusion visit', the criteria listed above were evaluated and therapy with long-acting nitrates and calcium-channel antagonists was suspended for at least four half-lives. During the 'selection visit', the first exercise treadmill test was performed. All patients were then administered placebo tablets to be taken b.i.d. (single-blind placebo run-in period) for 1 week, after which ('randomization visit', V0) a second ETT was performed. At this point, patients were randomized to receive PETN 80 mg or placebo b.i.d. (8 a.m. and 1 p.m.). Background antianginal therapy with beta-blockers, ivabradine, ACE-inhibitors and/or angiotensin receptor blockers, statins, and diuretics was protracted as indicated. Patients, investigators, central readers of the ETT data, and the sponsor were blinded to the treatment received by the patients. After 6 weeks and 12 weeks of therapy, a third (6-week ETT, 'control visit', V1) and fourth ETT (12-week ETT, 'end of trial visit', V2) were performed. At each visit, data on the frequency of angina attacks and consumption of short-acting nitrates were collected from patient diaries and standard questionnaires. Patients also underwent a physical examination as well as sampling of blood chemistry and haematology prior to randomization (selection visit) and at the end of the trial (V2). 12-lead ECGs at rest were performed on each visit. Concomitant treatment with long-acting nitrates and calcium antagonists or substances that would interfere with the interpretation of the ECG such as antiarrhythmic agents and digitalis was considered to be an exclusion criterion.

## Exercise treadmill tests

In order to reduce the variability in test performance, two ETTs were performed before randomization using a modified Bruce treadmill ergometer protocol. A positive ETT was defined as occurrence of limiting angina with ST-segment depression of at least 1 mm (horizontal or down sloping and persisting for at least 0.08 s after J-point, on at least three consecutive complexes) between 2.5 and 12 min of initiation of an ETT (between 2.5 and 9 in the first version of the protocol, later extended to 12 min to accelerate recruitment). The ECG changes had to be present in both ETTs performed before randomization with a difference of $<$20% in total exercise duration (TED) between visits. If one of the two ETTs was interrupted for any reason other than limiting angina, the patient was not included.

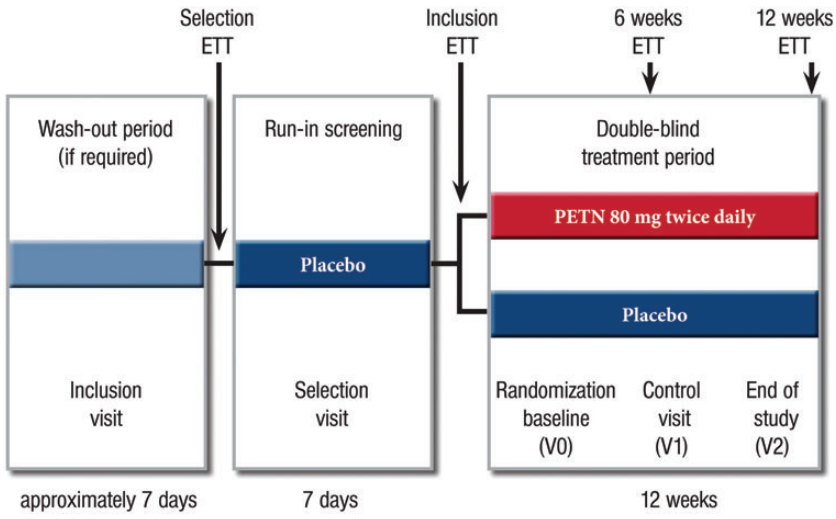



**Figure 1** Study protocol. All patients underwent four exercise treadmill tests: the first at the moment of enrolment into the study, the second 1 week later after a 7-day patient-blinded run-in period during which they received placebo treatment. The third and fourth treadmill tests were performed at 6 and 12 weeks into treatment.

## Exercise testing

All ETTs were performed at the end of the first daily dosing interval, i.e. 5 h after the intake of the morning dose. Symptom-limited ETTs (modified Bruce protocol[14]) were performed using calibrated treadmill ergometers. All ECG data were analysed centrally by a physician blinded to the patients' treatment and not involved in other study procedures. The following intervals were documented in seconds: time to onset of angina (TAP); time to limiting angina (exercise duration beyond which the patient would not be able to continue with the exercise due to anginal pain, TLA); time to 1 mm ST-segment depression (TST), as defined by a horizontal or down-sloping ST-segment for $>0.08$ s after the J-point; TED (indications for terminating exercise testing were based on the clinical criteria by Gibbons *et al.*[15]). Smoking and short-acting nitrates were prohibited for at least 2 h before the exercise test.

## Endpoints

The trial endpoints used in the current trial are in accordance with the EMA guideline CPMP/EWP/234/95 (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003316.pdf). Primary efficacy endpoint was the change in TED (in seconds) after 12 weeks of treatment with PETN 80 mg b.i.d. compared with placebo b.i.d. assessed in the trough between the morning and the mid-day dose (i.e. at 5 h after intake of morning dose of trial medication). Secondary efficacy endpoints included changes in TED (seconds) after 6 weeks of treatment as well as the following (at 6 and 12 weeks): TAP, TLA, TST, exercise capacity (METs), angina attack frequency (according to patient diary), concomitant use of short-acting nitrates (according to patient diary), health-related quality of life scores using the Seattle Standard Questionnaire and the EQ-5D; the patient's perceived exertion level was recorded using the Borg scale.

## Statistical analysis

All the data were collected using an electronic case report form and analysed by an independent statistician based on a pre-defined statistical analysis plan. The analysis of efficacy was performed for the intention-to-treat (ITT) population with regard to primary and secondary efficacy endpoints. All patients who received at least one dose of study medication and had at least one post-baseline efficacy measurement were included in the ITT population. Non-completers were included in the ITT population, using the last-observation-carried-forward approach. In addition, all analyses were performed on the per-protocol population as secondary efficacy analyses. Safety data were presented for the safety population, which includes all patients who received at least one dose of study medication.

The primary efficacy endpoint 'change in TED after 12 weeks' and the secondary efficacy endpoints were analysed using an analysis of covariance (ANCOVA), including country, treatment, use of anti-anginal background therapy as fixed class effects and baseline TED (ETT before randomization) as a covariate.

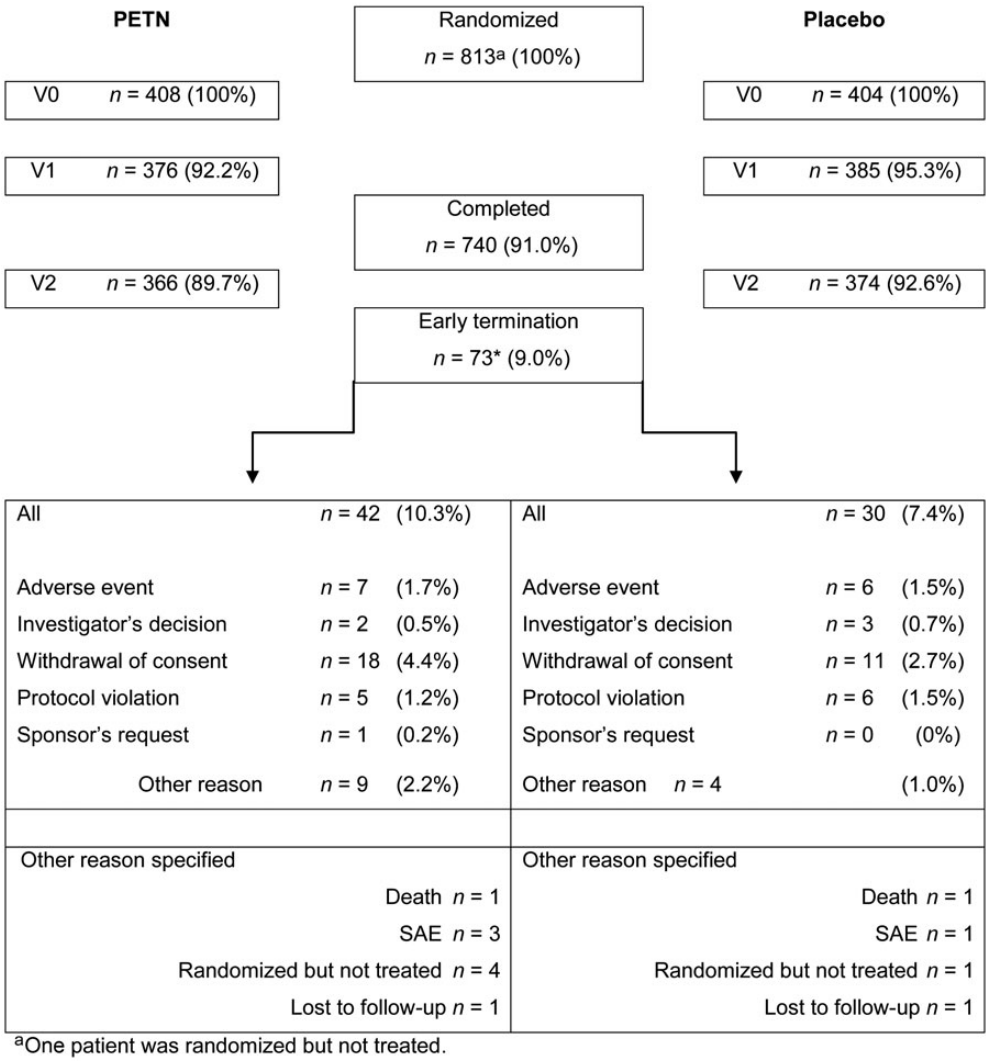
Subgroup analyses were carried out on the ITT population restricted to the change in TED, TAP, and TST from randomization to week 12. Subgroup analyses included country and anti-anginal background therapy, gender, age ($<$ or $>65$ years), TED at baseline (divided in quartiles), comorbidities (diabetes mellitus, hypertension, hyperlipidaemia as well as smoking habits), protocol version (version 1 allowing inclusion of patients with a baseline TED $\leq 9$ min only, version 2 extending this limit to 12 min). Since long-term therapy with organic nitrates is generally applied in symptomatic patients, the same analysis was performed in a subset of patients meeting the following criteria: TED at inclusion between 2.5 and 9 min; occurrence of more than one angina attack during the run-in week; consumption of more than one dose of short-acting nitrates during the run-in week.

With a one-sided significance level of 0.025 and anticipated 90% power, power calculations showed that 350 patients in each treatment group (700 overall) were needed to detect an anticipated therapeutic effect of 41.5 s for PETN vs. placebo (SD assumed: 169 s). Statistical analyses were performed using SAS® version 9.2.

# Results

The study started on 5 August 2009 and ended on 11 October 2011 (last patient last visit).

**Table 1** **Patient distribution**




[a]One patient was randomized but not treated.

## Patients characteristics

A total of 813 patients were randomized to double-blind treatment with PETN 80 mg b.i.d. or placebo on Visit 0 (408 to PETN, 404 to placebo, and 1 was randomized in error and was excluded from further procedures; see *Table 1*). Although 740 patients (91%) completed the trial, 72 patients (9%) terminated the trial early due to adverse events (13), investigator decision (5), withdrawal of consent (29), protocol violation (11), sponsor request (1), or other reasons (death: 2; serious adverse events: 4; randomized but not treated: 5; lost to follow-up: 2). The ITT population comprised 655 patients (328 on PETN, *Table 2*) after exclusion of patients with one or more of the following: no ETT at 6 and 12 weeks, $n = 39$; failure to recognize exclusion criteria like stability criterion, $n = 45$; maximum TED time longer than allowed for inclusion in the study, $n = 42$; or ECG criteria (e.g. left bundle branch block), $n = 46$. All patients had documented CAD. In the ITT population, 32.3% of the patients in the PETN group and 36.7% in the placebo group had a previous myocardial infarction; respectively, 25 and 23.2% had undergone a revascularization procedure (percutaneous or surgical). The other patients had contraindications to revascularization, a revascularization was anatomically or technically impossible, refused intervention, or where on a waiting list. Therapy with beta-blockers or ivabradine was used by 87.8% of the ITT population (*Figure 2*) without differences between groups. Similarly, age, sex, body mass index, ethnicity, the prevalence of smoking, alcohol use, diabetes mellitus (27%), hypertension (79.7%), congestive heart failure (NYHA class I and II, 0.8%), and hyperlipidaemia (40.9%), other co-morbidities as well as the use of concurrent medical conditions were similar between groups. Clinical characteristics of the patients randomized but excluded from the ITT analysis for one of the reasons above are presented in Supplementary material online, *Table S1*. The median duration of the wash-out period was 1 day (mean 3.5 days in the PETN and 3.2 days in the placebo group). There was no difference in the length of the double-blind treatment period (placebo: 85.3 vs. PETN: 85.4 days). The drop-out rate was also similar between PETN and placebo (72 patients in total, 10.3%

**Table 2** **Baseline characteristics, intention-to-treat set, *n* = 655**

| | PETN 80 mg (*n* = 328) | Placebo (*n* = 327) | Total |
|---|---|---|---|
| Age (years), mean ± SD | 62.9 ± 9.04 | 62.9 ± 8.54 | 62.9 ± 8.79 |
| Ethnicity, *n* (%) | | | |
| Asian | 69 (21.0) | 67 (20.5) | 136 (20.8) |
| Black | 0 | 1 (0.3) | 1 (0.2) |
| White | 258 (78.7) | 259 (79.2) | 517 (78.9) |
| Other | 1 (0.3) | 0 | 1 (0.2) |
| Sex, *n* (%) | | | |
| Male | 245 (74.7) | 248 (75.8) | 493 (75.3) |
| Female | 83 (25.3) | 79 (24.2) | 162 (24.7) |
| Weight (kg), mean ± SD | 78.2 ± 14.06 | 79.5 ± 14.97 | 78.8 ± 14.53 |
| Height (cm), mean ± SD | 167.9 ± 9.38 | 168.5 ± 9.36 | 168.2 ± 9.37 |
| BMI (kg/m$^2$), mean ± SD | 27.6 ± 3.86 | 27.9 ± 3.96 | 27.7 ± 3.91 |
| Waist circumference (cm), mean ± SD | 97.9 ± 11.08 | 99.0 ± 12.35 | 98.5 ± 11.73 |
| Pulse (b.p.m.) at baseline prior to the start of ETT, mean ± SD | 75.8 ± 14.56 | 75.0 ± 13.51 | 75.4 ± 14.04 |
| Anti-anginal background treatment, *n* (%) | 285 (86.9) | 290 (88.7) | 575 (87.9) |
| Diabetes, *n* (%) | 90 (27.4) | 87 (26.6) | 177 (27.0) |
| Hypertension, *n* (%) | 266 (81.1) | 256 (78.3) | 522 (79.7) |
| Hyperlipidaemia, *n* (%) | 146 (44.5) | 122 (37.3) | 268 (40.9) |
| Tobacco consumption, *n* (%) | | | |
| Current | 47 (14.3) | 43 (13.1) | 90 (13.7) |
| Former | 110 (33.5) | 112 (34.3) | 222 (33.9) |
| Never | 171 (52.1) | 172 (52.6) | 343 (52.4) |
| Congestive heart failure (NYHA class I or II), *n* (%) | 2 (0.6) | 3 (0.9) | 5 (0.8) |
| Alcohol consumption, *n* (%) | | | |
| Current | 106 (32.3) | 119 (36.4) | 225 (34.4) |
| Former | 16 (4.9) | 21 (6.4) | 37 (5.6) |
| Never | 206 (62.8) | 187 (57.2) | 393 (60.0) |

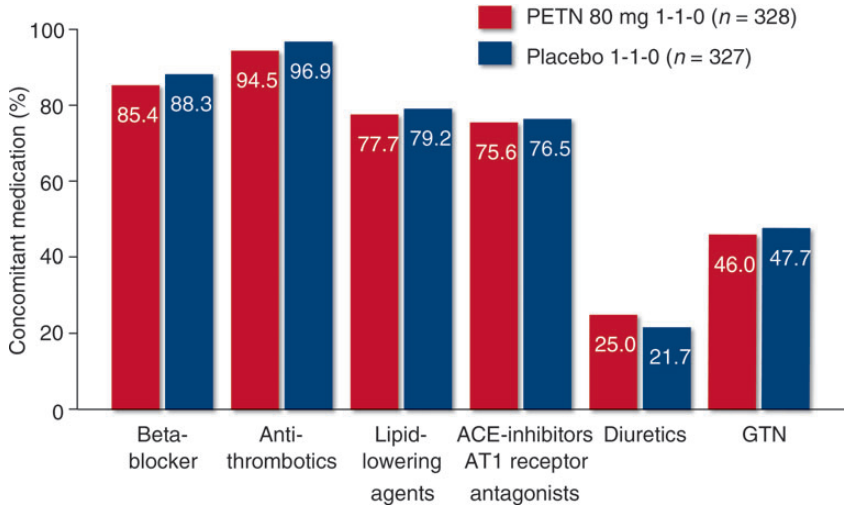



**Figure 2** Concomitant medical therapy during the trial.

**Table 3 Summary statistics (mean, standard deviation) for total exercise duration (total exercise duration in seconds) including change from baseline by treatment and visit, ITT set ($n = 655$)**

| Treatment | Visit | n | Absolute result | | Change from baseline | |
|---|---|---|---|---|---|---|
| | | | Mean | Standard deviation | Mean | Standard deviation |
| PETN 80 mg | Day −7 | 328 | 544.5 | 149.12 | | |
| | Day 0[a] | 328 | 549.6 | 144.50 | | |
| | Week 6 | 324 | 604.9 | 158.85 | 54.6 | 95.00 |
| | Week 12 | 313 | 631.3 | 166.41 | 78.0 | 118.35 |
| | Endpoint[b] | 328 | 627.3 | 167.20 | 77.7 | 119.11 |
| Placebo | Day −7 | 327 | 552.4 | 141.93 | | |
| | Day 0[a] | 327 | 560.5 | 137.28 | | |
| | Week 6 | 323 | 613.2 | 155.23 | 53.2 | 100.75 |
| | Week 12 | 311 | 632.6 | 158.20 | 68.3 | 107.52 |
| | Endpoint[b] | 327 | 628.4 | 163.48 | 67.9 | 108.46 |

[a]Baseline was Day 0 results of ETT.
[b]Endpoint takes all patients of the ITT set into account using the last-observation-carried-forward approach for non-completers.

of those on PETN and 7.4% of those on placebo). Withdrawal of consent was the most frequent reason for early termination (4.4% after PETN and 2.7% after placebo). There were two deaths (one in each group); the prevalence of serious and severe adverse events is described in *Table 1*. These events were evaluated by an external data safety monitoring board and none was judged as being related to the study medication. In total, 13 patients on PETN and 12 on placebo did not complete the 12 weeks of treatment and were included with their 6-week efficacy observation.

## Compliance with treatment

At the end of the treatment, in both groups, the median percentage of tablets taken by subjects was 100, with a mean of 99.4% (range 98.8–126%) under PETN and a mean of 99.6% (range 98.8–123%) under placebo.

## Efficacy

The data are presented in *Table 3* and in Supplementary material online. There was no difference between groups in any of the parameters before randomization. In the ITT population, TED improved after 12 weeks of treatment with PETN 80 mg b.i.d. by 77.7 ± 119.1 s and after placebo by 67.9 ± 108.5 s. ANCOVA on treatment differences including the variables described above as covariates showed no difference between treatments on the change in TED ($P = 0.423$). The covariates baseline TED and country, however, significantly affected the change in TED ($P < 0.0001$). These two factors showed an interference, i.e. differences between PETN and placebo for TED after 12 weeks were most pronounced in Russia (54.6 s) and Romania (39.4 s), where patients entered the study with baseline TED lower than the overall mean of the study. For the analysis of the effect of TED at inclusion, TED was categorized according to its quartiles in the ITT population (<7:40 min, between 7:40 and 10 min, and >10 min, with 10 min representing the median value). Patients included with lower TEDs at baseline showed more pronounced changes over the 12-week treatment with PETN and placebo when compared with those with higher TEDs at baseline.

A trend towards larger improvements in TED, TAP, and TST in the PETN group when compared with the placebo group was observed when the pre-specified analysis including only patients with a baseline TED ≤9 min, i.e. based on the original study protocol, was performed. When only these patients were included in the analysis ($n = 257$), TED improved by 120.5 s after PETN, whereas it increased by 88.6 s in those randomized to placebo; the difference between PETN and placebo with regard to change in TED after 12 weeks of treatment was 31.9 s (range −0.6 to 64.4; $P = 0.054$) in favour of PETN. Changes in TAP were also more pronounced in the PETN group than in the placebo group (134.8 vs. 104.4 s, $P = 0.11$). The change in TST was similar between groups, with 102.7 s in the PETN group and 92 s in the placebo group ($P = 0.585$).

## Sub-analysis in symptomatic patients

For the analysis of the effects of PETN in patients with refractory angina despite background anti-anginal therapy, subjects reporting at least two angina pectoris attacks and taking two doses of short-acting nitrates per week and with a baseline TED ≤9 min were selected. A total of 120 patients, 55 on PETN and 65 on placebo, met these criteria. Demographic characteristics in this subpopulation were similar to those of the ITT population and not different between groups. In this group of patients with distinct and clinically relevant symptoms of angina pectoris, the change in TED at 6 and 12 weeks was markedly larger in the PETN group than in the control group (*Figure 3*, $P = 0.05$ and $P = 0.017$). Similarly, changes in MET, TAP, TLA, and TST at 12 weeks in this group of symptomatic patients were markedly larger in the PETN group (respectively, $P = 0.03$, $P = 0.05$, $P = 0.003$, *Figures 4* and *5*). Finally, the frequency of angina pectoris attacks decreased after both PETN and placebo (a decrease in the angina stability scale was observed in 24.5% of those randomized to PETN and in 12.7% of those randomized to placebo; change in the angina frequency scale—PETN: 21.4%; placebo: 15.7%). The use of short-acting nitrates decreased in both groups

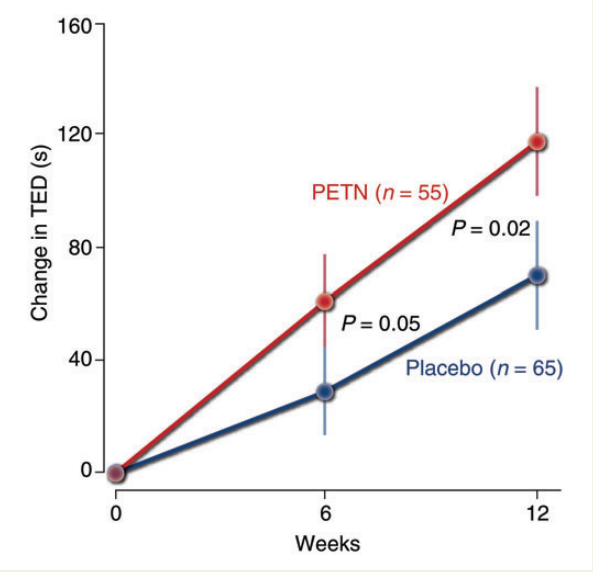



**Figure 3** In the subgroup of patients with refractory angina pectoris (defined as at least two episodes of angina per week, self-administration of at least two doses of sublingual nitrates per week, and total exercise duration ≤9 min), the change in total exercise duration at 6 and 12 weeks was markedly larger in the pentaerithrityl tetranitrate group than in the control group. ANCOVA means are presented with 95% confidence intervals. The change from baseline was 118.2 s in the pentaerithrityl tetranitrate group and 69.9 s in the placebo group at 12 weeks. A difference between pentaerithrityl tetranitrate and placebo was already observed at week 6 with an improvement of 61.2 s in the pentaerithrityl tetranitrate group and 28.8 s in the placebo group.

(PETN: −1.7 doses/week, median −2; placebo: −2.5 doses/week, median −2).

# Discussion

Therapy with organic nitrates is commonly used in the management of patients with angina pectoris, and the current guidelines encourage the use of long-acting nitrates in patients who remain symptomatic despite appropriate anti-anginal therapy with beta-blockers.[1,16,17] The major limitation of nitrate therapy, however, is that, due to the development of nitrate tolerance, it can only be applied on a 12 h intermittent basis, thus typically providing no protection during night hours and exposing patients to rebound phenomena.[18–23] A number of possible approaches have been proposed to address this issue, including co-administration of compounds aimed at limiting the oxidant effects of GTN and other nitrates, as well as the use of nitrates with independent antioxidant properties. PETN is an organic nitrate that has been shown to induce the expression of the antioxidant enzyme heme-oxygenase-1[24] and that, in human studies, has been shown to be deprived of the side effects common to other nitrates, including the induction of nitrate tolerance[25] and endothelial dysfunction.[9] To date, the anti-ischaemic efficacy of this drug has not been studied in large multicentre clinical trials.[26,27]

## Summary of the findings

The CLEOPATRA study was designed to investigate the anti-anginal efficacy of PETN administered on top of a background anti-ischaemic therapy. Patients enrolled received appropriate anti-anginal therapy with a beta-blocker or ivabradine with add-on PETN 80 mg b.i.d. or placebo. The study was run as a multicentre, randomized, double-blinded placebo-controlled trial with centralized analysis of data and

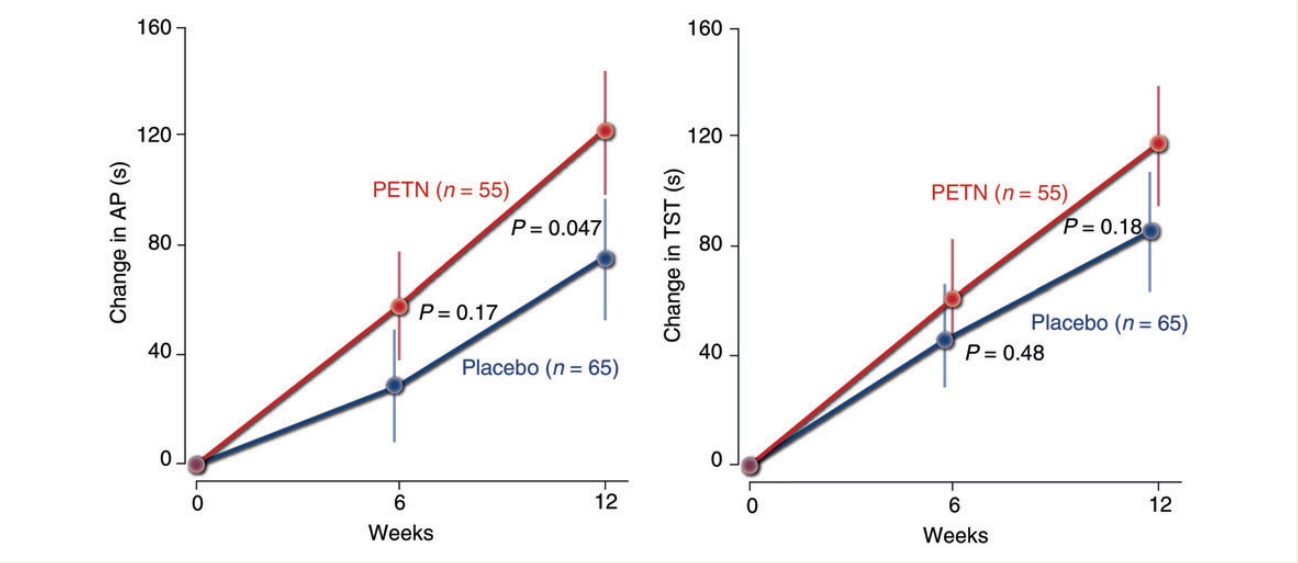



**Figure 4** In the subgroup of patients with refractory angina pectoris, the change in TAP at 12 weeks was markedly larger in the pentaerithrityl tetranitrate group than in the control group. The changes in TST tended to be larger in the pentaerithrityl tetranitrate group. ANCOVA means with 95% confidence intervals.

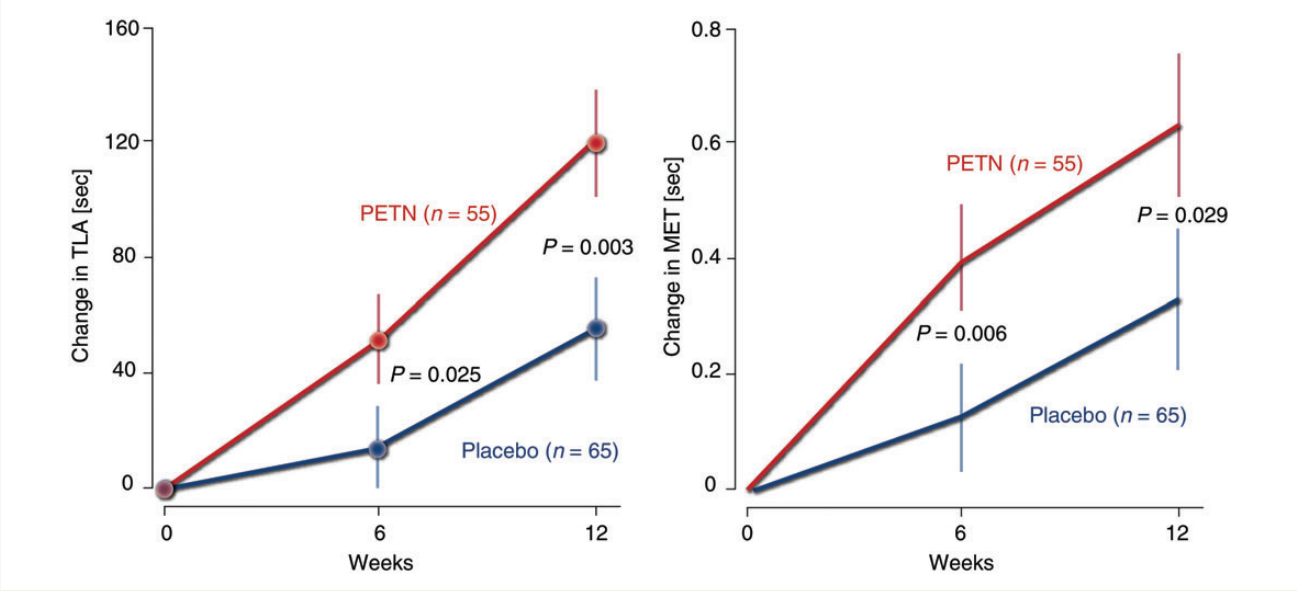



**Figure 5** In the subgroup of patients with distinct and clinically relevant symptoms of angina pectoris, the changes in TLA and MET at 6 and 12 weeks were markedly larger in the pentaerithrityl tetranitrate group than in the control group. ANCOVA means with 95% confidence intervals.

safety assessment, and the primary efficacy endpoint was the change in TED after 12 weeks of treatment. As expected, an important placebo (or time) effect was shown for all endpoints. When the analysis included the whole population of patients enrolled into the study, no difference was shown between PETN and placebo for any of the endpoints. Notably, an analysis that included the baseline TED as a covariate evidenced that the benefit of PETN was more pronounced in those patients who had a lower TED at randomization. In line with this, a clear superiority of PETN over placebo was demonstrated with regard to all clinically relevant efficacy endpoints in the subset of patients showing low exercise capacity and distinct symptoms of angina pectoris.

## Comparison with other anti-anginal agents

In the trial by Tardif *et al.*,[28] patients were randomized to receive ivabradine or placebo given in combination with atenolol 50 mg o.d. Although it needs to be emphasized that differences between designs and populations complicate any direct comparison between different trials, at 16 weeks, TED increased by 24.3 $\pm$ 65.3 s in the ivabradine group compared with 7.7 $\pm$ 63.8 s in the placebo group.[28] Remarkably, in the present study, the difference in the increase in TED observed in the subgroup of patients with baseline exercise capacity $<$9 min and anginal symptoms was as large as 32 s at 6 weeks and it reached 48 s in favour of PETN at 12 weeks. Similarly, combination therapy with the metabolic agent ranolazine administered on top of atenolol (50 mg/day), amlodipine (5 mg/day), or diltiazem (180 mg/day) in patients with severe angina pectoris resulted in an improvement in TED, although in this case the changes in time to ST-segment depression were not significant.[29] In contrast, therapy with different calcium-channel antagonists did not show benefit on TED when administered as an add-on to beta-blockers.[30–32]

## Limitations

There are several limitations that need to be acknowledged. The study was designed as an international multicentre trial, and the specific settings in which organic nitrates are used might not be the same among countries. For instance, the access to percutaneous revascularization varies significantly among countries due to differences in the availability of facilities and reimbursement policies. This is one of the possible explanations for the observed differences among countries in the effect of PETN. Also, we based the study design on the recommendation of the CPMP/EWP/234/95 (http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003316.pdf) (the difference between the two ETTs performed before randomization had to be $<$20%). Enforcing a smaller threshold would have made recruitment more difficult and the study less representative of the real world, but would have reduced intra-individual sources of variability. Finally, the large number of patients excluded from the analysis (detailed above under Patient characteristics) and the drawbacks of interpreting (positive) results of a subgroup from an overall negative trial are acknowledged.

# Conclusions

Nitrates are still commonly used as add-on therapy in patients who remain symptomatic despite administration of beta-blockers or calcium-channel antagonists. Although they are generally considered to belong to a homogenous class without relevant differences among molecules, important differences have been recently shown between PETN, on the one side, and GTN and isosorbide compounds, on the other.[2] The current trial formally addressed the anti-anginal effect of PETN. Although having no significant effect on exercise capacity in unselected CAD patients, PETN may provide an additional benefit as add-on therapy in selected symptomatic patients.

# Supplementary material

Supplementary material is available at *European Heart Journal* online.

## Acknowledgements

The study was designed and supervised by an independent steering committee, organized by a contract research organization (Kendle GmbH, Stefan-George Ring 6, 81929 Munich, Germany) and a medicines development support company (Pharmaplex bvba Avenue Saint-Hubert 51, 1970 Wezembeek-Oppem, Belgium) with the support of independent biostatisticians (Kendle GmbH and M.A.R.C.O. GmbH & CO. KG, Moskauerstr. 25, 40227 Duesseldorf, Germany). The central ECG reading facility was coordinated by Prof. U. Tebbe, Klinikum Lippe-Detmold, Klinik für Innere Medizin II, Roentgenstr. 18, 32756 Detmold, Germany.

## Funding

The CLEOPATRA study was sponsored by Actavis Deutschland GmbH&Co. KG.

**Conflict of interest:** H.T.S., Member of PETN advisory board, D.S has been Medical Director for Actavis. T.M, T.M and T.G. received speaker's honoraria and grant funding from Actavis.

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