TITLE OF TRIAL:	**Safety of the oral monophasic contraceptive GRT4248 (0.02 mg ethinylestradiol/2 mg chlormadinone acetate) in comparison to 0.02 mg ethinylestradiol/0.15 mg desogestrel given for 6 medication cycles**
SPONSOR/COMPANY:	**Grünenthal GmbH, 52099 Aachen, Germany**
COORDINATING INVESTIGATOR:	**Milano, Italy**
TRIAL CENTER(S):	**Thirty-three centers in total: 11 in Germany, 4 in Spain, 5 in France, 6 in Italy, 2 in Portugal, 5 in Russia**
PUBLICATION (REFERENCE):	**Not applicable**
TRIAL PERIOD (YEARS):	First subject enrolled: 08 NOV 2005 Last subject completed: 16 AUG 2006 Data-base lock 24 OCT 2006
PHASE OF DEVELOPMENT:	**Phase III**

OBJECTIVES:

To determine the safety of 0.02 mg ethinylestradiol/2 mg chlormadinone acetate, given for 24 days each 28-day cycle in comparison to 0.02 mg ethinylestradiol/0.15 mg desogestrel given for 21 days each 28-day cycle. Each investigational medicinal product (IMP) was to be taken for 6 cycles.

METHODOLOGY:

Randomized, multicenter, double-blind, desogestrel-controlled, parallel group, multiple administration, Phase III trial

NUMBER OF SUBJECTS:

Subjects were allocated by randomization to two medication groups, one receiving 0.02 mg ethinylestradiol/2 mg chlormadinone acetate (the GRT4248 group) and one receiving 0.02 mg ethinylestradiol/0.15 mg desogestrel (the EE/DSG group). The planned and actual sizes of the two groups were:

Medication group	Planned	Enrolled	Randomized and Entered	Evaluated		
				Safety set (treated)	Full analysis set	Per protocol set
GRT4248	200	201	201	196	195	165
EE/DSG	200	200	200	195	194	173

NUMBER OF DROP-OUTS:

Reason for withdrawal (multiple entry possible)	Medication group			
	GRT4248		EE/DSG	
	N	%	N	%
Overall	**36**	**18.4**	**26**	**13.3**
Adverse events	15	7.7	8	4.1
Informed consent withdrawn *	4	2.0	4	2.1
Loss to follow-up	6	3.1	6	3.1
Protocol deviation	5	2.6	6	3.1
No wish to continue trial medication	3	1.5	1	0.5
Bleeding abnormalities	1	0.5	1	0.5
Irregular bleeding	4	2.0	1	0.5
Pregnancy	1	0.5	0	0
Move	1	0.5	0	0
Other reason	3	1.5	1	0.5

* If the subject stated a reason for withdrawal of informed consent, then this is listed here instead.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:

Trial indication:

Oral contraception

Main criteria for inclusion:

- Healthy, sexually active women of child-bearing potential aged 18–40 years (non-smokers) or 18–35 years (smokers) on admission; women using nicotine replacement were considered smokers.
- Last 3 cycles before admission were regular (i.e., cycle length between 24–35 days).
- Laboratory values showed no deviations from normal range of clinical relevance for the trial in the opinion of the Investigator.
- Negative pregnancy test.
- Wish for contraception for 6 cycles.
- Body-mass index (BMI) $\leq$30 kg/m^2.
- Written informed consent given.

INVESTIGATIONAL MEDICINAL PRODUCT(S):

Test product	GRT4248 (active ingredients: 0.02 mg ethinylestradiol (EE) and 2 mg chlormadinone acetate (CMA)) encapsulated for blinding
Dose	In each 28-day medication cycle, once daily for 24 consecutive days followed by a hormone-free interval (administration of placebo) of four days.
Mode of administration	Oral
Batch number	E3128-004 and E3128-015
Duration of medication	Six 28-day medication cycles
Comparator product	EE/DSG (Lovelle®) (active ingredients: 0.02 mg EE and 0.15 mg desogestrel (DSG)) encapsulated for blinding
Dose	In each 28-day medication cycle, once daily for 21 consecutive day followed by a hormone-free interval (administration of placebo) of seven days.
Mode of administration	Oral
Batch number	E3128-003 and E3128-013
Duration of medication	Six 28-day medication cycles
Placebo	Matching placebo capsules with no active ingredient
Dose	See above
Mode of administration	Oral
Batch number	E3128-002 and E3128-014
Duration of medication	See above

CRITERIA FOR EVALUATION:

Since there was no single criterion of outstanding importance for the safety evaluation several endpoints were evaluated.

Endpoints:

- Adverse events (AEs).
- Cycle control.
- Effect on body weight.
- Dysmenorrhea.

STATISTICAL METHODS:

Sample size

With 200 subjects per medication group the estimate for an adverse event with an incidence of 1% would be within the range [0%; 2.4%] with 95% confidence.

Analysis

All data acquired in this trial were analyzed by standard descriptive statistics (N, mean, standard deviation, minimum, median, maximum and first and third quartiles), or by absolute and relative frequencies as appropriate. The following populations were analyzed:

- The 'safety set', comprising all subjects who received at least one dose of randomized IMP.
- The 'full analysis set', a subset of the safety set comprising all subjects who were not pregnant at the time of first intake of IMP; individual cycles were excluded from this analysis if the medication cycle was after conception, or if no bleeding data were available.
- The 'per-protocol set', derived from the full analysis set by excluding subjects who had no assessment of bleeding data, or of body weight, or of dysmenorrhea in medication cycle 6. In addition, subjects missing data at cycle 6 for one or two of the endpoints were excluded from the respective analyses but not from the per protocol set as a whole, and individual medication cycles were excluded under certain exactly defined conditions (in summary: certain deficiencies in compliance, or gastrointestinal conditions likely to affect uptake of medication).

SUMMARY:

This clinical trial was designed to evaluate adverse events, effect on dysmenorrhea, cycle control, gynecological findings, return to fertility, pregnancy, laboratory evaluation, vital signs and body weight of GRT4248 in comparison to EE/DSG over 6 cycles. All results are given for the safety set except those for cycle control which are given for the full analysis set.

Adverse events

At least one AE was reported for 156/196 (79.6%) of the subjects in the GRT4248 group and for 147/195 (75.4%) of those in the EE/DSG group.

There was no substantial difference between the medication groups in respect of the frequency pattern of AEs within the various SOCs.

The most common AEs in both groups were the same; however, as to be expected for a trial with a small number of subjects, their relative frequencies differed to some extent. AEs affecting more than 10% of subjects, listed in order of frequency for GRT4248, were headache, breast discomfort, metrorrhagia, nausea, vaginal discharge, fatigue, and dysmenorrhea. These AE types were expected to occur during the intake of any combined oral contraceptive (COC). The general profile of AEs reported for both IMPs is in broad agreement with those seen for other low-dose hormonal oral contraceptives. The majority of AEs was judged to be mild or moderate; 6.8% (74/1085) of AEs in the GRT4248 group and 12.0% (118/980) in the EE/DSG group were rated as severe. Most AEs (77.9% in the GRT4248 group, 76.7% in the EE/DSG group) did not require any countermeasures; when used, the two medication groups were very similar with respect to the countermeasures taken.

The incidence of AEs in both medication groups was highest in the first cycle, decreasing with subsequent cycles during continuation of intake of the IMP. AEs at least possibly related to the medication were reported for 112/196 (57.1%) of the subjects in the GRT4248 group, compared with 99/195 (50.8%) in the EE/DSG group. Breast discomfort, headache, metrorrhagia, and nausea in the GRT4248 and EE/DSG group were the most common 'at least possibly related' AEs with a relative frequency greater than 10%. No AE was judged to be certainly caused by the intake of GRT4248 or EE/DSG.

The most frequently reported unexpected AEs in the GRT4248 group were common complaints such as nasopharyngitis, followed by cystitis and influenza. Unexpected AEs considered at least possibly related to GRT4248 were recorded for 4 subjects.

Two serious adverse events (SAEs) occurred. Both SAEs were rated by the Investigator as unrelated to the IMP. No suspected unexpected serious adverse reaction (SUSAR) or AE of special interest occurred during the trial. No deaths occurred during this trial.

Effect on dysmenorrhea

GRT4248 appeared to have a positive effect on the symptoms of dysmenorrhea. The absolute and relative numbers of subjects reporting dysmenorrhea since the previous visit was lower in the GRT4248 group than in the EE/DSG group at cycle 3, and at cycle 6.

The proportion of subjects reporting increased severity of dysmenorrhea, the number of subjects using pain medication, and the number of days when pain medication was used was also markedly lower for the GRT4248 group than for the EE/DSG group.

Cycle control

Cycle control was analyzed both by reference period and by cycle.

Analysis by reference period

GRT4248 and EE/DSG showed good cycle control based on the reference periods of 84 days.

The mean number of bleeding days in the first and second reference periods was comparable in the two medication groups. The mean number of days with heavier bleeding was greater in the EE/DSG group than in GRT4248 group in both reference periods. Mean numbers of bleeding episodes in the two reference periods were comparable for the two medication groups. The length of bleeding episodes was very similar in the two medication groups and reference periods. The length of bleeding-free intervals (one or more consecutive days without bleeding; each interval is bounded by at least one bleeding day) was slightly shorter in the GRT4248 group than in the EE/DSG group. The length of bleeding segments (a bleeding episode and the immediately following bleeding-free interval) was slightly, but consistently, shorter in the GRT4248 group than in the EE/DSG group.

Analysis by cycle

The occurrence of withdrawal bleeding and the occurrence of intermenstrual bleeding were analyzed by cycle. Withdrawal bleeding was less frequent in the GRT4248 group (82.9%) than in the EE/DSG group (92.4%). The duration of withdrawal bleeding was comparable in the two groups. Withdrawal bleeding was heavier in the EE/DSG group: moderate and heavy bleeding in the EE/DSG group was documented in 69.7% of the cycles compared to 54.1% in the GRT4248 group. Intermenstrual bleeding was more frequent in the GRT4248 group than in the EE/DSG group. The rates of spotting and of break-through bleeding reflected the rates of intermenstrual bleeding for the respective medication groups.

Gynecological findings

Gynecological findings, including Papanicolaou status, did not reveal any notable findings or differences between the two medication groups.

Return to fertility

The item 'return to fertility' was not analyzed as no subject withdrew due to a wish to conceive.

Pregnancy

One pregnancy was reported in a subject taking GRT4248.

Laboratory evaluation

Changes in the mean values and ranges of laboratory values (for hematology, coagulation and clinical chemistry) were small and did not show any trends that might be associated with the medication in either group. No conspicuous differences were seen between the medication groups. Changes in laboratory variables for individuals revealed no notable findings. In both medication groups, small increases in mean laboratory values were observed for cholesterol, LDL, HDL and triglyceride levels.

Vital signs and body weight

Vital signs, weight, and BMI were monitored and analyzed, without any notable findings or any clear differences between the two medication groups. Weight changes as seen in this trial were well within the range of seasonal variation and thus have no clinical relevance. In this trial, weight gains were reported as AEs in only few cases, and only 1 subject in the GRT4248 group and 3 in the EE/DSG group left the trial prematurely because of a weight increase.

Sub-group analysis

The above analyses were also performed using the subgroups 'non-smoker', 'smoker', 'ex-smoker', and 'starter', 'switcher'. The results observed for these subgroups were comparable to those presented above.

CONCLUSION:

The results of this trial show that the combined oral contraceptive GRT4248 is well tolerated; and that its AE profile and cycle control is comparable to that of the comparator EE/DSG (Lovelle®) and other COCs. GRT4248 was found to have a particularly beneficial effect on women suffering from dysmenorrhea. The number of COC-related AEs and the incidence of intermenstrual bleeding decreased over the six medication cycles as expected. The results of this trial investigating the safety of GRT4248 do not give rise to any safety concerns.

Date of report: 04 MAR 2007