Synopsis of study report: 98/2002
Location in Module 5:

Study Code:
BY217/FHP035

Report Version:
1.0 (dated 22 April 2003)

Title of the study:

Investigation of the effects of repeated oral doses of 500 µg roflumilast on male reproductive parameters in healthy subjects - a double-blind, placebo controlled, randomized, parallel-group study

Study center(s):

FARMOVS-PAREXELl, 9300 Bloemfontein, South Africa
SACT, 6529 George, South Africa
Andrology Unit, Department of Urology, 0001 Pretoria, South Africa
Parexel GmbH, 14050 Berlin, Germany
Swiss Pharma Contract, 4123 Allschwil, Switzerland

Publication (reference):

Not applicable

Studied period (years):

10 months (2001 to 2002)

Clinical phase:

Phase I

Objectives:

Primary: Effects of 500 µg roflumilast on male reproductive parameters.

Secondary: Effects of 500 µg roflumilast on

- Male reproductive hormones;
- Safety and tolerability.

Methodology:

Standardized semen samples were collected and analyzed according to WHO criteria.

No. of subjects (total and for each treatment):

A total of 466 subjects was enrolled into the study. A total of 351 subjects was randomized at visit V0, 174 to roflumilast and 177 to placebo. A total of 304 subjects completed the study, 149 in the roflumilast- and 155 in the placebo group. A total of 273 subjects was eligible for the per-protocol analysis, 132 in the roflumilast- and 141 in the placebo group.

Diagnosis and criteria for inclusion:

Healthy male subjects, aged 18 to 45 years with sperm concentration $> 20 \times 10^6$/ ml and progressive motility > 50 % (grades a + b) at visits SC, B0 and B1 were eligible for inclusion.

Test product:

Roflumilast

Dose:

500 µg s.i.d.

Mode of administration:

oral

Batch No.:

101160

Duration of treatment:

12 weeks

Reference product:

Placebo

Dose:

Not applicable

Mode of administration:

Oral

Batch No.:

101160

Criteria for evaluation:

Primary variable: Percentage of subjects in each group (roflumilast or placebo) with 'clinically significant abnormalities' of sperm concentration or progressive motility after a standardized abstinence period of between 72 to 96 hours.

Secondary variables:

- Semen parameters (volume, viscosity, sperm concentration, total sperm number, progressive motility, total motility, sperm morphology, % alive sperm cells)
- Male reproductive hormones (testosterone, FSH, LH, inhibin B)
- Plasma trough levels of roflumilast and roflumilast-N-oxide
- Safety and tolerability parameters

Statistical methods:

Primary variable: Descriptive statistics, and explorative test for non-inferiority, based on dichotomized sperm concentration and progressive motility. A non-inferiority acceptance limit of 0.2 was used.

Secondary variables: Descriptive statistics.

SUMMARY - CONCLUSIONS

Summary:

Semen results: Equivalent effects were shown for the roflumilast- and placebo group (41 % vs. 45 %) with respect to the incidence of at least one 'clinically significant abnormality' according to Definition 1 (> 50 % decrease from baseline sperm concentration or progressive motility during the treatment and follow-up period). With respect to the incidence of at least one 'clinically significant abnormality'

according to Definition 2 (> 60 % decrease in sperm concentration from baseline or baseline dependent decrease in progressive motility during the treatment and follow-up period), equivalent effects were also shown for the roflumilast- and placebo group (36 % vs. 37 %). Hence, no adverse treatment effect of roflumilast was found with respect to the percentage of subjects with 'clinically significant abnormalities' in semen variables.

Safety results:

A total of 631 adverse events was reported in 238 subjects (70.7 % in the roflumilast- vs. 65.0 % in the placebo group). In the roflumilast group, subjects with headache (30.5 % vs. 16.4 % in the placebo group), diarrhoea (16.1 % vs 7.3 % in the placebo group), nausea (8.6 % vs. 2.8 % in the placebo group)' and 'back pain' (5.7 % vs. 1.7 % in the placebo group) were more frequently reported as adverse events. Also, subjects with 'definite' or 'likely' related adverse events were more frequently found in the roflumilast group (29.9 % vs. 11.9 % in the placebo group). A total of 5 subjects discontinued the study due to adverse events (1.7 % in the roflumilast- vs. 1.1 % in the placebo group). A total of 5 subjects reported serious adverse events (1.1 % in the roflumilast- vs. 1.7 % in the placebo group). No deaths were reported during the course of the study.

No differences were found between the roflumilast- and placebo group for variables of male reproductive hormones, clinical chemistry, hematology, and the ECG, as well as blood pressure and pulse rate.

Plasma trough level of roflumilast-N-oxide revealed that all subjects included in the per-protocol analysis were adequately exposed to either roflumilast or placebo. Also, no correlation was found between the plasma trough level of roflumilast-N-oxide, and sperm concentration or progressive sperm motility.

Conclusions:

No adverse treatment effect of roflumilast on sperm concentration or progressive sperm motility was found. 500 µg roflumilast per day for 12 weeks was safe and well tolerated in healthy men.