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Evaluation of different loading dose regimens for subcutaneous and intramuscular injection of a teverelix depot formulation in healthy male volunteers

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Introduction

Teverelix (TEV) is a GnRH antagonist with low histamine release and acceptable water solubility (Deghenghi et al, 1993) which may be useful to achieve gonadal suppression in patients suffering from prostate cancer and benign diseases such as Benign Prostatic Hypertrophy (BPH), endometriosis (End) and uterine fibromyomas (UF). Recently, a new TEV-trifluoroacetate (TFA) microcrystal formulation was developed, which showed in rats a prolonged inhibitory effect over a period of more than two months. This is dramatically longer than what was observed with microgranules formulation (about one week).
The aim of these studies was to evaluate a loading dose regimen in order to achieve complete hormonal suppression (testosterone; T) immediately after starting the treatment.

Objective

Two studies were performed:

A. Intramuscular (IM) injection:
The primary objective of this study was:
to assess the pharmacokinetics (PK) of TEV-TFA 90 mg administered intramuscularly

as a single dose	(n=6)
2 times 48 h apart	(n=6)
2 times 7 days apart	(n=6)
compared to placebo	(n=6)

B. Subcutaneous (SC) injection
The primary objective of this study was:
to assess the PK of TEV-TFA 60 mg administered subcutaneously

2 times 48 h apart	(n=6)

to assess the PK of TEV-TFA 90 mg administered subcutaneously

2 times 48h apart	(n=6)
2 times 24h apart	(n=4)
3 times 24h apart	(n=6)
compared to placebo	(n=8)

Secondary objectives of both studies were:
- to assess the pharmacodynamic (PD) effects on pituitary (LH and FSH) and gonadal (T) functions
- to assess the general and local safety and tolerability

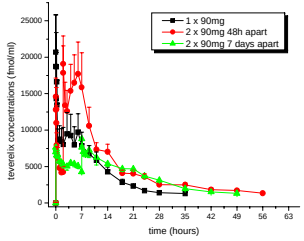
Study Methods

Both studies were single-center, randomized, single-blind, placebo-controlled, repeat dose trials.
Subjects: healthy male subjects, age 18 – 45 years
SC injections were given into the lower abdominal wall, IM injections into the buttocks.
TEV depot consists of microcrystals of TEV-TFA which are suspended in suspension liquid (D-mannitol 5% solution). TEV was supplied as 45 mg lyophilisate vials to be reconstituted (2 per dose) in 0.6 ml of suspension liquid. To reach the doses of 60 or 90 mg a volume of 0.80 or 1.20 ml, respectively was administered.
For assessment of PD effects, serum concentrations of FSH, LH and T were determined. Only T-data are reported here. Blood samples for TEV and hormone determination were drawn up to 1344h after administrations.

Results

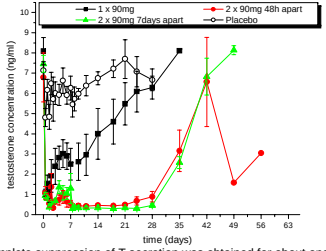
TEV injections were well tolerated by the subjects. With subcutaneous administration the most frequently reported adverse events were mild to moderate injection site reactions (induration; redness and itching) and transient in nature. With intramuscular administration injection site reactions were rare (n=2) and these were mild and transient in nature.

A. Intramuscular Injection
Mean plasma concentration of TEV (fmol/ml)



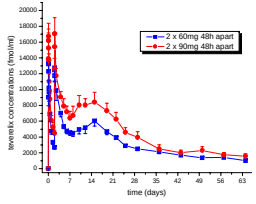
Results cont.

The corresponding mean (±SEM) T data (ng/ml) are given in the following figure:



Complete suppression of T secretion was obtained for about one month with the two treatments:
2 times 90mg 48h apart and
2 times 90mg 7 days apart

B. SC Injection
Mean (±SEM) plasma concentration of TEV (fmol/ml)

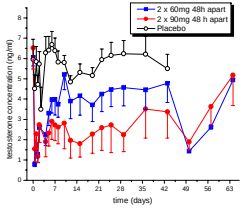


*) Median (min,max)

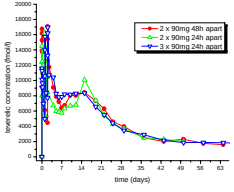
Testosterone concentrations could be significantly inhibited during the first 2-3 days.

Results cont.

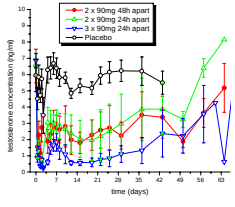
Mean (±SEM) testosterone concentrations (ng/ml)



Mean (±SEM) TEV concentrations (fmol/ml)



Mean (±SEM) testosterone concentrations (ng/ml)



Results cont.

It has been demonstrated that by varying the dose and the intervals between dosing of TEV, results in varying degree and duration of suppression of testosterone to either castrate levels (<0.5 ng/ml) or low normal range.

Conclusion

TEV-TFA depot injections given either IM or SC are well tolerated. The inhibitory effects of TEV-TFA injections on testosterone secretion are more pronounced after IM than after SC injection.

The different pharmacokinetic and pharmacodynamic profiles of TEV-TFA when administered either IM or SC provide the opportunity for tailoring the TEV-TFA dosing regimen for different indications. Suppression of T to castrate level (<0.5 ng/ml) and dose-dependent reduction of T have been demonstrated and justifies the further development of TEV-TFA for the treatment of prostate cancer; and BPH; End and UF respectively.

References

Deghenghi, R.et al Biomed. & Pharmacother. 47, 107-110.