SYNOPSIS REPORT

Study number HMR4003B/4027

Title

A Randomized Multicenter Parallel Group Study to Determine If Knowledge of Baseline Vertebral Fracture Prevalence (as Determined by Hologic Instant Vertebral Assessment) and Bone Turnover Marker Levels Improves Persistence with Actonel® 5 mg Daily Therapy in Subjects Receiving Chronic Glucocorticoid Therapy

Investigator(s), study site(s):

Multicenter study with multiple investigators, 42 sites

Study duration and dates	Duration Per Subject (planned): 12 months First Subject First Visit: 27 July 2002 Last Subject Last Visit: 6 December 2004	**Phase** IV

Objectives

The objective of the study was to determine whether subject knowledge of baseline vertebral fracture prevalence and awareness of results of bone turnover marker (BTM) determinations would result in an increase in persistence with Actonel 5 mg daily therapy as determined by electronic caps.

Study design

This was a 12-month, multi-center, open-label to drug, single-blinded (subject blinded to randomization) study in which subjects were randomized with a 1:1 allocation into one of two groups:

- INFO+ subjects were informed of instant vertebral assessment (IVA), BTM, and BMD determinations. Subjects were required to have at least a 50% decrease from baseline in urinary NTx or OST to qualify for a positive message, and a similar increase in urinary NTX or OST to qualify for a negative message.
- INFO- subjects were informed of BMD determinations, but were not informed of IVA and BTM determinations.

This randomization was stratified by site and steroid treatment (i.e. new [prevention (Px) stratum] or chronic treatment with steroids [treatment (Tx) stratum]), so that the intervention was balanced within both site and steroid treatment.

This trial was also called the ACTIVATE (ACTonel In the prevention and treatment of glucocorticoid induced osteoporosis (GIO) using Vertebral Assessment TEchnology) trial.

Number of subjects planned

350

Inclusion criteria

- Ambulatory male and female subjects, 30-85 years old, inclusive with a variety of rheumatologic, pulmonary, and skin conditions.
- Subjects were to be on oral glucocorticoids with a mean daily dose of ≥5.0 mg prednisone (or its equivalent) and were expected (although not required) to remain on a daily dose of ≥5.0 mg prednisone (or its equivalent) for 12 months after the study started.
- Women must have been at least one year post-menopausal or surgically sterile.
- Subjects must have had evaluable BMD site at the lumbar spine (LS) and proximal femur.
- Subjects unable to open study medication with the child-resistant TrackCap closure could be included in the study provided that an adult in the subject's household was able and willing to open and close the medication for the subject every morning throughout the treatment period.

Treatments

Actonel 5 mg orally once daily (OD), calcium 500 mg + vitamin D 200 units twice daily (BID)

Efficacy data

Efficacy data were evaluated using the following parameters. Persistence data were evaluated using the electronic caps (3, 6, 9 and 12 months). Persistence was defined as the number of days out of 365 that a subject opened the electronic cap (see Statistical Procedures).

Safety data

Safety data were evaluated using the following parameters:

- Reported adverse events (particularly those on-treatment, assessed at 3, 6, 9 and 12 months)
- Laboratory values (screening and baseline as specified in protocol)
- Physical examination, including vital signs (screening)

Statistical procedures

Efficacy: The intent-to-treat (ITT) population was the main population for the efficacy analysis. Completer population (those ITT subjects attending the 12-month visit, Visit 6) results are also presented. Statistically significant effects are those at $p<0.05$.

The efficacy variable of interest was persistence, defined as the number of days out of 365 that a subject opened the electronic cap.

Safety: The safety population was defined as those randomized subjects who had opened the Actonel 5 mg bottle at least once as documented by the electronic cap. Incidence tables were provided for this population for adverse events for all and possibly related treatment-emergent adverse events (TEAE), by system organ class, frequency, intensity, and type of event (eg, deaths, serious adverse events, withdrawals).

Interim analysis

Only baseline data to determine the relationship of treatment practices and underlying risk factors of osteoporosis were analyzed at several times during 2003 and 2004, for abstracts presented at the American Society for Bone and Mineral Research (ASBMR) and the American College of Rheumatology (ACR) meetings. No other interim analyses were done.

Results – Study subjects and conduct

The number of subjects screened for this study was 422 at 42 sites. Of these, 75 subjects were not randomized (screening failures), and 347 subjects were randomized into the INFO+ (n=179) or INFO- (n=168) groups. The INFO+ group was informed of IVA and BTM results while the INFO- group was not. Both groups received knowledge of their BMD results. The Tx stratum consisted of 257 subjects (INFO+, n=133; INFO-, n=124) and the Px stratum consisted of 90 subjects (INFO+, n=46; INFO-, n=44).

Three major analysis populations were defined for this study. The safety population consisted of all randomized subjects who opened the Actonel bottle at least once as documented by the electronic cap (n=347). The ITT population (n=345) was defined in the protocol to include subjects who left the site with an Actonel bottle and electronic cap. Further clarification to this definition was made for analysis purposes to include the requirement that the cap had to be functioning correctly, as 2 subjects had malfunctioning electronic caps. The completer population (n=204) was defined as ITT subjects who attended the 12-month visit, Visit 6.

Results – Efficacy

The efficacy variable of interest in the ACTIVATE trial was persistence. Persistence was high for subjects in both the INFO+ and INFO- groups, with no significant differences observed based on feedback or based on strata. Therefore, intervention did not further improve persistence in this trial.

Results – Safety

Adverse events in the ACTIVATE trial were consistent with the adverse event profile reported in other studies of subjects receiving risedronate and concomitant corticosteroid therapy. The most common possibly-related adverse events in either strata were gastroesophageal reflux disease, dyspepsia, and nausea, which occurred at an incidence of 1.1%-3.1% of subjects.

Twelve subjects had 13 fractures at sites of interest where fragility fractures would typically occur. None of these fractures were assessed as related to treatment and none of these subjects withdrew from the study due to the fracture. The incidence of fractures in this open-label study is similar to what has been observed in other osteoporosis trials.

Two subjects experienced serious TEAE (restricted cardiomyopathy and respiratory failure) leading to death during the study. Of 65 subjects experiencing a serious TEAE, only 7 subjects had serious TEAE considered possibly related to treatment, primarily affecting the gastrointestinal system. Thirty-eight subjects experienced TEAE (serious or non-serious) leading to withdrawal from the study. Possibly-related TEAE leading to withdrawal were primarily in the gastrointestinal system.

Conclusions

The ACTIVATE trial evaluated the effect of subject knowledge of their disease status on persistence in subjects receiving risedronate 5 mg daily over a 12-month period for the prevention and treatment of GIO. The study subjects demonstrated very good persistence on drug during the observation period, but informing them of IVA and BTM results (INFO+ group) did not increase their persistence compared to subjects randomized to the INFO- group.

Adverse events in the ACTIVATE trial were consistent with the adverse event profile for risedronate, as reported in subjects receiving concomitant corticosteroid therapy. The most common possibly-related adverse events in either strata were gastroesophageal reflux disease, dyspepsia, and nausea, which occurred at an incidence of 1.1%-3.1% of subjects.