The REDUCE Follow-Up Study: Low Rate of New Prostate Cancer Diagnoses Observed During a 2-Year, Observational, Followup Study of Men Who Participated in the REDUCE Trial

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Purpose: The primary objective of the REDUCE (REduction by DUtasteride of prostate Cancer Events) Follow-Up Study was to collect data on the occurrence of newly diagnosed prostate cancers for 2 years beyond the 4-year REDUCE study.

Materials and Methods: The 4-year REDUCE study evaluated prostate cancer risk reduction in men taking dutasteride. This 2-year observational study followed men from REDUCE with a clinic visit shortly after study conclusion and with up to 2 annual telephone calls during which patient reported data were collected regarding prostate cancer events, chronic medication use, prostate specific antigen levels and serious adverse events. No study drug was provided and all biopsies during the 2-year followup were performed for cause. The primary objective was to collect data on the occurrence of new biopsy detectable prostate cancers. Secondary end points included assessment of Gleason score and serious adverse events.

Results: A total of 2,751 men enrolled in the followup study with numbers similar to those of the REDUCE former treatment groups (placebo and dutasteride). Few new prostate cancers were detected during the 2-year followup period in either former treatment group. A greater number of cancers were detected in the former dutasteride group than in the former placebo group (14 vs 7 cases). No Gleason score 8–10 prostate cancers were detected in either former treatment group based on central pathology review. No new safety issues were identified during the study.

Conclusions: Two years of followup of the REDUCE study cohort demonstrated a low rate of new prostate cancer diagnoses in the former placebo and dutasteride treated groups. No new Gleason 8–10 cancers were detected.

Key Words: dutasteride, prostatic neoplasms, diagnosis, biopsy, neoplasm grading

The REDUCE trial evaluated 0.5 mg dutasteride daily for prostate cancer risk reduction in men considered to be at increased risk for prostate cancer based on age (50 to 75 years old), increased PSA (2.5 to 10.0 ng/ml) and a previous biopsy negative for prostate cancer. During the 4-year study dutasteride reduced the relative risk of biopsy detectable prostate cancer by 22.8% (95% CI 15.2–29.8) compared with placebo. This reduction in pros-
tate cancer incidence was mainly observed for Gleason score 5–6 cancers.

Despite some differences in trial design, the primary findings of the REDUCE trial were similar to those of the PCPT (Prostate Cancer Prevention Trial). Investigators in the PCPT found a 24.8% reduction in the 7-year prevalence of prostate cancer with finasteride. In both trials there was an increased number of high grade (Gleason 8–10) cancers in the 5ARI treatment arms. Potential reasons for these findings include the suppression of lower grade tumors by 5ARIs, decreased prostate volume resulting in increased biopsy sensitivity for high grade cancers and the trial design of REDUCE, which led to the removal of 141 men with prostate cancers for an additional 2 years beyond the 4-year REDUCE trial. Information on SAEs was also collected.

MATERIALS AND METHODS

Study Design
The REDUCE Follow-Up Study was a 2-year observational followup of a convenience sample of men from the 4-year REDUCE trial. The primary objective was to collect data on the occurrence of new cases of prostate cancer for 2 years beyond REDUCE (Part A) and to collect biopsy material for biomarker analysis in men diagnosed during REDUCE (Part B). Part B was cancelled because of inherent limitations of biomarker analyses due to the short followup period of diagnosed subjects and no samples were collected. Only data from Part A are presented here.

Followup consisted of 1 clinic visit and up to 2 telephone calls approximately 1 year apart. For men enrolled more than 1 year after their REDUCE 4-year contact, information recorded during the year 1 and/or year 2 telephone contact was collected during the post-REDUCE clinic visit.

Patient reported data were collected regarding prostate cancer events, chronic medication use, PSA test results and SAEs. As no study drug was provided, information on nonSAEs was not recorded. In some cases in which subject reported information was incomplete, data were also obtained from available medical records or laboratory reports. There were no limitations on medications and some subjects may have been prescribed 5ARI therapy during followup.

Study Population
Subjects were eligible for study entry if they had participated for 4 years in the REDUCE study, on treatment or in followup, after withdrawing from REDUCE due to prostate cancer diagnosis or other reasons. Men who withdrew early from REDUCE were included in this population to study cancer end points and to capture events of interest if they occurred in these patients. Twelve countries that provided 76% of the REDUCE population were selected to participate in this study. All participants provided written informed consent and the protocol was approved by the institutional review board at each site.

Assessment of Prostate Biopsies and Surgeries
Biopsies or surgical samples positive for prostate cancer based on local pathology review and radical prostatectomy specimens were reviewed by a central laboratory which included confirmation of prostate cancer diagnosis and assessment of Gleason score using the classic scoring system to maintain consistency with the primary REDUCE study analysis. The Gleason scoring system used by local pathology laboratories was unknown. All biopsies were performed for cause when clinically indicated.

Study End Points
The primary end point was the occurrence of new biopsy detectable prostate cancers. Other end points included Gleason score, TNM stage, SAEs, overall survival, death from prostate cancer and change in serum PSA.

End Point Analysis
No formal statistical hypothesis tests were planned. Data were summarized overall and according to former REDUCE treatment group. New cases of prostate cancer were also summarized according to 5ARI use. The extension safety population included all subjects who were previously in the REDUCE safety population. The at risk population (primary end point population) included all subjects in the extension safety population not previously diagnosed with prostate cancer during REDUCE. The extension biopsied population consisted of all men in the at risk population who had at least 1 for cause biopsy reviewed by a local or central pathology laboratory. The extension prostate cancer population consisted of all subjects in the at risk population who were diagnosed with prostate cancer by central or local pathology.

For the primary analysis prostate cancer incidence was calculated using a crude rate approach in which all subjects in the at risk population were included. A restricted crude rate analysis was also performed which only included subjects from the extension biopsied population. Time to biopsy detectable prostate cancer was summarized using cumulative incidence estimates, treating death from causes other than prostate cancer as the competing risk.

PSA Analysis
PSA testing was performed at physician discretion and samples were analyzed by local laboratories. Changes in total PSA from baseline (REDUCE year 4 PSA value) to year 1 were summarized according to prior treatment group, prostate cancer status and 5ARI use for the at risk population. Only men who had a PSA value determined within 6 weeks of the year 1 cutoff were included in the study.

Safety Analysis
SAEs of special interest were defined as common events that could occur with 5ARIs due to their pharmacological
The effects (i.e., SAEs related to reproductive system and breast disorders) or were of special interest to regulatory agencies (cardiovascular events).

## RESULTS

### Baseline Characteristics

It was estimated that 2,700 subjects would participate in the follow-up study. The actual enrollment was 2,751 subjects, representing 65% of the 4,220 randomized REDUCE subjects at participating sites (fig. 1). Baseline characteristics of the at-risk population (men without cancer diagnosed in REDUCE) are summarized in table 1. Men in the former dutasteride group had a smaller prostate volume and lower total PSA than those in the former placebo group.

### Number of Biopsies

In the at-risk population 216 of 2,237 subjects underwent biopsy during the 2-year follow-up period (extension biopsied population). More men in the former placebo group underwent biopsy (124 of 1,071 [11.6%]) than in the former dutasteride group (92 of 1,166 [7.9%]). Increasing PSA was the most frequent reason for biopsy (76 subjects from the placebo group and 64 from the dutasteride group).

Men in the extension biopsied population had a higher median PSA at baseline than those in the at-risk population (2.9 vs 2.0 ng/ml for the former dutasteride group and 8.0 vs 6.1 ng/ml for the former placebo group).

### Table 1. Baseline characteristics of follow-up study populations

<table>
<thead>
<tr>
<th></th>
<th>Extension Safety Population</th>
<th>At Risk Population</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Former Dutasteride Group</td>
<td>Former Placebo Group</td>
</tr>
<tr>
<td>No. subjects</td>
<td>1,383</td>
<td>1,368</td>
</tr>
<tr>
<td>Subject age on Follow-up Study entry:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>66.6 (5.91)</td>
<td>66.4 (5.94)</td>
</tr>
<tr>
<td>Median (range)</td>
<td>66.0 (53–79)</td>
<td>66.5 (53–80)</td>
</tr>
<tr>
<td>No. subject race [%]:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1,309 (95)</td>
<td>1,284 (94)</td>
</tr>
<tr>
<td>Black</td>
<td>13 (less than 1)</td>
<td>11 (less than 1)</td>
</tr>
<tr>
<td>Asian</td>
<td>7 (less than 1)</td>
<td>8 (less than 1)</td>
</tr>
<tr>
<td>Hispanic American</td>
<td>54 (4)</td>
<td>65 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>No. family history of prostate cancer [%]</td>
<td>185 (13) 178 (13) 363</td>
<td>148 (13) 125 (12) 273 (12)</td>
</tr>
<tr>
<td>Median ng/ml total PSA (range):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REDUCE baseline*</td>
<td>5.6 (2.5–11.9)</td>
<td>5.6 (1.8–14.2)</td>
</tr>
<tr>
<td>Follow-up study baseline</td>
<td>2.0 (0.1–18.2)</td>
<td>3.6 (0.1–142.7)</td>
</tr>
<tr>
<td>Median % free PSA (range):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REDUCE baseline*</td>
<td>16.09 (2.1–52.9)</td>
<td>16.11 (2.1–52.9)</td>
</tr>
<tr>
<td>Follow-up study baseline</td>
<td>17.39 (2.8–72.5)</td>
<td>18.75 (4.9–83.7)</td>
</tr>
<tr>
<td>Median cc prostate vol (range):</td>
<td></td>
<td></td>
</tr>
<tr>
<td>REDUCE baseline*</td>
<td>42.88 (8.8–113)</td>
<td>42.98 (3.7–161.8)</td>
</tr>
<tr>
<td>Follow-up study baseline</td>
<td>36.19 (5.1–170.2)</td>
<td>54.14 (5.4–169.3)</td>
</tr>
<tr>
<td>Median cores sampled in baseline biopsy (range):</td>
<td></td>
<td></td>
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</tbody>
</table>

* Based on information collected from the REDUCE study.
placebo group, respectively). Furthermore, a higher proportion of subjects in the extension biopsied population underwent biopsy for cause during REDUCE compared with the at risk population (16% vs 9% for the former dutasteride group, 20% vs 11% for the former placebo group).

**Primary End Point**

**Biopsy detectable prostate cancer.** Overall the number of subjects with prostate cancer in the at risk population (after central pathology review) was 21 of 2,237 (0.9%). The prostate cancer crude rate for the former dutasteride group was 14 of 1,166 (1.2%) and for the former placebo group was 7 of 1,071 (0.7%) (fig. 2, A). The prostate cancer restricted crude rate was 15.2% in the former dutasteride group (14 of 92 subjects who underwent biopsy) and 5.6% in the former placebo group (7 of 124 subjects who underwent biopsy) (fig. 2, B).

The prostate cancer crude rate in both groups was lower in men who took a 5ARI during the followup study than in those who did not take a 5ARI, with 0 of 237 (0%) vs 7 of 834 (0.8%) subjects in the former placebo group, and 2 of 235 (0.9%) vs 12 of 931 (1.3%) in the former dutasteride group, respectively (fig. 2, C). However, the associated confidence intervals were wide. A similar trend was seen in the extension biopsied population (fig. 2, D).

In the former dutasteride group 16 men and in the former placebo group 10 men were diagnosed with prostate cancer by local pathology review. In the at risk population 5 men were diagnosed with prostate cancer by local pathology but not by central review because samples were not submitted (for 2 subjects), a reading of atypical small acinar proliferation was based on an incomplete set of slides (2 subjects) and there was a reading of no cancer (1 subject) at central pathology.

**Time to biopsy detectable prostate cancer.** The cumulative incidence curves for time to first biopsy detectable prostate cancer in the at risk population by previous treatment group and overall are shown in figure 3. The incidence of prostate cancer remained low throughout the 2-year study period overall and for both groups.

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**Figure 2.** Incidence of biopsy detectable prostate cancer in at risk population (crude rate analysis, A), in extension biopsied population (restricted crude rate analysis, B), according to 5ARI use during followup study (central pathology, at risk population; crude rate analysis, C) and according to 5ARI use during followup study (central pathology, extension biopsied population; restricted crude rate analysis, D). Error bars represent 95% CIs for incidence values.
Pathological End Points

Gleason scores. Table 2 summarizes Gleason scores for subjects diagnosed with prostate cancer in the extension biopsied population based on central pathology review. Most Gleason scores were based on needle biopsies (16 subjects) as opposed to surgical samples (5 subjects). No Gleason score 8–10 prostate cancers were diagnosed in either treatment group on central review, but 2 Gleason score 9 cancers were diagnosed in the former placebo group by local pathology review. In 1 case no slides were available for central pathology review and in the other case the cancer was downgraded to Gleason score 7 by central review.

Biopsy results and TNM staging. Overall a median of 12 cores were sampled and 1 core was positive. The percentage of core involved was low (median 5%). All prostate cancers initially diagnosed during the followup study were localized cancers (clinical stage T1 or T2, N0, M0) based on local pathology review.

Other End Points

Overall survival. No deaths from prostate cancer were reported during the followup study. There were 5 noncancer deaths in the former dutasteride group (0.4%) and 3 in the former placebo group (0.2%). Of the men who died 1 was taking dutasteride and 1 was taking finasteride at the time of death. No deaths were considered by the investigators to be drug related.

Safety and side effects. Table 3 summarizes the incidence of SAEs which was similar in both groups. SAEs that were drug related, or led to permanent discontinuation of treatment or withdrawal from the study, were rare. Most men (82% of extension safety population) did not take a 5ARI during the 2-year followup period.

No SAEs of special interest were reported for altered (decreased) libido, impotence, ejaculation disorders or breast disorders, and no cases of breast cancer were reported. The proportions of men with cardiovascular SAEs of special interest in both groups were comparable. No SAEs of special interest were reported for cardiac arrhythmias or peripheral vascular disease and the incidence of cardiac failure events was similar between the groups.

Among men who used 5ARIs 1 in the former placebo group had a SAE of cardiac failure. Other cardiovascular SAEs of special interest, including acute coronary syndrome, ischemic coronary artery disorders/atherosclerosis and ischemic cerebrovascular events, were reported by few subjects in both groups.

PSA analysis. Among the 370 men who did not use a 5ARI, the median change in PSA at year 1 in the former dutasteride group was 2.20 ng/ml for the 183 subjects not diagnosed with prostate cancer and 5.23 ng/ml for the 4 who were diagnosed. In contrast, a median PSA change of 0.7 ng/ml was recorded for the 3 patients diagnosed with prostate cancer in the former placebo group. Among the 151 men who used a 5ARI and were not diagnosed with prostate cancer,

Table 2. Incidence of biopsy detectable prostate cancer based on central pathology review (extension biopsied population, restricted crude rate analysis)

<table>
<thead>
<tr>
<th></th>
<th>No. Former Dutasteride Group (%)</th>
<th>No. Former Placebo Group (%)</th>
<th>No. Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Needle Biopsy</td>
<td>Surgery</td>
<td>Needle Biopsy</td>
</tr>
<tr>
<td>Total No. Ca (any grade)</td>
<td>10 (10.9)</td>
<td>4 (4.3)</td>
<td>6 (4.8)</td>
</tr>
<tr>
<td>Gleason 2–5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Gleason 6</td>
<td>5 (5.4)</td>
<td>3 (3.3)</td>
<td>4 (3.2)</td>
</tr>
<tr>
<td>Gleason 7: 3+4</td>
<td>5 (5.4)</td>
<td>1 (1.1)</td>
<td>2 (1.6)</td>
</tr>
<tr>
<td></td>
<td>5 (5.4)</td>
<td>1 (1.1)</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>4+3</td>
<td>0</td>
<td>0</td>
<td>1 (0.8)</td>
</tr>
<tr>
<td>Gleason 8–10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values included are the first Gleason score value for each subject within procedure type (needle biopsy, surgery). Subjects could have undergone needle biopsy and had surgery Gleason scores reported.

Figure 3. Cumulative incidence estimates of time to biopsy detectable prostate cancer (at risk population).
the median change in PSA at year 1 in the former placebo and dutasteride groups was $-2.96$ ng/ml and $0.3$ ng/ml, respectively. Because only a small proportion of men had a PSA test performed at year 1, it is difficult to draw conclusions from these data.

**DISCUSSION**

The primary objective of the REDUCE Follow-Up Study was to collect data on the occurrence of new prostate cancers after REDUCE. As previously reported, the likelihood of detecting prostate cancer decreases with the number of biopsies completed. Therefore, the overall cancer detection rate was low. More cancers were detected in the former dutasteride group than in the former placebo group (14 vs 7 cases, based on central review).

A possible reason for this difference is that any prostate cancer that may have been suppressed by dutasteride during REDUCE was no longer being suppressed for those subjects who did not continue 5ARI therapy. To some extent, observations during the followup study support this concept. In the former dutasteride group, prostate cancer rates among men who continued on 5ARIs were similar to those of men in the former placebo group who did not take a 5ARI (0.9% and 0.8%, respectively). However, a higher incidence of prostate cancer (1.3%) was observed for men in the former dutasteride group who did not continue 5ARIs (fig. 2, C). Overall, men in either former treatment arm who took a 5ARI during the followup study tended to have fewer cancers.

No new Gleason 8–10 cancers were diagnosed in either group based on central pathology review. In the former placebo group 2 subjects had Gleason score 9 prostate cancer diagnosed on local pathology review. As PSA levels increase after 5ARIs are discontinued, it was anticipated that more biopsies would be observed in subjects previously treated with dutasteride. However, there were fewer biopsies performed in the former dutasteride group than in the former placebo group (14 vs 7 cases, based on central review).

SAEs were collected to capture events of special interest in a nonbiased fashion. No new safety signals were noted and few subjects reported SAEs of...
special interest including cardiovascular events. The observed rates were similar across both groups.

Although this study provides real-world observational data for subjects who had been randomized to 4 years of dutasteride therapy, it has limitations. Men in the at risk population had a low risk of prostate cancer diagnosis due to several prior negative biopsies \(^{10-12}\) and corresponding conclusions are specific to the population studied. In addition, some men who discontinued from REDUCE early may have been off dutasteride treatment for longer than the 2-year observational period.

Differences in biopsy criteria and schedules, PSA testing schedules, PSA assays and local pathology laboratory Gleason grading procedures may have contributed to variability in the observed results. Furthermore, because of the observational nature of this study, no formal statistical hypothesis tests were conducted as subjects were not randomized into the followup study. Finally, most of the data collected was based on subject recollection.

**CONCLUSIONS**

Two additional years of followup of the REDUCE study cohort demonstrated a low rate of new prostate cancer diagnoses in the former placebo and dutasteride groups. No new Gleason 8–10 cancers were detected in the former dutasteride group (based on central pathology review). No new safety issues were identified.

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**REFERENCES**


