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

Robert L. Grubb,*,† Gerald L. Andriole,‡ Matthew C. Somerville,§ Chrysa Mahoney,§ Michael J. Manyak§ and Ramiro Castro§

From Washington University School of Medicine in St. Louis, St. Louis, Missouri (RLG, GLA), GlaxoSmithKline, Research Triangle Park, North Carolina (MCS, CM, MJM), and GlaxoSmithKline R&D, King of Prussia, Pennsylvania (RC)

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

Abbreviations and Acronyms

5ARI = 5α-reductase inhibitor

PSA = prostate specific antigen

SAE = serious adverse event

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Study received institutional review board approval.

Clinical Trial Registration NCT00883909 (www.clinicaltrials.gov).

* Correspondence: Division of Urologic Surgery, Washington University School of Medicine in St. Louis, 4960 Children's Place, Box 8242, St. Louis, Missouri 63110 (telephone: 314-454-8775; FAX: 314-454-5244; (e-mail: grubbr@wudosis.wustl.edu).

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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.[1] 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-

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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.[2] In both trials there was an increased number of high grade (Gleason 8–10) cancers in the 5ARI treatment arms.[1,2] Potential reasons for these findings include the suppression of lower grade tumors by 5ARIs,[3] decreased prostate volume resulting in increased biopsy sensitivity for high grade cancers[4–6] and the trial design of REDUCE, which led to the removal of 141 men with lower grade (Gleason 5–6) tumors from the placebo arm during the first 2 years of this study.[1] Despite these possible explanations, concerns remain about the potential risks of using these agents for prostate cancer risk reduction.[7] The primary objective of this REDUCE Follow-Up Study was to collect data on the incidence of newly diagnosed 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[8] 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,[9] 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