Design and Analysis of a Cancer Prevention Trial: Plans and Results

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Overview

- Objective: Review the planned analyses for a large prostate cancer prevention study and the corresponding observed results; methods of handling categorical time to event data; and issues encountered.

- Outline:
  - study design
  - planned analyses
  - results and issues

- Expansion of Chapter 17 "Design, Summarization, Analysis and Interpretation of Cancer Prevention Trials" in "Design and Analysis of Clinical Trials with Time-to-Event Endpoints", edited by K. Peace, CRC Press, 2009

Study Design

REDUCE (Reduction by Dutasteride of Prostate Cancer Events) Study

Primary Objective: To assess the effect of repeat oral once daily dosing of 0.5mg dutasteride compared to placebo on the risk of biopsy-detectable carcinoma of the prostate after 2 years and 4 years of treatment

Primary Endpoint: Biopsy detectable prostate cancer after 2 and 4 years of treatment

Canada

Finland

Norway, Sweden

Belgium

Netherlands

Poland, Latvia

Slovenia, Slovakia,

USA

UK, Ireland

Switzerland

Croatia, Russia

France

Austria, Germany

Japan

Portugal

Greece

Spain, Italy

Puerto Rico

Mexico

Argentina

Chile

Australia

South Africa

New Zealand

Additional countries: Belarus, Brazil, Bulgaria, Denmark, Estonia, Lithuania, Hungary, Romania, Tunisia, Turkey, Ukraine

Trial Design Considerations

Population: Subjects at increased risk of PCa
Endpoint: Biopsy proven PCa (central review)
Study control: Placebo-controlled
Blinding: Subject/investigator/sponsor blinded
Duration: 4 years – biopsies at 2 and 4 years
Sample size: 8000 subjects (4000 pbo, 4000 dut)
Power: 90% (α=0.01) after 4 years
Randomization: Center-based
Interim Analysis: Yes, at 2 years
IDMC: Yes, met every 6 months

Main Entry Criteria

- Men aged ≥50 and ≤75 yrs
- PSA 2.5–10 ng/mL (men aged <60 yrs) or 3.0–10 ng/mL (men aged ≥60 yrs)
- Single, negative prostate biopsy within six months prior to enrollment
- Prostate volume ≤80 cc

Men at increased risk of prostate cancer

Study Schematic

Single Study for Regulatory Submission

Literature indicates considerations include:
- large multicenter study with consistent effect
- consistency across subsets
- multiple studies within a study
- multiple endpoints involving different events
- statistically persuasive finding

REDUCE: $\alpha=0.001$ after 2 years, $\alpha=0.01$ after 4 years (with guidance from regulatory agencies)

Planned Analyses

Populations

Safety: Randomized subjects

Efficacy: Randomized subjects who received study drug and had negative entry biopsy per Central Pathology

Time Periods

Scheduled endpoint assessments (vs continuous)

Based on biopsy schedule, time periods were determined as follows:
- Years 1-2
- Years 3-4
- Overall (Years 1-4)

Handling of withdrawals

Method	Numerator	Denominator
Crude rate	# subjects with prostate cancer	# subjects in the efficacy population
Restricted crude rate	# subjects with prostate cancer	# subjects in the efficacy population with 1+ post baseline biopsy
Modified crude rate	# subjects with prostate cancer	# subjects in the efficacy population with PCa or an end of interval biopsy

Investigator site clusters

Pooled into clusters that:
- corresponded to interpretable factors (geographic)
- ensured at least one event per cluster
- provided approx. 5-10 expected events per cluster for
    cluster x treatment interaction

Clusters determined before unblinding using country as basic unit (some were pooled, others were split as needed)

Resulted in 33 clusters

Mantel-Cox test

Mantel-Haenszel test for treatment differences using sets of 2x2 tables having a life table format:

- – Clusters (33)

- – Time period (Years 1-2, Years 3-4)

- – Treatment (placebo, dutasteride)

- – Prostate cancer status (yes,no)

Relative risk reduction (%) computed as 100*(1- Mantel-Haenszel estimate of relative risk)

Covariates

Regression modelling done using both log-binomial and logistic regression

- log-binomial provides relative risks but sometimes can have model-fitting issues

- logistic provides odds ratios but typically has few model-fitting problems.

Timing of Analyses

Interim analysis (after two years) conducted by independent statistical group (SDC) and reviewed by IDMC; GSK blinded.

Four year analysis conducted by GSK.

Results

Timeline

First subject randomized: April 2003

Last subject randomized: January 2005

Last subject last visit: January 2009

Interim Analysis

SDC prepared summaries for the IDMC closed session meetings. Beforehand, GSK and the SDC compared results using a dummy set of treatment codes.

Based on interim analysis results after Year 2, IDMC indicated to continue trial.

Post-Baseline Biopsies

Time Period	Placebo n (%)	Dutasteride n (%)
Treatment Start to Month 18	193 (4.7)	166 (4.1)
After Month 18 to end of Yr 2	3294 (80.9)	3181 (78.6)
Start of Yr 3 to Month 42	256 (6.3)	176 (4.3)
After Month 42	2300 (56.5)	2428 (60.0)

Analysis Populations

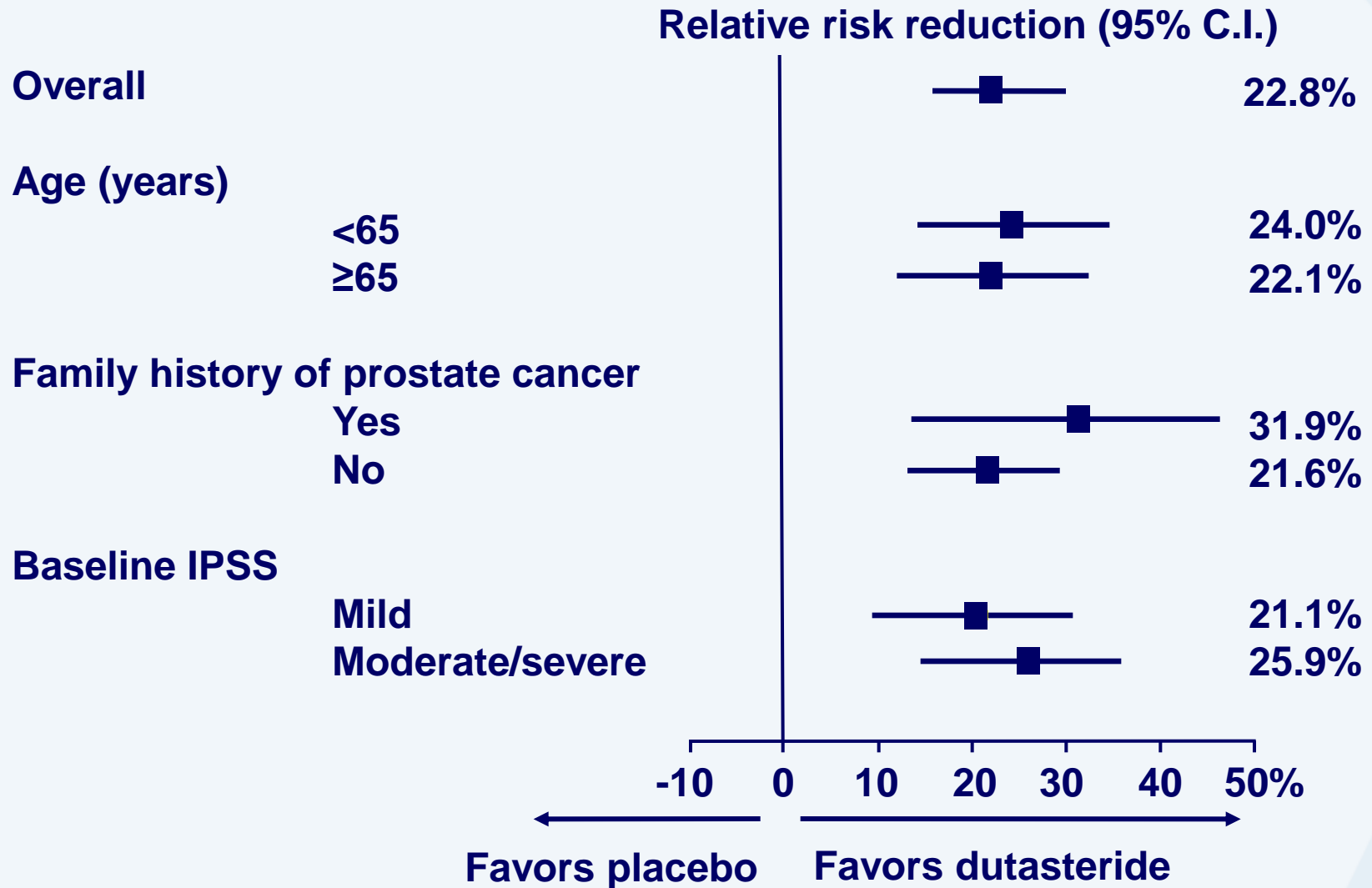|	Placebo n (%)	Dutasteride n (%)
Safety population	4126	4105
Crude rate (efficacy population)	4072	4049
Restricted crude rate (one or more biopsies)	3423 (84.1%)	3303 (81.6%)
Modified crude rate (+ biopsy or biopsy after Month 42)	2898 (71.2%)	2867 (70.8%)

4 Year Incidence and Relative Risk Reduction

	PCa		Relative Risk Reduction
	Pbo	**Dut**	
Assumption	*19%*	*15.2%*	*20.0%*
Crude rate (efficacy population)	21.0%	16.3%	23.2% (15.5%,30.2%)
Restricted crude rate (one or more biopsies)	25.0%	20.0%	22.8% (15.2%,29.7%)
Modified crude rate (+ biopsy or biopsy after Month 42)	29.6%	23.0%	23.1% (15.5%,30.0%)

Time Period
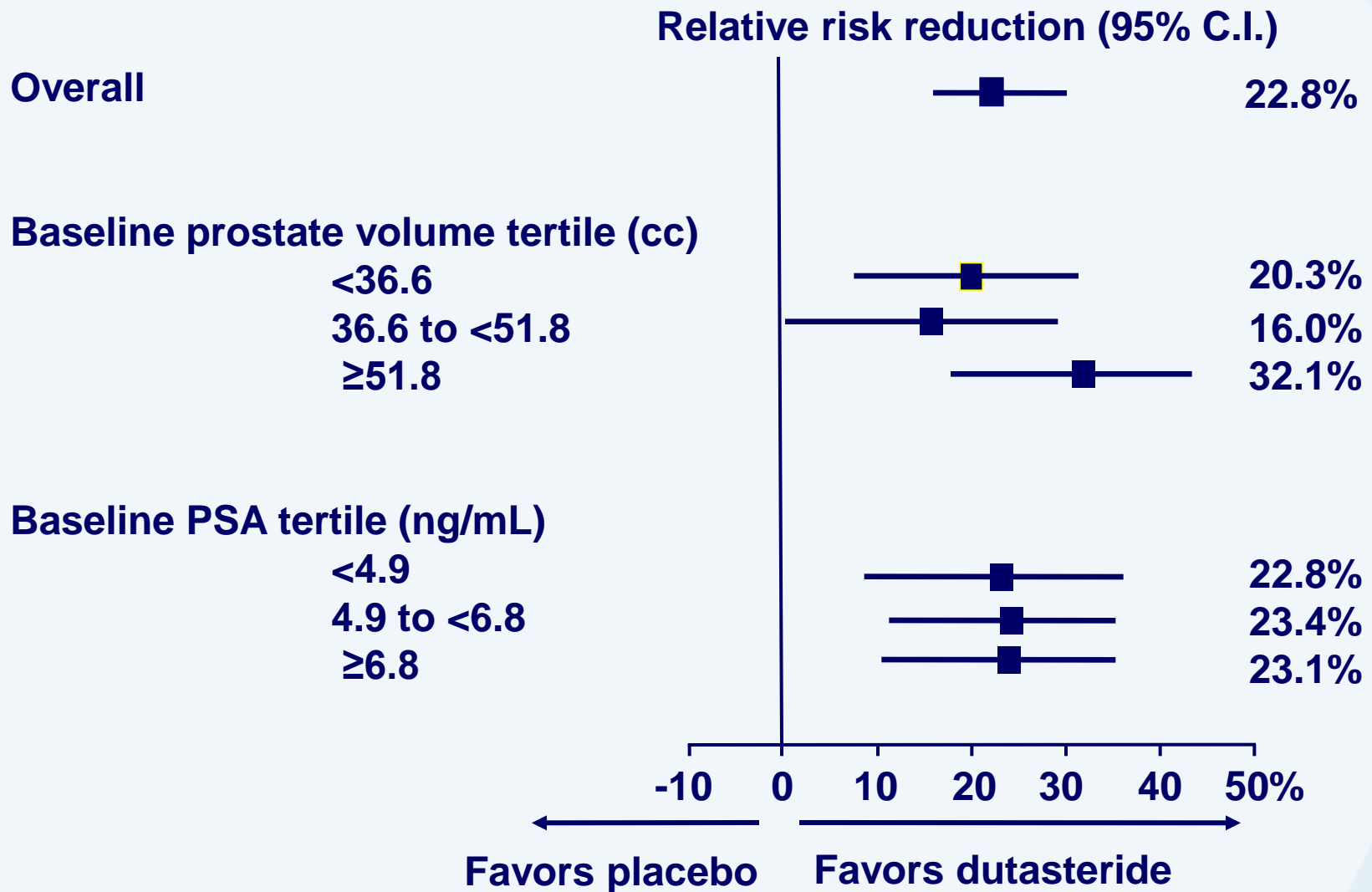
	Relative Risk Reduction		
	Years 1-2	Years 3-4	Overall
Crude rate (efficacy population)	24.4%	20.9%	23.2%
Restricted crude rate (one or more biopsies)	22.5%	23.5%	22.8%
Modified crude rate (+ biopsy or biopsy after Month 42)	22.6%	24.1%	23.1%

Subgroups (restricted crude rate)

Relative risk reduction (95% C.I.)

Overall	**22.8%**
Age (years)	
<65	**24.0%**
≥65	**22.1%**
Family history of prostate cancer	
Yes	**31.9%**
No	**21.6%**
Baseline IPSS	
Mild	**21.1%**
Moderate/severe	**25.9%**

-10 0 10 20 30 40 50%

← **Favors placebo**   **Favors dutasteride** →

Subgroups (continued)

Relative risk reduction (95% C.I.)

Overall — 22.8%

Baseline prostate volume tertile (cc)
- <36.6 — 20.3%
- 36.6 to <51.8 — 16.0%
- ≥51.8 — 32.1%

Baseline PSA tertile (ng/mL)
- <4.9 — 22.8%
- 4.9 to <6.8 — 23.4%
- ≥6.8 — 23.1%

-10   0   10   20   30   40   50%

← Favors placebo   Favors dutasteride →

Log-binomial results (occurrence of PCa)

	Relative Risk (95% CI)	P-value
Treatment (dut vs pbo)	0.77 (0.70, 0.85)	<0.0001
Time Period (Yrs 1-2, Yrs 3-4)	0.71 (0.64, 0.78)	<0.0001
Age (yrs)	1.05 (1.04, 1.06)	<0.0001
Family History of Prostate Cancer	1.39 (1.23, 1.57)	<0.0001
Baseline Prostate Volume (cc)	-	<0.0001
Baseline % Free PSA	-	<0.0001
Prostate Volume x % Free PSA	-	0.0008
Number of Cores at Entry biopsy	0.96 (0.94, 0.98)	<0.0001

Log-binomial results (high grade PCa)

Model failed to converge

Interactions

Log-binomial models with main effects and interaction:

- Treatment x Cluster: 32 df, p=0.31

- Treatment x Time Period (Yrs 1-2, Yrs 3-4): 1 df, p=0.88

Summary

Analysis plan considerations:

- Event assessment (continuous vs scheduled)
- Handling of withdrawals
- Single study submission
- IDMC, SDC and interim analysis

Results:

- Consistency of treatment effect (analysis approach, time period, subgroups, regressions, interactions)
- Regression convergence issues