SYNOPSIS

Name of Sponsor/Company: Active Biotech AB	**Individual Study Table Referring to Part of the Dossier**	***(For national authority use only)***
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Title of study: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study of Tasquinimod in Men with Metastatic Castrate-Resistant Prostate Cancer
Study number: 10TASQ10

Investigators: Co-ordinating investigators: Michael A Carducci, MD, John Hopkins Kimmel Cancer Center, Baltimore, MD, USA.
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Study centre(s): 241 active investigational sites in 37 countries across North America (NA); Europe, the Middle East, and Africa (EMEA); Asia-Pacific (APAC); and Latin America (LA).

Publication (reference): None

Studied period (years): 46.5 months **Date of first enrolment:** 29 March 2011 **Date of last completed (data cut-off):** 13 February 2015	**Phase of development:** III

Objectives:
The primary objective of this study was to confirm the effect of tasquinimod on delaying disease progression (DP) or death compared with placebo.
The secondary objectives of this study were:

- To determine the effect of tasquinimod on overall survival (OS), time to symptomatic progression, additional radiological and clinical efficacy endpoints, quality of life (QoL) parameters, and safety as compared with placebo.
- To assess the pharmacokinetics of tasquinimod in men with metastatic castrate-resistant prostate cancer (mCRPC).

Methodology:
This was a phase III randomised, double-blind, placebo-controlled study of tasquinimod in asymptomatic to mildly symptomatic patients with mCRPC to confirm the effect of tasquinimod on delaying DP compared with placebo. Patients were randomly assigned in a 2:1 ratio to one of two treatment groups: Treatment Group A (tasquinimod 0.25, 0.50, or 1.00 mg/day) or Treatment Group B (placebo). Randomisation was stratified by Karnofsky score (≥90% vs. <90%), presence or absence of visceral disease (all prostate cancer metastatic soft tissue except lymph nodes and local recurrence), and geographic region of enrolment (NA; EMEA; APAC; LA). The study consisted of the Screening Phase (Weeks -4 to -1), the Treatment Phase (Week 1 until the End-of-Study Treatment Visit), the End-of-Study Treatment Visit, and the Follow-up Phase with visits every 3 months until 727 patients had reached the survival endpoint. Study treatment was administered in a

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double-blind manner, throughout the study. Patients in both treatment groups received once-daily oral dosing with study drug.

During the Treatment Phase, patients had the dose of study treatment titrated up from 0.25 mg through an intermediate dose of 0.50 mg (each for at least 2 weeks) to reach the target dose of 1.00 mg daily of study treatment to achieve the individual maintenance dose. The treatment maintenance dose was a maximum of 1.00 mg of tasquinimod (or matching placebo). If a patient could not tolerate the 1.00 mg/day dose, they received the individually tolerated dose (0.25 or 0.50 mg/day) as their treatment maintenance dose. Particular attention was to be paid to patients who were older than 75 years of age as the phase II data indicated that these patients may have been more prone to develop nontolerable adverse events (AEs). Ongoing review of unblinded safety data was conducted by an independent Data Safety Monitoring Board (DSMB) as defined in the DSMB charter. The DSMB was established prior to the First Interim Analysis and was superseded by an Independent Data Monitoring Committee (IDMC) for review of unblinded safety and efficacy data at the time of Interim Analyses, as described in the IDMC charter.

Number of patients (planned and analysed): It was planned that approximately 1200 patients were to be treated and analysed in a ratio of 2:1 (tasquinimod:placebo), 800 and 400 patients, respectively. A total of 1245 patients were randomly assigned. Of these, 1241 patients were treated and analysed (830 patients with tasquinimod and 411 patients with placebo).

Diagnosis and criteria for inclusion:

(1) Aged at least 18 years at the time of signing the informed consent form (ICF). For patients in Taiwan, the minimum age was 20 years.
(2) Historically confirmed diagnosis of adenocarcinoma of the prostate.
(3) Evidence of bone metastatic disease on radiographic examination, whether from bone scan (bone lesions) or other imaging modality.
(4) Castrate levels of serum testosterone (≥50 ng/dL or 1.7 nmol/L).
(5) Evidence of progressive disease after castration levels of testosterone had been achieved, defined by any of the following criteria:
    - Increasing serum prostate-specific antigen (PSA) levels, the most recent value ≥2 ng/mL (increasing levels had to be confirmed by 3 consecutive PSA measurement, within 15 months [preferably within 14 days, but with at least 7 days between each measurement]).
    - Progression of soft tissue metastasis documented within 6 weeks of enrolment (computed tomography [CT] scan or magnetic resonance imaging [MRI]).
    - Progression of bone disease (at least 1 new bone lesion as measured by bone scan within the past 12 weeks before screening).
(6) Karnofsky score ≥70%.

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(7) Laboratory values as follows:
- Haemoglobin ≥100 g/L (>10 g/dL)
- Absolute neutrophil count ≥1500/μL
- Platelets ≥100,000/μL
- Serum creatinine ≤1.5 times the upper limit of normal (ULN)
- Total bilirubin ≤1.5 times ULN
- Aspartate aminotransferase and alanine aminotransferase ≤3 times ULN

(8) If sexually active with partner of childbearing potential, patient had to agree to use adequate contraceptive methods (barrier contraceptive with spermicide or vasectomy) while on study treatment. The adequate contraceptive method had to be continued for 14 days after the patient stopped taking study treatment.

(9) No evidence (within 5 years of screening) of prior malignancies (except successfully treated basal cell or squamous cell carcinoma of the skin).

(10) Able to swallow and retain oral medication.

(11) Able to adhere to the study visit schedule and other protocol requirements.

(12) Ability to comprehend the full nature and purpose of the study, including possible risks and side effects, and to cooperate with the investigator and to comply with the requirements of the entire study.

(13) Able (or patient's legal guardian, if applicable) to sign and date the ICF after being informed of the full nature and purpose of the study, including possible risks and side effects, and given ample time and opportunity to read and understand this information.

Test product, dose and mode of administration, batch number:
Tasquinimod was presented as hard gelatin capsules in doses of 0.25 mg, 0.50 mg, or 1.00 mg, to be taken orally with water (~200 mL) and food preferably at the same time each day. The batch numbers used in the study were:
- Tasquinimod 0.25 mg: 2714530, 3004722, 3010313, 3014670, and 3023871
- Tasquinimod 0.50 mg: 2715826, 3004731, 3010346, 3014682, and 3023880
- Tasquinimod 1.00 mg: 2697136, 3004770, 3010363, 3014690, and 3023899

(blinded batch numbers: 159097-01, 159097-3, 167629-01, 167629-02, 185444-01, 185444-02, 191383-01, 191383-02, 207603-02, 207603-01, and 207603-03).

Duration of treatment:
The study was predicted to have an 18-month recruitment period followed by a 30-month study duration. Patients in both treatment groups received once daily oral dosing of study treatment (tasquinimod or matched placebo). There was no fixed length of the Treatment Phase, therefore treatment continued until any criterion for withdrawal from the study drug was reached and the study drug was withdrawn.

Reference therapy, dose and mode of administration, batch number:
Placebo capsules were identical in appearance and composition to the tasquinimod capsules, but without the active ingredient. Administration was identical to tasquinimod. The batch

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numbers used in the study were: 2713493, 3004800, 3010302, 3014661, and 3023864 (blinded batch numbers: 159097-01, 159097-3, 167629-01, 167629-02, 185444-01, 185444-02, 191383-01, 191383-02, 207603-02, 207603-01, and 207603-03).

Criteria for evaluation:
Efficacy:

Primary Efficacy Endpoint
The primary endpoint was radiological progression-free survival (rPFS) defined as the time from the date of randomisation to the date of radiological progression or death (whatever the cause). Radiological progression was defined by any of the following criteria:

- Progression of soft tissue lesions according to the Response Evaluation Criteria in Solid Tumours, version 1.1 (RECIST 1.1)
- Progression of bone lesions detected with bone scan according to Prostate Cancer Working Group 2 criteria
- Radiologically confirmed skeletal-related events.

Radiological scans (CT or MRI) and bone scans were performed at Baseline and every 3 months until radiological DP was documented. DP was evaluated both locally by the study investigator and by a central review performed by independent reviewers.

Secondary Efficacy Endpoints
The key secondary endpoint was:

- OS

The other secondary endpoints were:

- Time to radiological progression
- Time to symptomatic progression (including death due to prostate cancer)
- Time to first radiological or symptomatic progression
- Time to first radiological or symptomatic progression or death (due to any cause)
- Time to initiation of salvage systemic therapy, including radionuclide, chemotherapy, or radiation therapy
- Time to new soft tissue lesion
- Time to progression due to soft tissue lesions (according to RECIST 1.1)
- Time to skeletal-related events
- Time to new bone lesion
- Time to new lesion (soft tissue or bone lesion)
- Time to new visceral metastases
- Time to opiate use for cancer pain
- Time to initiation of further cytotoxic therapy
- Time to tumour-related pain progression including palliative interventions

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- QoL measured by the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire and by the EuroQoL 5-Dimension QoL Instrument (EQ-5D)
- Changes in Karnofsky score
- Changes in visual analogue scale (VAS) for tumour-related pain
- Changes in serum PSA over time
- Changes in bone-specific alkaline phosphatase (BAP) over time
- Changes in vascular endothelial growth factor (VEGF) over time
- Population pharmacokinetics of tasquinimod

Quality of Life measured by FACT-P, EQ-5D (Health Status), VAS and Performance status assessed by Karnofsky scores were measured at Baseline, Week 13, and every 3 months during the Treatment and Follow-up Phases. Karnofsky score assessment was optional during the Follow-up Phase. Blood samples for pharmacokinetics were taken at Weeks 3, 5, 7, 9, 13, 25, 37, 49, 61, and every 12 weeks until the End-of-Study Treatment Visit. Biomarkers for PSA, BAP, and VEGF assessment were measured at Weeks 1, 13, 25, 37, 49, 61 and every 12 weeks until the End-of-Study Treatment Visit.

Subgroup and Exploratory Endpoints

For patients with soft tissue lesions at randomisation:
- Time to progression of soft tissue lesions
- Response assessment for soft tissue lesions

For patients with bone metastases at randomisation:
- Time to progression of bone metastases
- Response assessment for bone metastases

For patients with visceral disease at randomisation:
- Time to progression of visceral metastases

For patients without visceral disease at randomisation:
- Time to progression due to new visceral metastases

The exploratory analysis endpoints included:
- Time to symptomatic progression due to pain including palliative interventions
- Time to death due to prostate cancer
- Time to symptomatic progression due to skeletal-related events
- Radiological response
- Symptomatic progression assessment
- Overall assessment of radiological progression
- Dose level dispensed
- Changes in C-reactive protein (CRP), fibrinogen, serum lipase, serum amylase, and lactate dehydrogenase (LDH).

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Safety:

Safety assessments included AEs, serious AEs (SAEs), death rates, vital signs, body weight measurements, laboratory values, electrocardiograms (ECGs), and physical examinations. Adverse events, SAEs, vital signs, and basic laboratory tests (haematology and biochemistry) were performed at Baseline, every visit of the Treatment Phase, and the End-of-Study Treatment Visit. Additional laboratory tests (fibrinogen, CRP, serum amylase, and triacylglycerol lipase) were performed at Weeks 1, 5, 9, 25, 37, 49, 61 and every 12 weeks until the End-of-Study Treatment Visit. Physical examinations were performed at Baseline, Weeks 13, 25, 37, 49, 61 and every 12 weeks until the End-of-Study Treatment Visit. Electrocardiograms were performed at Baseline and the End-of-Study Treatment Visit.

Statistical methods:

Efficacy:

The primary efficacy analysis was conducted on the Intent-to-treat (ITT) population and consisted of a stratified log-rank test to compare the rPFS for tasquinimod vs. placebo. The test was stratified by the randomisation stratification variables as recorded in the interactive voice response system (IVRS) (Karnofsky score, presence of visceral disease, and geographic region of enrolment). An unstratified Kaplan-Meier plot for the analysis was produced. The median rPFS and the estimated proportion of progression free patients after 3, 6 and 12 months were estimated from the Kaplan-Meier curve. Treatment effect was estimated by calculating the HR and its 95% confidence interval (CI) from a proportional hazards model stratified by Karnofsky score, presence of visceral disease, and geographic region of enrolment as recorded in the IVRS.

The key secondary efficacy analysis was conducted on the ITT population and consisted of a stratified log-rank test to compare the OS for tasquinimod vs. placebo. The test was stratified by the randomisation stratification variables (Karnofsky score, presence of visceral disease, and geographic region of enrolment). An unstratified Kaplan-Meier plot for the analysis was produced. The median OS and the survival rates after 12, 24 and 36 months were estimated from the Kaplan-Meier curve. Treatment effects were estimated by calculating the HR and its 95% CI from a proportional hazards model stratified by Karnofsky score, presence of visceral disease, and geographic region of enrolment.

A hierarchical testing approach was used to analyse the primary and key secondary endpoints of rPFS and OS. This approach preserved the overall significance level of 0.05 for the study.

Radiological PFS was analysed at the time of the First Interim Analysis for OS (473 events). If $p \leq 0.05$ for the primary efficacy comparison of rPFS (based on local assessments), then the First Interim Analysis of OS was to be performed. If the First Interim Analysis of OS was

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not significant then follow-up was to continue and a Second Interim Analysis performed when 582 events had been observed. The Final Analysis was anticipated to be completed once 727 deaths had been observed.

The OS endpoint incorporated group sequential design by including two interim analyses and one Final Analysis using the O'Brien Fleming boundaries as implemented by the Lan DeMets alpha spending method. This method ensured that the type I error rate (≤5%) was not inflated.

The following sensitivity analyses were performed on the primary and key secondary endpoints:

- The log-rank tests for rPFS and OS and estimation of the HR and 95% CI were calculated without stratification.
- The rPFS analysis (both the stratified log-rank test and proportional hazards model) was repeated using the Per-protocol (PP) population.
- The rPFS analysis (both the stratified log-rank test and proportional hazards model) was repeated using the central or local reviewer assessment that was not used for the primary analysis. A cross-tabulation of local versus central review response data were also tabulated by treatment group and visit.
- The OS analysis was repeated (both the stratified log-rank test and proportional hazards model) using the PP population.
- The log-rank tests for rPFS and OS and estimation of the HR and 95% CI were calculated using the actual stratification. This was to assess any potential impact on inadvertent mis-stratification.
- As survival and rPFS were expected to differ within regions, a sensitivity analysis was performed whereby geographic region EMEA was split into West EMEA and East EMEA, and Asia-Pacific was split into Australia/New Zealand and Asia-Pacific (Rest) in the stratification variable for region.
- The OS analysis were repeated where, for patients who died but had a missing death date, or only the year of death was recorded, patients were considered as censored in the analysis with last known to be alive date or the 1st of January of death year whichever occurred last) used as the censoring date.

Analyses of other secondary efficacy endpoints for time to event analyses were conducted on the ITT population and also on relevant subsets of patients and consisted of a stratified log-rank test to compare the endpoint for tasquinimod versus placebo. The tests were stratified by the randomisation stratification variables (Karnofsky score, presence of visceral disease, and geographic region of enrolment). Treatment effect was estimated by calculating the HR and 95% CI from a proportional hazards model stratified by Karnofsky score,

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presence of visceral disease, and geographic region of enrolment. Unstratified Kaplan-Meier plots for the analyses were also produced. The percentage of patients without events at 12 months and 24 months was to be presented.

Secondary efficacy analyses also assessed changes in Karnofsky score, VAS for tumour-related pain, BAP and VEGF by summarising actual and change from Baseline in BAP and VEGF by treatment group and visit. Changes in serum PSA were evaluated by PSA response (30%, 50% decrease in PSA from Baseline at Month 3 and Month 6), Percentage change in PSA from Baseline to nadir measurement up to Month 6, PSA doubling time (DT), PSA slope (at Month 3, Month 6 and Month 9) and time to PSA progression.

Quality of Life Endpoints

All FACT-P scores were summarised in the ITT population by presenting summary statistics for the actual and change from Baseline for all available parameters and visits. The rates of FACT-P completion at all visits were computed overall and by treatment group. The primary FACT-P outcome for the analysis was time to deterioration.

To take advantage of the power gained from repeated QoL assessments, a longitudinal mixed model to estimate and test treatment group differences at each time point as well as the difference in rates of change (Slopes) between study treatment groups was also fitted on FACT-P total score. Models included treatment group, time and the interaction between time and treatment as fixed effects. Nonlinear effects of time may have been explored by including quadratic and possibly cubic time terms in the models, as well as their interactions with treatment. An unstructured correlation matrix was used to model the correlation between repeated observations. A sensitivity analysis was conducted using a different analytical method with different missing data assumptions. A pattern mixture model was fitted to assist in the analysis of potentially nonignorable missing data. For this method, patients were stratified into groups based on time and reason for study discontinuation (i.e. for DP), as it was likely to be linked to missing data mechanism. Repeated measures mixed effects models were fitted within each stratum. Parameter estimates for each stratum were then combined into a weighted average for the entire study population. While both ordinary longitudinal mixed effects models and pattern mixture models were fitted, the pattern mixture model results were considered primary since the assumption of nonignorable missing data was more realistic than the missing at random assumption of the mixed effects model.

Only descriptive analyses were performed for EQ-5D (Health Status) data. The responses to the five EQ-5D items (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) were described by treatment groups and overall at each visit when the

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EQ-5D was collected in the Treatment Phase, at the End-of-Study Treatment Visit, and Follow-up visits.

Subgroup and Exploratory Endpoints
Exploratory analyses of the primary and key secondary endpoints were conducted within additional predefined subgroups.

Safety:
For all safety data, patients were summarised by treatment received. Should a patient have received both tasquinimod and placebo during the study, they were included in the safety analyses under the tasquinimod treatment group.

Adverse event data were listed for all patients and summarised using the Safety population by treatment group and overall by system organ class (SOC) and preferred term (PT), causality, intensity, seriousness, and outcome. Treatment-emergent AEs (TEAEs) and non-treatment-emergent AEs were summarised separately.

Summary statistics for vital signs for changes from Baseline to each scheduled visit were presented by treatment group. Shifts from Baseline to End-of-Study Treatment Visit for ECGs and physical examinations were presented by treatment group.

Laboratory data (haematology, biochemistry, and additional tests) were listed for all patients. Additionally, abnormal laboratory values were listed according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 and v4.03 laboratory toxicity grades.

Continuous parameters were summarised for the actual values and change from baseline for all available parameters and visits (scheduled visits only). Ratios of actual laboratory values/baseline value were also calculated for each parameter at each visit and presented in a summary table. Shifts from baseline tables of the number and percentage of patients in each of the CTCAE categories were also presented for each treatment group for each parameter and visit (scheduled visits only). An overall shift summary was also provided comparing baseline to worst post-dose toxicity observed across all visits. Boxplots for all continuous laboratory parameters were presented by treatment for each visit. Additionally, for fibrinogen, CRP, serum amylase, triacylglycerol lipase, and LDH, summary statistics were presented graphically by treatment group for each visit. Creatinine clearance was derived and presented using the formula proposed by Cockcroft and Gault. Renal clearance was also derived and presented.

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Summary - conclusions:

Demographics, Medical History, Prior and Concomitant Medications

In general, demographics, medical history, other baseline parameters, and prior and concomitant medications were well balanced between treatment groups. Notable exceptions were imbalances observed for demography in current smokers (or patients who had never smoked), for prostate cancer medical history for the time since diagnosis of prostate cancer and also that a higher proportion of patients in the tasquinimod group had a high VAS score for tumour-related pain at Baseline compared with the placebo group. However, any imbalances identified were not considered to have any significant impact on the efficacy or safety results of the study.

Efficacy results:

Primary Endpoint

The primary analysis (i.e. First Interim Analysis) of local and central review-determined rPFS in the ITT population met the predefined level of statistical significance ($p<0.05$ at First Interim Analysis). The stratified log-rank test was statistically significantly in favour of tasquinimod compared with placebo in the ITT population ($p<0.001$ per local review and $p<0.001$ per central review). Median (95% CI) (months) values for duration of rPFS were 5.7 (5.5, 6.2) months vs. 4.1 (3.1, 5.1) months for the tasquinimod and placebo groups, respectively, by local review and 7.0 (5.8, 8.2) months vs. 4.4 (3.5, 5.5) months for the tasquinimod and placebo groups, respectively, by central review. Hazard ratios (HRs), from the proportional hazards model, demonstrated a reduction in the risk of progression of 31% and 36% for tasquinimod compared with placebo when analysed by both local and central review, respectively.

Results from the sensitivity analyses, including analysis of the PP population and analysis of the final database with First Interim Analysis Data cut off as well as with Final Analysis Data cut off, confirmed the primary endpoint results.

Key Secondary Endpoint

At the Final Analysis, the difference in OS between the tasquinimod and placebo groups was not statistically significant ($p=0.247$). None of the sensitivity analyses conducted showed any statistically significant differences between study treatment groups and as such confirmed the findings for the key secondary endpoint of OS. The median follow-up time was similar between the tasquinimod and placebo groups.

In conclusion, although tasquinimod significantly improved the primary endpoint of rPFS in patients with chemotherapy naïve mCRPC compared with placebo, there was no significant

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improvement in the key secondary endpoint of OS.

Other Secondary Endpoints

Disease Progression

Essentially all radiology-based secondary endpoints showed statistically significant differences between the tasquinimod group and the placebo group in favour of tasquinimod. These included Time to Radiological Progression, Time to New Bone Lesion, Time to New Lesion (Soft Tissue or Bone Lesion), Time to New Soft Tissue Lesion, Time to Progression due to Soft Tissue Lesions (according to RECIST 1.1), Time to First Radiological or Symptomatic Progression, and Time to First Radiological or Symptomatic Progression or Death (Due to Any Cause). The exceptions were Time to New Visceral Metastases and Time to Skeletal-Related Events (Radiologically Confirmed), which both had few events not allowing firm conclusions to be made.

However, Time to Symptomatic Progression (Including Death Due to Prostate Cancer) demonstrated statistically significant differences in favour of placebo compared with tasquinimod.

Exploratory analyses were performed for the three subcategories of symptomatic progression (Time to Symptomatic Progression Due to: Pain Including Palliative Interventions, Death Due to Prostate Cancer, and Skeletal-Related Events) but no significant differences were found between the tasquinimod group and the placebo group.

Exploratory analyses showed in an overall assessment that the proportion of patients with radiological progression determined by local and central review was generally lower in patients in the tasquinimod group compared with patients in the placebo group.

Exploratory analyses of Time to Progression of Soft Tissue Lesions for Patients with Soft Tissue Lesions at Baseline, and Time to Progression of Bone Lesions for patients with Bone Metastases at Baseline, showed statistically significant differences between the tasquinimod group and the placebo group (in favour of tasquinimod) by local and central review. Time to Progression of Visceral Lesions for Patients with Visceral Metastases at Baseline, and Time to New Visceral Lesions for patients with Visceral Metastases at Baseline, showed statistically significant differences between the tasquinimod group and the placebo group (in favour of tasquinimod) by local review only.

Initiation of Further Therapy

For the endpoints analysed that were associated with initiation of further therapy, the following endpoints showed statistically significant differences in favour of tasquinimod

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compared with the placebo group: Time to Initiation of Salvage Therapy Including Radionuclide, Chemotherapy or Radiation Therapy; and Time to Initiation of Further Cytotoxic Therapy. Statistically significant differences in favour of placebo compared with tasquinimod were shown for Time to Opiate Use for Cancer Pain.

These results are aligned with what is known about tasquinimod delaying radiological progression. For Time to Opiate Use for Cancer Pain, these results reflect the findings for symptomatic progression, patients on placebo had less symptomatic progression.

Quality of Life
Analyses of QoL (FACT-P Questionnaire, EQ-5D VAS (Health Status), Karnofsky score deterioration, and Tumour-related Pain Progression) were in favour of placebo, which was in line with the findings for symptomatic progression.

Changes in Biomarkers
Median PSA levels, as well as historical PSA DT and Slopes, were similar between the tasquinimod and placebo groups at Baseline. A statistically significant difference in favour of tasquinimod was shown for Time to PSA Progression, decrease in PSA from Baseline to Month 3, as well as for PSA DT post-baseline.

For other biomarkers, there was an overall decrease in BAP levels over time for the tasquinimod group, and levels of VEGF were stable, and generally similar over time in both study treatment groups.

To summarise results of other secondary endpoints, results from statistical tests are presented in the table below.

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Table 1 Summary of Results for Secondary Endpoints

	Local		Central		Tasquinimod Treatment vs. Placebo	
Endpoint	**P-value [a]**	**Hazard ratio[b]**	**P-value**	**Hazard ratio**	**Risk reduction[c]**	**Favours Tasquinimod[d]**
Time to radiological progression	<0.001	0.683	<0.001	0.628	32%	Yes
Time to new bone lesion	<0.001	0.723	<0.001	0.735	27%	Yes
Time to new lesion (soft tissue or bone lesions)	<0.001	0.703	<0.001	0.736	26%	Yes
Time to new soft tissue lesion	<0.001	0.612	<0.001	0.678	32%	Yes
Time to new visceral metastases [e]	0.057	0.732	0.222	0.773	N/A	N/A
Time to progression due to soft tissue lesions (according to RECIST 1.1)	<0.001	0.586	<0.001	0.621	38%	Yes
Time to skeletal-related events (radiologically confirmed) [f]	0.310	1.252	0.190	3.716	N/A	N/A
Time to symptomatic progression (including death due to prostate cancer)	0.031	1.171			N/A	No
Time to first radiological or symptomatic progression	0.002	0.812	0.013	0.849	15%	Yes
Time to first radiological or symptomatic progression or death (due to any cause)	0.001	0.812	0.009	0.845	16%	Yes
Time to symptomatic progression due to skeletal-related events [g]	0.972	1.007			N/A	N/A
Time to initiation of salvage therapy including radionuclide, chemotherapy or radiation therapy	0.001	0.778			22%	Yes
Time to initiation of further cytotoxic therapy	0.021	0.809			19%	Yes

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Time to opiate use for cancer pain	0.013	1.328			N/A	No
Time to deterioration in FACT-P (criterion 1)	p<0.001	1.447			N/A	No
Time to deterioration in Karnofsky score	p<0.001	1.292			N/A	No
Time to tumour-related pain progression including palliative interventions	p<0.001	1.259			N/A	No
PSA doubling time	p<0.001	0.734			27%	Yes
Time to PSA progression	0.003	0.826			17%	Yes

Abbreviation: N/A=not applicable as not a statistically significant difference when the tasquinimod group compared with the placebo group.

a The p-value was obtained from a stratified log-rank test with Karnofsky score, presence of visceral disease and geographic region of enrolment as stratification variables.

b The hazard ratio and 95% CI were estimated using a proportional hazards model stratified by Karnofsky score, presence of visceral disease and geographic region of enrolment. The hazard ratio is based on a comparison of tasquinimod/placebo.

c Minimum risk reduction calculated from local and central hazard ratios.

d Statistically significant differences.

e, f, g The number of events are too low for accurate evaluation.

Adjustments for Covariates

Following adjustment for other prognostic factors in the model for rPFS and OS, the HR for tasquinimod vs. placebo remained similar.

Efficacy Subgroup Analyses

In general, the effects on rPFS and OS were consistent among subgroups analysed and only a few showed statistically significant interactions). Overall, there was no interaction considered clinically relevant for any subgroups for rPFS or for OS. These findings support the robustness of the primary and key secondary endpoint results.

For rPFS the following variables showed a potential interaction ($p<0.1$) with the effect of study drug: Baseline VAS; other prior second generation hormonal therapies and diabetes history (by local and central review); region (local review); and bone metastases (central review).

For OS the following variables showed a potential interaction ($p<0.1$) with the effect of

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study drug: bone metastases, Gleason score, and prior antiandrogen treatment.

Pharmacokinetic Evaluation
A one compartmental model was identified to fit the plasma concentration-time data of tasquinimod well. The apparent oral clearance (CL/F) and apparent volume of distribution following oral administration (V/F) for a typical patient were determined to be 0.176 L/h and 15.1 L, respectively, confirming a low CL/F and small V/F as reported in previous studies with tasquinimod.

Age and CYP2C19 inhibitors were found to be statistically significant covariates on CL/F ($p<0.001$). The model predicted a lower CL/F at higher age. Concomitant use of CYP2C19 inhibitors resulted in slightly lower CL/F values (8% lower, with narrow CIs), which was not deemed to be of clinical significance.

Safety results:

Extent of Exposure
Median treatment duration was 137 and 133 days for tasquinimod and placebo, respectively, and most patients (81.6 and 92.5%, respectively) escalated to the maximum 1 mg dose. The median treatment times in days for patients who received 0.25 mg and 0.50 mg of tasquinimod or placebo were identical at 14 days, which corresponded to the two-week dose escalation procedure; and were similar for patients that received the 1.00-mg tasquinimod dose or placebo. The majority of patients in both treatment groups reached a maximum dose level of 1.00 mg; most of these patients had duration of exposure of ≥3 months.

At all time points evaluated, a similar proportion of patients who remained in the study received either tasquinimod or placebo. A higher proportion of patients in the placebo group reached the 1.00-mg dose level compared with patients in the tasquinimod group (92.5% vs. 81.6%, respectively) and patients in the placebo group generally reached this dose level at an earlier time point compared with patients in the tasquinimod group.

Adverse Events
The safety results of the study demonstrated a higher per-patient incidence of TEAEs in the tasquinimod group compared with the placebo group. Events experienced by patients in the tasquinimod group were more likely to be Grade 3-5, which was primarily driven by a higher incidence of Grade 3 events in the tasquinimod group.

The proportion of patients who experienced a TEAE was similar between the tasquinimod and placebo groups (95.3% in the tasquinimod group compared with 92.7% in the placebo

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group); although there was an increased incidence of AEs per patient in the tasquinimod group compared with patients in the placebo group.
With the exception of TEAEs at CTCAE Grade 1 and Grade 3, the proportion of patients who experienced TEAEs at each grade was similar in the tasquinimod and placebo groups. More Grade 3 TEAEs were experienced by patients in the tasquinimod group compared with patients in the placebo group (36.7% vs. 26.3%, respectively) and more Grade 1 TEAEs were experienced by patients in the placebo group than in the tasquinimod group (20.4% vs. 11.3%, respectively).

At least one third of patients in the tasquinimod group reported TEAEs from the following SOCs: gastrointestinal disorders (60.2% vs. 47.9% in placebo), general disorders and administration site conditions (55.1% vs. 39.9%), musculoskeletal and connective tissue disorders (48.2% vs. 36.7%), neoplasms benign, malignant and unspecified (including cysts and polyps) (34.5% vs. 32.6%), and metabolism and nutrition disorders (38.1% vs. 20.4%).

Treatment-emergent AEs experienced by ≥10% patients in the tasquinimod group were: cancer pain (31.8%), decreased appetite (30.1%), nausea (26.7%), fatigue (26.1%), constipation (23.4%), anaemia (21.6%), asthenia (16.9%), weight decreased (15.1%), back pain (12.7%), pain in extremity (12.5%), arthralgia (12.2%), diarrhoea (11.3%), insomnia (10.5%), vomiting (10.5%), and oedema peripheral (10.2%).

Notable differences of >5% between the tasquinimod and placebo groups in the proportion of patients who experienced TEAEs were observed for: decreased appetite (30.1% in tasquinimod vs. 16.3% in placebo, respectively), nausea (26.7% vs. 21.7%), fatigue (26.1% vs. 17.5%), constipation (23.4% vs. 16.3%), anaemia (21.6% vs. 16.3%), weight decreased (15.1% vs. 8.5%), and pain in extremity (12.5% vs. 7.5%).

During the first 6 weeks of time on study treatment, the incidence of patients with TEAEs in both study treatment groups appeared to increase, more notably in patients in the tasquinimod group. From 6 weeks to Month 18 of time on study treatment the incidence of patients who experienced TEAEs in the tasquinimod group steadily increased, whereas the incidence of patients who experienced TEAEs in the placebo group remained similar.

Treatment-Emergent AEs of Grade 3-5
The proportion of patients who experienced a Grade 3-5 TEAE was higher in the tasquinimod group compared with the placebo group (42.8% vs. 33.6%, respectively). At all time points, the incidence of Grade 4 or Grade 5 TEAEs experienced by patients was similar between the tasquinimod and placebo groups, whereas the incidence of Grade 3 TEAEs experienced by patients was typically higher in the tasquinimod group (36.7% vs. 26.3% in

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placebo).

In all SOCs, Grade 3-5 TEAEs were reported by <10% of patients in each study treatment group. At least 5% of patients in the tasquinimod group reported Grade 3-5 TEAEs from the SOCs of blood and lymphatic systems disorders; general disorders and administration site conditions; renal and urinary disorders; musculoskeletal and connective tissue disorders; and gastrointestinal disorders.

Grade 3-5 TEAEs experienced by >1% patients in the tasquinimod group were anaemia (8.3%), fatigue (3.4%), cancer pain (3.3%), asthenia (2.8%), decreased appetite (1.8%), weight decreased (1.8%), acute renal failure (1.6%), hydronephrosis (1.3%), back pain (1.2%), pain in extremity (1.2%), urinary retention (1.2%), urinary tract infection (1.2%), atrial fibrillation (1.1%) haematuria (1.1.%), and pneumonia (1.1%). Notable differences of ≥1% between the tasquinimod and placebo groups in the proportion of patients who experienced Grade 3-5 TEAEs were observed for fatigue (3.4% in tasquinimod vs. 2.2% in placebo, respectively), urinary retention (1.2% vs. 2.2%), arthralgia (1.0% vs. 0%), back pain (1.2% vs. 0.2%), pain in extremity (1.2% vs. 0.2%), urinary tract infection (1.2% vs. 0%), weight decreased (1.8% vs. 0.7%), atrial fibrillation (1.1% vs. 0%) and hypertension (0.6% vs. 1.7%).

Treatment-Related TEAEs

The incidence of treatment-related TEAEs was higher in patients in the tasquinimod group (70.7%) compared with patients in the placebo group (57.2%). Treatment-related TEAEs experienced by ≥10% patients in the tasquinimod group were constipation, nausea, fatigue, and decreased appetite. Notable differences of >5% between the tasquinimod and placebo groups in the proportion of patients who experienced treatment-related TEAEs were observed for decreased appetite (22.8% in tasquinimod vs. 9.5% in placebo), and fatigue (18.9% vs. 10.9%).

Treatment-Emergent SAEs

There were no notable differences between the tasquinimod and placebo groups in the proportion of patients who experienced TEAEs leading to death. The majority of TEAEs leading to death were assessed by the investigator as not related to study drug. Treatment-emergent AEs leading to death experienced by more than 1 patient in the tasquinimod group were death and sudden death (4 patients each) and bronchopneumonia and disseminated intravascular coagulation (2 patients each). Treatment-emergent AEs leading to death experienced by more than 1 patient in the placebo group were pneumonia and respiratory failure (2 patients each). No other PTs were reported for more than 1 patient in either study treatment group.

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The proportion of patients who experienced a treatment-emergent SAE was higher in the tasquinimod group compared with the placebo group (27.6% vs. 23.6%, respectively). There were no notable differences between the tasquinimod and placebo groups in the proportion of patients who experienced Grade 1, Grade 2, Grade 4, or Grade 5 treatment-emergent SAEs. The proportion of patients who experienced a Grade 3 treatment-emergent SAE was higher in the tasquinimod group than in the placebo group (17.0% vs. 12.7%, respectively). Treatment-emergent SAEs experienced by ≥1% patients in the tasquinimod group were anaemia, urinary retention, acute renal failure, atrial fibrillation, haematuria, hydronephrosis, pneumonia, and urinary tract infection. No notable differences of ≥1% between the tasquinimod and placebo groups were reported for any other individual PT.

Notable differences of >1% between the tasquinimod and placebo groups in the proportion of patients who experienced TEAEs were observed for atrial fibrillation (1.3% in tasquinimod vs. 0% in placebo) and acute renal failure (1.8% vs. 0.7%).

Treatment-Emergent AEs Leading to Treatment Discontinuation

A higher proportion of patients in the tasquinimod group compared with patients in the placebo group experienced TEAEs that led to treatment discontinuation (17.7% vs. 10.2%, respectively). The proportion of patients who experienced a TEAE that led to treatment discontinuation was higher in the tasquinimod group compared with the placebo group at 0.25-mg and 0.50-mg dose levels; whereas at the 1.00-mg dose the proportion of patients who experienced a TEAE that led to treatment discontinuation in each study treatment group was comparable. When analysed by dose, a higher proportion of patients in the tasquinimod group compared with patients in the placebo group experienced a TEAE leading to a temporary interruption of study drug at each dose level. The proportion of patients in the tasquinimod group who experienced a TEAE leading to delayed dose escalations was also higher at both the 0.25-mg and 0.50-mg dose levels in the tasquinimod group compared with patients in the placebo group.

The most frequently reported TEAE PTs leading to treatment discontinuation in the tasquinimod group were: decreased appetite (1.9%), fatigue (1.6%), asthenia (1.4%), and nausea (1.3%). All other TEAEs leading to treatment discontinuation were reported by <1.0% patients in either study treatment group.

When analysed by age subgroup, incidences of TEAEs leading to treatment discontinuation were higher in the tasquinimod group at each age subgroup; for both treatment groups the highest proportion of patients who experienced TEAEs leading to treatment discontinuation were from the >80 years of age subgroup.

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When analysed by CTCAE grade, incidences of TEAEs leading to treatment discontinuation were higher in the tasquinimod group for all CTCAE grades with the exception of TEAES of Grade 4; the majority of TEAEs leading to treatment discontinuation were CTCAE Grade 2.

Notable differences of ≥1% between the tasquinimod and placebo groups in the proportion of patients who experienced TEAEs leading to treatment discontinuation were observed for decreased appetite (1.9% in tasquinimod vs. 0.2% in placebo, respectively), and nausea (1.3% vs. 0.2%).

Treatment-Emergent AEs Leading to Dose Modification

Treatment-emergent AEs leading to dose modification (increase or reduction) were more frequently reported in the tasquinimod group (16.5%) than in the placebo group (5.1%). In the tasquinimod group, the proportion of patients who experienced a dose reduction was approximately twice as high at 1.00 mg compared with 0.50 mg; whereas in the placebo group the proportion of patients who experienced a dose reduction at 0.50 mg and 1.00 mg was similar.

Adverse Events of Special Interest

With the exception of pericardial and pleural disorders, for each AE of special interest (AESI) group the proportion of patients who experienced treatment-emergent AESIs was slightly higher in the tasquinimod group. Notable differences were observed in the proportion of patients who experienced treatment-emergent AESIs in the pericardial and pleural disorders AESI group (4.0% in the tasquinimod group compared with 1.0% in the placebo group). The proportion of patients who experienced CTCAE Grade 3, 4, or 5 AESIs was similar in each study treatment group. Notable differences between the tasquinimod and placebo groups in the proportion of patients who experienced AESIs were observed for anaemia (21.6% in tasquinimod vs. 16.3.% in placebo, respectively), oedema peripheral (10.2% vs. 6.8%), nocturia (4.1% vs. 1.5%), acute renal failure (2.0% vs. 0.7%), atrial fibrillation (2.8% vs. 0.7%), cardiac failure (1.2% vs. 0.2%)/cardiac failure chronic (0.4% vs 0%), dyspnoea (6.6% vs. 3.9%), hypertension (4.9% vs. 6.6%), contusion (1.0% vs. 0%), pleural effusion (2.7% vs. 0.7%)/pleurisy (0.5% vs 0.2%) and pericardial effusion (0.8% vs 0%)/pericarditis (0.4% vs 0%).

Clinical Laboratory Evaluation

There was consistent increase from Baseline in median erythrocytes distribution width, leukocytes, neutrophils, and creatine clearance in the tasquinimod group, and there was a consistent decrease from Baseline in median haemoglobin, haematocrit, and erythrocytes, bilirubin, and LDH with little change in the placebo group. Initial increases were also observed for fibrinogen, CRP, amylase and triacylglycerol lipase in the tasquinimod group,

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with little change in the placebo group over time.
Haematology, biochemistry, and additional test parameters (fibrinogen, CRP, amylase, and triacylglycerol lipase) at worst post-baseline CTCAE grade were mostly of Grade 1 and Grade 2 intensity. Worst post-baseline platelet values were more frequently reported for patients in the tasquinimod group. Notable differences of ≥2% of patients with shifts from not graded or Grade 1 at Baseline to a worst post-baseline CTCAE value of Grade 3 or 4 were reported for haemoglobin (low), alkaline phosphatase, sodium (low) and triacylglycerol lipase values in the tasquinimod group and neutrophil values in the placebo group.

The incidence of worst post-baseline Grade 3 or Grade 4 values for laboratory parameters was generally comparable between the tasquinimod and placebo groups and there were no notable differences of ≥2% between the tasquinimod and placebo groups in the proportion of patients who experienced worst post-baseline Grade 3 or Grade 4 grades. However, worst post-baseline platelet values and low haemoglobin values at all grades were more frequently reported for patients in the tasquinimod group.

Vital Signs, Physical Examinations and ECG
There were no notable differences in vital signs between the tasquinimod and placebo groups. There were no notable changes from the Baseline values to any post-baseline visit values for vital signs, but changes did occur in weight values. Weight decreased from Baseline values over time for both study treatment groups, and more rapidly in the tasquinimod group to a median weight loss of 5 kg vs. 1 kg by Month 12.

Notable differences between the tasquinimod and placebo groups in changes in physical examination results from Baseline up to the Month 24 and End-of-Treatment (EOT) visit were observed for general appearance; head, ears, nose and throat; musculoskeletal; nervous system; other; respiratory; abdomen; and skin assessments. For all assessments during the follow-up visits, changes from Baseline to abnormal after baseline were similar between the tasquinimod and placebo groups.

There were no notable changes in ECG findings (heart rate, QRS, and QT interval) between the tasquinimod and placebo groups from Baseline to the EOT visit.

Conclusion:
The primary objective of this study, namely, to confirm the effect of tasquinimod on delaying DP or death (rPFS; radiological progression or death) compared with placebo, was met. However, this positive effect on rPFS did not translate into an improved OS. Sensitivity and secondary endpoint analyses confirmed that tasquinimod reduced the risk of radiological

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progression but provides no advantage for symptomatic DP. Furthermore, Time to Opiate Use, QoL and Karnofsky score deterioration were not in favour of tasquinimod compared with placebo. Safety data demonstrated a higher incidence of TEAEs and poorer tolerability in the tasquinimod group compared with the placebo group. Therefore, the benefit/risk ratio was not favourable for treatment with tasquinimod in this population. Date of report: 25 September 2015		