## 2 SYNOPSIS

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| **Name of Sponsor/Company:**<br><br>Active Biotech AB | **Individual Study Table**<br><br>**Referring to Part of the Dossier** | ***(For national authority use only)*** |
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**Title of study:** Phase II Randomized Double Blind Placebo-Controlled Study to Determine the Efficacy of ABR-215050 in Asymptomatic Patients with Metastatic Castrate-Resistant Prostate Cancer
**Study number:** 07TASQ08

**Investigators:** Coordinating investigator: Roberto Pili, MD, Roswell Park Cancer Institute, Buffalo, NY, US

**Study centre(s):** 38 centres in US, 4 centres in Canada and 3 centres in Sweden

**Publication:** Pili R, Haggman M, Stadler WM, Gingrich JR, Assikis VJ, et al. Phase II Randomized, Double-Blind, Placebo-Controlled Study of Tasquinimod in Men With Minimally Symptomatic Metastatic Castrate-Resistant Prostate Cancer. J Clin Oncology 2011;20(30):4022-8.

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| **Studied period (months):** 48 weeks (double blind + open label phases) + Extension phase<br>**Date of first enrolment:** 06 December 2007<br>**Date of last completed:** 17 March 2014 (two patients ongoing) | **Phase of development:** II |

**Objectives:**
The primary objective was to evaluate the efficacy of ABR-215050 (tasquinimod) versus placebo in asymptomatic patients with metastatic castrate-resistant prostate cancer (CRPC), as measured by the proportion of patients who had not progressed at 6 months (24 weeks).
The secondary objectives were to evaluate the effect of tasquinimod versus placebo in asymptomatic patients with metastatic CRPC on:

- Time to symptomatic progression (TTSP)
- Tumour response rate in patients with measurable disease
- Impact on bone metastases
- Progression free and overall survival
- Quality of life
- Prostate specific antigen (PSA) constructs
- Molecular markers of angiogenesis and bone turnover
- Pharmacokinetics of tasquinimod
- Safety and tolerance

**Methodology:** This was a phase II randomised, double blind, and placebo-controlled, parallel-group study to determine the efficacy of tasquinimod in asymptomatic patients with metastatic CRPC. Patients were randomised to receive active treatment or placebo (in a 2:1 ratio) and were stratified according to their Karnofsky score (scores of 70-80 versus 90-100, respectively). Study treatment was administered in a double blind fashion. Patients in the active group received 0.25 mg/day tasquinimod for 2 weeks, 0.5 mg/day for the next 2 weeks, in the dose escalation phase, and then 1.0 mg/day dose or individual maximum tolerated dose (MTD), for the next 5 months (20 weeks) or until there was evidence of DP. If a patient did not tolerate the 1.0 mg/day dose then they could be treated at the individual MTD. Placebo group patients received placebo capsules that were identical in appearance to active drug.

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Unblinding occurred upon evidence of DP or after 24 weeks' treatment. Patients in the active group with DP were withdrawn. Active group patients with no DP after 24 weeks' therapy were offered an additional 24 weeks' open label treatment with tasquinimod, 1.0 mg/day or the individual MTD. At the Investigator's discretion, asymptomatic patients in the placebo group with or without DP during the first 24 weeks were also offered 24 weeks' open label treatment with tasquinimod. Placebo group patients, who started treatment with tasquinimod at the open label stage, first underwent dose titration for 4 weeks (0.25 mg/day for 2 weeks followed by 0.5 mg/day for 2 weeks) before progressing to 20 weeks' open label treatment at 1.0 mg/day or the individual MTD.
The open label continuation phase was extended after Week 48 for patients without DP, at the investigator's discretion (extension phase).
Study measurements included DP, quality of life (QOL), biomarkers, safety and pharmacokinetics (PK).

**Number of patients (planned and analysed)**: It was planned that approximately 200 patients were to be treated and analysed in a ratio of 2:1 (tasquinimod:placebo treatment), 133 and 67 patients, respectively. A total of 206 patients were randomised. Of these, 201 patients were treated and analysed (134 patients with tasquinimod and 67 patients with placebo).

**Diagnosis and criteria for inclusion**:

(1) Age ≥18 years at the time of signing the informed consent form.
(2) Histologically confirmed diagnosis of adenocarcinoma of the prostate.
(3) Asymptomatic metastatic CRPC (VAS pain score ≤3). The patient may take non-opioid analgesics for non-cancer pain discomfort.
(4) Evidence of metastatic disease from computed tomography (CT) or bone scans.
(5) Evidence of PD after castration levels of testosterone have been achieved defined by any of the following criteria:
    - Increased serum prostate-specific antigen (PSA) levels (confirmed by three consecutive PSA measurements within one year with at least 14 days between each measurement).
    - Progression of bidimensionally measurable soft tissue (nodal) metastasis (CT scan or magnetic resonance imaging (MRI)).
    - Progression of bone disease (new bone lesions by bone scan within the past 12 weeks)
(6) Castrate levels of serum testosterone (< 50 ng/dL or 1.7 nmol/L. Testosterone levels were not be required for patients who had bilateral orchiectomy).
(7) Karnofsky score 70-100

**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 1.0 mg, to be taken orally with water and preferably with food. The batch numbers used in the study were 2219744, 2219745, 2219746, 3010346, 3023880, 2226609, 2264808, 2226675, 2265907, 2226691, 2272678, 204003-177823, 310003-207021, 2242596, 2272748, 2475401, 2242599, 2272749, 2475405, 2242601, 2272752, 2475407, 2242581, 2272744, 2475397, 2245378, 2274858, 2336439, 2387954, 2475414, 2292229, 2415954, 2292241, 2415960, 2292244, 2415961, 2292227, 2374253, 2374281, 185902-01, 215189-01, 2334523, 2334524, 2334525, 2334522, 2337693, 2351192, 2351193, 2351194 and 2351189.

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**Duration of treatment**: Tasquinimod was administered at 0.25 mg/day for the first 2 weeks, then 0.5 mg/day for the next 2 weeks and then 1.0 mg/day (or individual MTD) for 20 weeks'. After the first 24 months' double blind treatment, asymptomatic patients were given the option of a further 24 weeks' open label treatment with tasquinimod (1.0 mg/day or individual MTD). The open label continuation phase was extended after Week 48 for patients without DP, at the investigator's discretion (extension phase: two patients are still ongoing as of 17 March 2014).

**Reference therapy, dose and mode of administration, batch number**: Placebo capsules were identical in appearance and composition to the tasquinimod ones, without the active ingredient. Administration was identical to tasquinimod. The following batch number was used: 2219259, 2225985, 2261442, 2242606, 2272754, 2475412, 2245382, 2274860, 2336446, 2387959, 2475416, 2334526 and 2337697.

**Criteria for evaluation**:

Efficacy:

*Primary Endpoint*

The primary endpoint was the proportion of patients with DP at 6 months (24 weeks), defined as any one or more of the following:

- Onset of tumour-related cancer pain (symptomatic progression):
  - Narcotic analgesics required for control of tumour-related pain
  - Progression by pain criteria was based on pain due to prostate cancer requiring one or more of the following palliative interventions:
    Opioid Therapy:
    - Intravenous, intramuscular or subcutaneous opioid therapy administered as a single dose
    - An increased amount of oral or transdermal opioid analgesic use administered for 10 out of 14 consecutive days requiring radionuclide or radiation therapy
    - Evidence of disease at the site of pain was required; pain, requiring only nonopioid analgesics, was not considered DP.
  - VAS (pain) rating >4 due to cancer pain on two consecutive ratings on different days
- Measurable disease progression (soft-tissue lesion progression):
  - At least a 20% increase in the Sum of Longest Diameter (Sum LD) of target lesions, taking as reference the smallest Sum LD recorded since the treatment started, or the appearance of one or more new lesions
  - Appearance of new metastatic lesions outside of the bone
  - Unequivocal progression of existing nontarget lesions
- Bone metastases or other non-target lesions (bone metastasis progression):
  - Worsening bone scan as evidenced by the appearance of two or more skeletal lesions that are not felt to be consistent with tumour flare.
    - Progressive disease in bone scan at 12 weeks needed to be confirmed by second scan (6 weeks later) and for PD at least one additional lesion has to be observed in the confirmatory scan.
- Need for radiotherapy or surgery for pathological fracture or spinal cord compression.

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In all patients, the primary efficacy endpoint was assessed by CT and bone scans at Baseline, Week 24, Week 48 and Withdrawal, with further bone scans at Week 12 and Week 36. Additional CT scans, at Week 12 and 36, were performed in patients with evidence of a lesion at a previous scan. If two or more bone lesions were recorded at Week 12, a confirmatory scan at Week 18 showing at least one new lesion compared to the Week 12 scan was required to document DP. A clinical examination was performed at every visit to assess opioid medication and any requirements for radiotherapy or surgery. Pain (Visual Analogue Scale (VAS) score) was assessed at Baseline, Week 0, 4, 8, 12, 18, 24, 36, 48 and Withdrawal.

*Secondary efficacy endpoints*
The secondary efficacy endpoints were as follows:

- TTSP: Time from first dose to symptomatic progression (onset of tumour-related cancer pain; start of radiotherapy or start of surgery for pathological fracture or spinal cord compression or start of chemotherapy)
- Tumour response of measurable disease
- Time to Soft-Tissue Lesion Progression (TTSLP)
- Analysis of bone metastases
  - Time to bone metastasis progression (TTBMP)
  - Number of patients with stable disease (SD) at various time points
  - Number of patients with decreased number of bone metastases
- Overall survival (OS = Time from first dose (randomisation) to death (any cause))
- Progression Free Survival (PFS)
- Time to Progression (TTP)
- Quality of life (QOL)
  - Functional Assessment of Cancer Therapy – Prostate (FACT-P)
  - VAS pain score
  - Karnofsky score
- Changes in pre- and post-treatment serum PSA (PSA doubling time (PSA DT), PSA slope, time to PSA progression (≥25% increase and an absolute increase of ≥2 ng/mL over nadir, confirmed by a second measurement 3 or more weeks after) and PSA change (percentage of change in PSA from Baseline to 12 weeks, and maximum decline in PSA at any point after treatment for each patient). If PSA increase was not confirmed by second measurement (missing data) this was regarded as PSA progression.
- Biological markers
  - Circulating Tumour cells (CTC)
  - Angiogenic factors (Vascular Endothelial Growth Factor (VEGF))
  - Bone alkaline phosphatase (BAP)
- Pharmacokinetics of tasquinimod

Secondary endpoints assessing PSA values, and QOL using FACT-P were measured at Baseline, and Week 0, 4, 8, 12, 18, 24, 36, 48 and Withdrawal. Performance status assessed by Karnofsky scores were measured at Baseline, Week 12, 24, 48 and Withdrawal. Blood samples for

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pharmacokinetics (PK) were taken at Week 2, 4, 8, 12, 24, 36, 48 and at Withdrawal. Biological markers were assessed at a number of time points during the study.

Safety: Safety assessments included adverse events (AEs), serious adverse events (SAEs), death rates, vital signs, laboratory values and physical examination were performed every visit of the double blind phase. Vital signs, laboratory values and AEs, were assessed at Baseline, Week 0, 2, 4, 8, 12, 18, 24, 36, 48, and Withdrawal. A 12 lead electrocardiogram (ECG) was recorded at Baseline, Week 24, 48, and Withdrawal in all patients.

A substudy was performed on the first 50 eligible patients, during the dose titration phase, to evaluate the effect of tasquinimod on cardiac conduction, particularly the QT/QTc interval.

**Statistical methods:**

Primary efficacy endpoint

For the primary efficacy endpoint, the number (%) of patients with DP at 24 weeks was tabulated by overall and by Karnofsky Performance Status 70-80 and 90-100 separately. Between group differences were tested by the Cochran-Mantel-Haenszel (CMH) statistic. The primary efficacy variable CMH test was stratified by Baseline Karnofsky Performance Status (70-80 versus 90-100). Equality of the treatment effect (i.e. odds ratio) across strata was assessed by the Breslow-Day test. The same analysis was performed using both local and central readings (the latter retrospectively). All data were listed by treatment arm, patient and visit.

The primary summary and analysis was repeated for the primary endpoint in the following four sensitivity analyses using the ITT population and presented for the double-blind phase only:

- Excluding patients included in the study in major violation of inclusion/exclusion criteria.
- Excluding patients leaving the study for any reason prior to 6 months (Week 24) without DP.
- Excluding patients leaving the study for any reason prior to Day 140 (Week 20) without DP.
- Considering patients leaving the study for any reason prior to 6 months (Week 24) as DP.

Secondary efficacy endpoints

Each of the secondary efficacy endpoints were summarized and analysed for both the ITT and PP populations and presented for the double blind and open label phase. The time-to-event variables were analysed using the survival technique Kaplan Meier (KM). The median survival time was estimated for each treatment arm using KM product-limit estimation for each Karnofsky stratification level and overall. In addition, observed and KM cumulative estimators were computed for survival rates at 3, 6, 9 and 12 months. A KM survival plot was provided and included the number of patients at risk, p-value and 95% CI on the difference between treatment arms.

The treatment differences were tested using unadjusted log rank test as well as using log rank test adjusted for the Baseline Karnofsky Performance Status (70 to 80 versus 90 to 100), for the country and for the clinical subtype (PCWG2) for the overall analysis and the p-value was presented. The hazard ratio and its 95% CI were estimated using Cox Proportional Hazard Model for both unadjusted and adjusted for the Baseline Karnofsky Performance Status, the country and the clinical subtype (PCWG2).

Subgroup analysis

For PFS only, Forest plots were produced to present hazard ratios and 95% CI for the following subgroups : Age (40-75 years, 76-99 years), Karnofsky scale (≤80), Karnofsky scale (≥ 90), alkaline phosphatase (> upper limit of normal (ULN) and ≤ ULN), haemoglobin (< lower limit of

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normal (LLN), ≥LLN), lactate dehydrogenase (>ULN, ≤ ULN), PSA DT (<4 months, ≥4 months), PSA Day1 (< 24 ug/L, ≥24 ug/L) and PCWG2 (visceral, node only, bone only, bone metastasis).

Quality of Life

Quality of life (QOL) was assessed in three ways: the FACT-P questionnaire, the patient VAS (pain) and Karnofsky Performance status. All outputs used the ITT and PP populations and were presented separately in the double blind and open label phase. Changes from baseline were compared between treatment arms using a Wilcoxon test. All data were listed by treatment arm, patient and visit.

The treatment arms for the double blind and open label phase were compared using analysis of covariance (ANCOVA), allowing for treatment as the main effect in the model.

Biomarkers

The observed and ratio to Baseline values of biological markers (CTC, VEGF, BAP) and NTx were summarised using descriptive statistics by treatment arm and available visits for the ITT and PP populations. Ratio from baseline was compared between treatment arms using a Wilcoxon test.

Safety

Adverse event data were listed for all patients and summarized using the safety population by treatment arm and overall and presented separately in the double blind and open label phases by System Organ Class (SOC) and Preferred Term (PT), causality, intensity, seriousness and outcome.

Summary statistics (mean, median, standard deviation and range as appropriate) of clinical laboratory tests, physical examination, vital signs and ECG parameters, were provided for the safety population by treatment arm and presented separately for the double blind and open label phases. In addition, summary statistics for changes in vital signs and ECG from Baseline to each study visit were presented.

Laboratory observed values and change from baseline were summarized at each available visit by parameter and treatment arm (if applicable) using descriptive statistics for either continuous or categorical variables. Laboratory parameters with available toxicity grade in the National Cancer Institute Common Toxicity Criteria (NCI-CTCAE) were scored accordingly and if the parameter value was within normal range then it was reported as 'not graded'. Laboratory parameter results were categorized into Low, Normal and High based on the central laboratory reference range. A shift table was presented for this categorized laboratory result by parameter, visit and treatment arm according to Baseline.

Exploratory analyses

Exploratory analyses were performed by the Sponsor. The influence of the following prognostic factors was investigated: PSA slope at Baseline, PSA level, Karnofsky score, age, race, Tumour, node, metastasis (TNM), Gleason score, visceral metastasis, number of bone lesions, number of CT lesions, total number of lesions, sum of target lesions, time since diagnosis, orchiectomy, line of treatment, radiotherapy, VAS-pain, FACT-P, weight, systolic/diastolic BP, biomarkers, haemoglobin, lactate dehydrogenase (LDH) and other laboratory data. The factors were log transformed or split by median in order to get robust analyses. The effect of treatment and other factors were tested as well as the correlation of biomarkers in other parameters.

For each of the time to event endpoints, the influence of potentially important prognostic factors was assessed using Cox proportional hazards regression. Univariate associations between

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covariates of potential interest with each time to event endpoint were evaluated using Wald's chi-square test from the Cox regression model. Parameters found to be statistically significant in univariate analyses ($p<0.05$) were retained for multivariate Cox analyses. The same analysis was also performed considering a threshold of $p<0.20$.

Summary - conclusions:

Efficacy results:

Analysis of the primary endpoint of this double blind randomised study demonstrated that a significantly lower percentage of patients had DP at Week 24 in the tasquinimod group (29.9%) compared to placebo group (62.7%), with CMH p-value <0.0001, in the ITT population. Similar results were seen in the PP population (34.7% versus 60.45%, p=0.0047).

The sensitivity analysis that excluded patients with major violations of the inclusion and exclusion criteria supported the results of the primary endpoint ($p<0.0001$) and the sensitivity analysis that excluded patients leaving the study for any reason prior to Week 24 other than DP missed statistical significance (p=0.0533).

Most secondary endpoints PFS, TTP, TTRDP, TTSTL, TTNSTL and TTBM, adjusted for the baseline Karnofsky scale (70 to 80 versus 90 to 100), were significantly longer in the tasquinimod group. The hazard ratios reported for these endpoints are equivalent to reductions of risk ranging from 31.9% to 78.1% in tasquinimod compared to placebo. While differences in median (when reached) and hazard ratios were numerically in favour of tasquinimod for TTNBL and TTSP, they were not statistically significant (see table below).

**Summary of Time to Event Secondary Endpoints up to Week 24 (ITT)**

| | **Tasquinimod N=134** | **Placebo N=67** | **Log rank test[a] p-value** | **Cox analysis[a]** | |
|---|---|---|---|---|---|
| | | | | **HR (95% CI)** | **p-value** |
| Median progression free survival up to Week 24 (months) (95% CI) | 5.6 (5.4, NR) | 3.0 (2.8, 5.4) | 0.0016 | 0.511 (0.335, 0.780) | 0.0018 |
| Median time to progression (months) (95% CI) | 5.7 (5.5, NR) | 3.0 (2.8, 5.5) | 0.0015 | 0.503 (0.326, 0.777) | 0.0020 |
| Median time to radiological disease progression up to Week 24 (months) (95% CI) | 5.7 (5.5, NR) | 3.1 (2.8, 5.7) | 0.0004 | 0.461 (0.290, 0.734) | 0.0011 |
| Median time to soft-tissue lesion progression (months) (95% CI) | 5.6 (5.4, NR) | 3.0 (2.8, 5.8) | 0.0126 | 0.512 (0.284, 0.924) | 0.0263 |
| Median time to bone metastasis progression (months) (95% CI) | NR (5.7, NR) | 5.9 (4.5, NR) | 0.0005 | 0.211 (0.080, 0.557) | 0.0017 |
| Median time to new soft-tissue lesions (months) (95% CI) | NR (NR, NR) | 5.7 (5.4, 6.2) | 0.0401 | 0.516 (0.271, 0.979) | 0.043 |
| Median time to new bone lesions (months) (95% CI) | 5.4 (3.2, NR) | 3.0 (2.8 - 5.3) | 0.0600 | 0.652 (0.422, 1.005) | 0.0529 |
| Median time to symptomatic progression (months) (95% CI) | NR (NR-NR) | NR (NR, NR) | 0.0707 | 0.421 (0.169, 1.050) | 0.0635 |
| Median time to prostate specific antigen progression (months) (95% CI) | 2.8 (2.0, 4.2) | 1.8 (1.6, 2.6) | 0.0389 | 0.681 (0.470, 0.987) | 0.0424 |

Abbreviations: CI: confidence interval; HR: hazard ratio; NR: not reached

a Adjusted treatment group effect for the baseline Karnofsky scale (70 to 80 versus 90 to 100)

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The exploratory multivariate analyses of the data indicated that the differences in PFS between treatment groups were not due to an imbalance in prognostic factors between these groups, but were due to an effect of tasquinimod.
Subgroup analysis, for a treatment effect in PFS in the ITT population at Week 24, revealed that the following subgroups had a significant treatment effect in a specified category: age (40 to 75 years), Karnofsky score (≥90), alkaline phosphatase (≤ULN), Hb (≥LLN), LDH (≤ULN), PSA DT (<4 months), PSA DT (≥4 months), PSA Day 1 <24 µg/L), bone and bone only. However, because of the low number of patients per subgroups, this needs to be confirmed in a larger population.
TTPP was longer in the tasquinimod treated group than in the placebo group. PSA constructs and Waterfall plots showed no clear treatment or time effect on the levels of PSA.
Analysis of change from Baseline FACT-P data showed that QOL deteriorated over time in both treatment groups. However, the QOL deteriorated continuously over the double blind phase, while in the tasquinimod arm, QOL deterioration was more pronounced over the first 8 weeks, with a significant drop at Week 4 and 8, and thereafter QOL improved from Week 8 until the end of the double blind phase. This significant difference in QOL deterioration was explained by more severe impairment on "*Physical well-being*" and "*Additional concerns*" domains in the first visits, likely to be related to drug tolerability issues.
Similarly, pain (VAS scale) and Karnofsky score deteriorated over the initial weeks of tasquinimod treatment, with Karnofsky score data achieving statistical significance at Week 12. After Week 12, an improvement was noted in both pain and Karnofsky score in tasquinimod treated patients for the rest of the double blind phase. In contrast, a continuous decrease in Karnofsky score and increase in pain was noted in placebo patients during the double blind phase. By the end of the double blind phase, tasquinimod patients had a similar QOL score as placebo patients.
The median ratio to baseline of BAP was stable in tasquinimod treated patients during the first 12 weeks of treatment, whereas the ratio to baseline increased in patients receiving placebo. The median ratio to baseline of VEGF levels increased transiently in tasquinimod treated patients at Weeks 4 and 8 compared to the placebo group. The biomarker analyses suggested a favourable impact of tasquinimod over time on BAP level stabilisation and a transient induction of VEGF levels with tasquinimod.
Central review was performed retrospectively on CT and bone scans from a smaller subset of patients. Central review for the primary endpoint was statistically significant in favour of tasquinimod for the PP population but not for the ITT population. Central review of PFS and TTRDP were numerically in favour of tasquinimod treatment but not statistically significant.

<u>Pharmacokinetic results:</u>
The PK of tasquinimod was assessed using population analysis of data from 166 patients. The PK of tasquinimod was best described by a 1-compartment model, with inter-individual variability on apparent clearance (CL/F), apparent volume of distribution (V/F) and with proportional residual error. Absorption rate constant and lag time were fixed to 0.46 $h^{-1}$ and 0.99 h, respectively. In the final model, the predicted apparent clearance and volume of distribution were 0.182 L/h and 13.5 L during treatment phase, respectively, for a patient of 73 years. Age had a significant impact on

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CL/F; lower CL/F was associated with older patients (1.4 % decrease per year from 48 to 89 years). The small changes observed in CL/F over time, 15% lower during the titration phase compared to the treatment phase, are unlikely to have any clinical relevance.
No significant correlations were observed between average plasma concentration ($C_{av}$) and changes in laboratory parameters. Furthermore, no difference in PFS could be detected between patients with low and high $C_{av}$ in this study, where patients were titrated up to a tolerable maintenance dose.

Safety results:
***Adverse events***
*Double Blind Phase*
The incidence of treatment emergent adverse events (TEAEs) was higher in the tasquinimod treated patients compared with placebo treated patients (97.0% versus 83.6%, respectively).
The SOCs with the highest proportion of TEAEs in both tasquinimod and placebo treated patients were gastrointestinal disorders (64.9% versus 46.3% patients) and musculoskeletal and connective tissue disorders (60.4% versus 44.8% patients).
The most frequently reported TEAE PTs after tasquinimod treatment, were fatigue (29.1%), nausea (26.9%) constipation (25.4%) and back pain (23.9%). These were generally of mild to moderate intensity, suggesting tolerability issues rather than more serious safety concerns. For TEAEs of Grade 3 and above, the most frequent SOCs were musculoskeletal disorders and investigations (9.7% of tasquinimod treated patients for both SOCs versus 3.0% and no incidence of placebo treated patients, respectively). The incidence of TEAEs appeared to reduce with time on study treatment, notably in tasquinimod treated patients.
The incidence of treatment related TEAEs (affecting ≥5% of patients) was higher in tasquinimod treated patients (71.6%) compared to placebo treatpatients (40.3%). The distribution was similar to that of TEAEs overall with nausea (24.6%), fatigue (23.1%) and constipation (18.7%) being the most commonly reported treatment related TEAEs in tasquimod treated patients.
In tasquinimod treated patients, the most frequent SAEs by SOC were gastrointestinal (6.7%), renal and urinary disorders (6.0%), cardiac disorders (5.2%), vascular disorders (4.5%), blood and lymphatic system disorders (3.7%) and infections and infestations (3.7%), all more frequently reported than in the placebo group. By PT, pneumonia, anaemia, deep vein thrombosis and vascular disorders were reported by four patients each and renal failure and atrial fibrillation by three patients each; all other SAE PTs were reported in either one or two patients only.
TEAEs leading to discontinuation were more frequently reported in tasquinimod treated patients than in placebo treated patients (22.4% versus 1.5%, respectively) and there were only either one or two patients per PT.
TEAEs leading to dose reduction were more frequently reported in tasquinimod treated patients (25.4%) than in placebo treated patients (7.5%). The most frequent TEAEs leading to dose reduction by PT were nausea and fatigue (8.2% and 4.5% in tasquinimod treated patients). For other TEAEs, there were only either one or two patients per PT.
*Open Label Phase*
The incidence of TEAEs was higher in placebo treated patients who had switched to tasquinimod compared to patients continuing with tasquinimod (97.6% versus 69.4%, respectively). TEAEs

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were more frequently reported for gastrointestinal disorders, musculoskeletal disorders, investigations, and infections and infestations in placebo patients who switched to tasquinimod compared with those patients who continued on tasquinimod. The most frequent TEAE PT (22.0%) and treatment related PT (14.6%) in placebo patients who switched to tasquinimod was nausea
There were more SAEs, treatment related TEAEs, TEAEs leading to treatment discontinuation and TEAEs leading to dose reduction in patients who crossed over from placebo to tasquinimod.
During the double blind and open label phases, there were nine deaths; three were due to DP and six were not related to DP. All of them were considered not related to study drug.

***Laboratory and Other Safety Parameters***

During the double blind and open label phases, most laboratory parameter abnormalities were Grade 1 or Grade 2 in intensity. A total of 4.5% of tasquinimod patients had Grade 4 lipase in the double blind phase, compared with no placebo patients. No change in kidney and liver function parameters was observed.
There was a consistent increase in erythrocyte sedimentation rate, C-reactive protein, amylase, lipase, fibrinogen, white blood cells and platelets in the tasquinimod group and a consistent drop in lymphocytes, red blood cells, haemoglobin, lactate dehydrogenase and bilirubin, with little change in the placebo group. These changes often increased in amplitude from Week 2 but recovered (fully or partially) to the Baseline value by the end of the double blind phase.
No notable differences in ECG, vital signs and physical examination were observed between treatment groups.

Conclusion:

This phase II study demonstrated a superior treatment effect of tasquinimod over placebo in patients with asymptomatic metastatic CRPC, including bone lesion and soft tissue lesion subpopulations. Despite low grade, transient and manageable adverse events, affecting tolerability, no major safety concerns were raised.

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