

1 **TITLE:** Padeliporfin Vascular-targeted Photodynamic Therapy Versus Active Surveillance:
2 A Randomised Clinical Trial in Men with Low-risk Prostate Cancer

3 **RUNNING TITLE:** Photodynamic Therapy for Low-risk Prostate Cancer

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42 **SUMMARY**

43 *Background*

44 Vascular-targeted photodynamic therapy (VTP), a novel tissue-preserving treatment for low-
45 risk prostate cancer (PC), has shown favorable safety and efficacy results in single-arm Phase
46 I and II studies. This report presents results of a randomised, controlled, parallel-group
47 clinical trial of padeliporfin VTP versus the standard of care, active surveillance (AS).

48 *Methods*

49 Men with low-risk, localised PC (no Gleason patterns 4 or 5) and no previous treatment were
50 recruited from March 8, 2011 to April 30, 2013 at 47 European university centres and
51 community hospitals. They were randomised (stratification by centre using balanced blocks)
52 to VTP or AS. VTP consisted of 4 mg/kg padeliporfin administered intravenously over ten
53 minutes via optical fibres inserted into the prostate to cover the desired treatment zone and
54 subsequent activation by laser light for 22 minutes and 15 seconds. Both groups were
55 followed-up for 24 months in accordance with best AS practice at the time of study design,
56 i.e., biopsy at 12-month intervals and prostate-specific antigen measurement and digital rectal
57 exam at 3-month intervals. The prespecified co-primary efficacy endpoints were histological
58 progression of cancer and absence of any histology result definitively positive for cancer at
59 Month 24. Treatment was open-label, but primary efficacy outcomes were evaluated in a
60 blinded manner.

61 *Findings*

62 Of the 206 subjects randomised to VTP, 196 received treatment. At completion of the trial,
63 all 413 randomised subjects (intention-to-treat population) were analysed for efficacy. VTP
64 doubled time to progression (from 14.1 [95% CI: 12.9 to 23.8] months to 28.3 [95% CI: 26.0

65 to 30.6] months; $p < 0.0001$) and reduced the progression rate to approximately one-third that
66 of AS (adjusted hazard ratio = 0.34; 95% CI: 0.24, 0.46; $p < 0.0001$). VTP increased the
67 probability of a negative prostate biopsy at 24 months post-treatment from 13.5% (28 of 207
68 subjects) to 49.0% (101 of 206 subjects) (adjusted risk ratio: 3.67; 95% CI: 2.53, 5.33);
69 $p < 0.0001$).

70 VTP was well tolerated. Genitourinary function showed transient deterioration in the VTP
71 group, but no significant effects were seen at Month 24. The most common AEs in the VTP
72 group were urinary tract infections (21 subjects) and AEs in the renal and urinary disorders
73 (133 subjects) and reproductive system and breast disorders system organ classes (121
74 subjects). The most common serious side effect was retention of urine. Typically this event
75 occurred on the first attempt to withdraw the urinary catheter (day-1 post-op). This was
76 managed with immediate re-catheterization. The timing of a second attempt at removal of the
77 urinary catheter was left to the discretion of the local investigator. This event occurred in 15
78 subjects, was severe in 3 subjects, and resolved within two months in all cases.

79 ***Interpretation***

80 Padeliporfin VTP is a safe effective treatment for low-risk, localised PC that reduces the rate
81 of histological progression compared to AS. It may allow more men to consider a tissue-
82 preserving approach and defer or avoid radical therapy.

83 ***Funding***

84 STEBA Biotech S.A.

85 ***Registration***

86 ClinicalTrials.gov NCT01310894

87

88 **RESEARCH IN CONTEXT**

89 *Evidence before this study*

90 The idea of modifying our therapeutic target from the host organ to the tumour plus a margin
91 has been the mainstay of surgical oncology during the latter half of the 20th century. The
92 principle is probably best exemplified in breast cancer, for which the previous standard of
93 care, the Halsted radical mastectomy, has, with time and accumulating evidence, largely been
94 replaced by breast preservation achieved by local excision with or without radiotherapy. We
95 have seen the same process in renal cancer. Radical nephrectomy is currently performed only
96 when partial nephrectomy and nephron preservation is neither practical nor possible. Ten
97 years ago it was performed in all patients. The principles behind this transition are
98 equivalence in terms of cancer-related outcomes but better function, greater patient
99 acceptability, quicker recovery, and enhanced survivorship. Prostate cancer (PC) is the only
100 solid organ cancer left for which this principle is not generally applied. Over the last decade
101 several proof-of-concept studies of focal therapy for PC have been published, but they have
102 typically been single-centre, small, and of relatively low quality. Having said this, these
103 studies demonstrated the feasibility of more targeted treatment for PC and more importantly
104 suggested high levels of patient acceptability because of excellent functional outcomes. More
105 recently we have seen registered prospective development studies and formal Phase I and
106 Phase II studies that demonstrate both safety and early (short-term) oncological efficacy.
107 These studies have been summarised in Valerio's systematic review.

108 *Added value of this study*

109 Valerio's systematic review identified the need for comparative studies. To our knowledge,
110 ours is the first such study. Because vascular-targeted photodynamic therapy (VTP) is an
111 intervention involving both a drug (in this case, padeliporfin) and a device (laser light
112 introduced into the prostate), it was subject to regulatory approval as a drug through the
113 European Medicines Agency (EMA). A pivotal comparative study was thus necessary but
114 was challenging to design in a manner that would be acceptable to both patients and
115 clinicians and in which the same primary outcome could be assessed for both VTP and the
116 comparator. We had three options for the comparator: surgery, radiotherapy, or active
117 surveillance (AS). The first two were problematic in arriving at a primary outcome that could
118 be applied to both the experimental arm and the control. Surgery (radical prostatectomy)
119 would not be suitable for a biopsy-based outcome because there would be no prostate to
120 biopsy. Radiotherapy, on the other hand, would be amenable to a protocol-required biopsy,
121 but the histological outcome would be confounded by the necessary neoadjuvant and
122 adjuvant androgen suppression that comprises the standard of care. Therefore, AS was the
123 only comparator that could reasonably be employed over the intended time frame of the
124 study. The task for the EMA and the PCM301 Study Group was to determine the upper and
125 lower risk thresholds of this low-risk group that would define the upper and lower bounds of
126 the study entry criteria. These criteria had the effect of excluding, within the limits of
127 precision of the diagnostic methods available to us at the time, men that were at very low risk
128 and therefore unlikely to progress and men that were at higher risk and therefore unlikely to
129 be offered or indeed consent to AS.

130 These thresholds of low risk were in keeping with standard practice at the time of study
131 design. Recent publications from Scandinavia and Canada on mature AS populations have
132 subsequently shown that men towards the upper threshold of low-risk PC do fare worse in
133 progression than men with very-low-risk disease. Modern diagnostic methods, including

134 magnetic resonance imaging, allow us to identify these risk groups with considerably greater
135 precision today than was possible at the time when the study was being considered by the
136 EMA. Our results show that men with localised, low-risk PC can be treated in a way that not
137 only preserves their genitourinary function but also results in a lower progression rate, greater
138 chance of being declared disease-free, and reduction in need for whole-gland radical therapy
139 in the form of surgery or radiotherapy.

140 *Implications of all the available evidence*

141 When this study was designed, our risk stratification methods at diagnosis were poor. The
142 correction that was applied to mitigate the consequences of this imprecision was to offer
143 radical therapy to nearly all men, irrespective of attributed risk. Today we attribute risk with
144 greater precision using risk calculators, biomarkers, and imaging. Our study adds
145 considerable weight to the argument that we need to move away from a one-size-fits-all
146 approach to treatment and gradually replace it with a more risk-stratified approach to care.
147 We have AS for men at very low risk. We have radical therapy and multimodality treatments
148 for men at high risk for whom the consequences of treatment are matched by benefit.
149 Between these two extremes, we now have VTP, an intervention that preserves prostate tissue
150 when it is both possible and practical to do so. Given the precision of today's risk
151 stratification, future research will need to explore both the patient preferences and the upper
152 threshold of risk (as defined by tumour grade, volume, location, multiplicity) that should
153 determine where the transition point exists where tissue preservation is likely to confer
154 diminishing returns and should be supplanted by whole-gland radical therapy.

155

156 **INTRODUCTION**

157 Active surveillance (AS), a policy of delayed selective intervention, is an appropriate
158 therapeutic option for low-risk prostate cancer (PC) that helps to mitigate the consequences
159 of overtreatment.¹ Most studies—though admittedly single-centre and noncomparative—have
160 demonstrated favorable outcomes, but AS has been associated with fairly high intervention
161 rates especially in cohorts with less stringent eligibility criteria.² Intervention, or crossover to
162 radical treatment (surgery or radiotherapy) or systemic therapy (androgen suppression), tends
163 to be driven by—in descending order of frequency—pathological upgrading on repeat biopsy,
164 biochemical progression, and patient choice.³

165 Focal therapy and AS are both tissue-preserving strategies. They share the goal of preserving
166 prostate tissue and consequently function by delaying or avoiding radical whole-gland
167 treatment in men in whom it is safe to do so.⁴ However, focal therapy differs from AS in that
168 it treats disease—by the process of selective tissue ablation—above a certain risk threshold
169 and monitors disease below that threshold, as the latter is deemed to be clinically
170 insignificant. A risk-stratified clinical pathway that offers men focal therapy in a manner
171 complementary to AS might result in two potential benefits: a reduction in the probability of
172 failure or crossover to radical therapy and an increase in the proportion of men eligible and
173 willing to undergo a tissue-preserving treatment.

174 Neither focal therapy nor AS has previously been assessed in a prospective, comparative
175 efficacy study. Both have been assessed only in single-centre series,^{2,5,6} in which the
176 outcomes were dependent on the population studied, the diagnostic precision at baseline, the
177 intensity and manner of the reclassification tests, and the study duration. These limitations
178 challenge informed decision-making by the patient because the attributes that are most likely
179 to influence treatment selection are the failure rates and toxicity profiles of the two
180 approaches and the likelihood of avoiding radical therapy. We present the results of what is to
181 our knowledge both the first prospective comparative evaluation of the efficacy and safety of

182 focal therapy and the first evaluation of AS in a comparative setting—rather surprisingly
183 given that it is a recommended standard of care. The selective ablation in our focal therapy
184 arm was achieved using vascular-targeted photodynamic therapy (VTP) with padeliporfin, an
185 agent that achieves its tissue effects nonthermally and had previously been evaluated in both
186 preclinical and clinical settings.^{7,8}

187 **METHODS**

188 *Study design and participants*

189 Study CLIN1001 PCM301 was a randomised, controlled, parallel-group clinical trial of
190 padeliporfin VTP versus AS for treatment of low-risk, localised PC. Men aged ≥ 18 years
191 with low-risk, localised PC diagnosed by transrectal ultrasound (TRUS)-guided biopsy and
192 no previous treatment were enrolled, provided they were eligible to be exposed to a
193 photosensitising agent and had no contraindications to undergoing magnetic resonance
194 imaging (MRI). Participants were required to have low-risk PC but not very–low-risk PC.
195 Men were eligible if one core of cancer that was free of Gleason patterns 4 or 5 was present
196 provided that the cancer core length was between 3 and 5 mm. In other words, if only one
197 core was positive, only Gleason pattern 3 was permitted but in order to qualify the cancer
198 core length had to be greater than or equal to 3mm and less than or equal to 5mm. Men with 2
199 or 3 cores positive were also permitted, but cancer core length could not exceed 5 mm.
200 Clinical stage was limited to $\leq T2a$ (pathological or radiological up to T2c disease permitted),
201 prostate-specific antigen (PSA) ≤ 10 ng/mL, and prostate volume ≥ 25 and < 70 cc). These
202 criteria were based on a study of prediction determinants prediction in AS subsequently
203 reported by Welty et al.⁹ The performance status of the subjects was not a criterion for study
204 inclusion. Instead, two overarching requirements had to be satisfied: men had to have a
205 predicted life expectancy of 10 years or more and, in addition, had to be free of any medical

206 conditions that were deemed to be a contraindication to general anaesthesia. Men with a
207 contraindication to MRI (e.g. cardiac pacemaker), factors excluding accurate reading of
208 pelvic MRI (e.g. bilateral hip replacements), or any condition or history of illness or surgery
209 that may have posed an additional risk to men undergoing VTP procedure were excluded.
210 Criteria for subject removal from the study were occurrence of a serious adverse event (SAE)
211 if recommended by the investigator, subject withdrawal, or a major protocol violation.

212

213 The study was conducted in compliance with Good Clinical Practice and according to a
214 written protocol approved by each centre's ethics committee. All subjects provided written
215 informed consent. The trial was completed in accordance with the protocol.

216

217 ***Randomisation and masking***

218 Investigators enrolled subjects and allocated them to the VTP and AS groups in a 1:1 ratio
219 using a web-based randomisation system generated by the sponsor and stratified by centre
220 using balanced blocks of varied size (2 or 4 subjects). Treatment was open-label (subjects
221 and investigational site staff were not blinded to study treatment), but primary efficacy
222 outcomes were evaluated in a blinded manner.

223 ***Procedures***

224 AS was conducted according to best practice at the time of study design.^{10,11} It comprised a
225 protocol-directed biopsy at 12-month intervals and 3-monthly PSA measurement coupled
226 with a digital rectal exam.

227 The aim of VTP was to treat a complete prostate lobe. Subjects randomised to padeliporfin
228 VTP underwent pretreatment multiparametric MRI, which was centrally reviewed with the

229 biopsy results by a committee composed of radiologists and urologists who made detailed
230 recommendations on the number, length, and position of interstitial optical fibres using
231 treatment guidance software.^{8,12} The treatment-guidance software was used to generate a
232 light-density index (LDI; a measure of the energy exposure per unit volume of target tissue)
233 of >1, which had been associated with a high probability of a single-lobe ablation in earlier
234 studies.⁸ However, the urologist in charge of the treatment was allowed to adapt the treatment
235 recommendations to the actual volume and shape of the prostate observed on the TRUS
236 images at the time of the procedure. Once the fibres were accurately positioned in the
237 prostate to cover the desired treatment zone, 4 mg/kg padeliporfin (Aptuit Glasgow Ltd,
238 Glasgow, UK) was administered intravenously over ten minutes. The drug was activated in
239 the treatment zone by laser light at 753 nm with a fixed power of 150 mW/cm over
240 22 minutes and 15 seconds, corresponding to an energy dose of 200 J/cm.¹³ Subjects with
241 bilateral cancer received a second procedure for contralateral lobe treatment. Retreatment of
242 lobes positive for PC at the Month 12 biopsy was permitted. The VTP procedure was carried
243 out under a general anaesthetic during a 2-hour operating theatre allocation with a planned
244 overnight stay. The urethral catheter was removed the morning after the procedure.

245 For subjects in both groups, PSA was measured and digital rectal examination performed
246 every three months. TRUS-guided, 12-core biopsy (6 cores directed to each prostate lobe)
247 was performed at Months 12 and 24. Thus, the sampling density (number of cores per unit
248 volume of tissue) in the subjects who received VTP was greater than in those in the AS
249 group, particularly for VTP-treated lobe(s) with reduced volume associated with post-
250 treatment fibrosis. Biopsy samples were read centrally by an independent pathologist blinded
251 to treatment assignment and local pathologist reading. An independent, blinded Outcomes
252 Review Panel reviewed all PSA data and TRUS-guided biopsy reports to assess these results
253 and determined the number and location of positive cores. In the case of discrepancy between

254 the local and central biopsy readings, the panel's pathologist adjudicated. Any additional
255 radical PC treatments, metastases, evidence of T3 disease, and severe PC-related events were
256 recorded at Months 12 and 24. Any man who underwent radical PC treatment without
257 histological progression (because of patient or physician preference) continued in the study
258 until the end (Month 24) and returned to standard care after that.

259 The International Prostate Symptom Score (IPSS) and International Index of Erectile
260 Function – 15 Questions (IIEF-15) questionnaires were administered every three months
261 through Month 12 and at Month 24 (and at seven days postprocedure for subjects who
262 received padeliporfin VTP). Validity and sensitivity of these questionnaires to detect change
263 in genitourinary function have been established.^{14,15} The EuroQol-5D (EQ-5D) questionnaire
264 was administered at Month 12 and Month 24 to assess quality of life. All adverse events
265 (AEs) were recorded from the signing of the consent form through the end of the study
266 (including any occurring after the initiation of additional PC treatment). At each study visit,
267 the investigator questioned the subject about AEs and intercurrent illnesses since his last visit.
268 The questions were general, and the presence or absence of specific AEs was not solicited
269 from subjects. AE severity was graded according to the National Cancer Institute Common
270 Terminology Criteria for Adverse Events version 4.03. The investigator assessed the
271 relationship of each AE to the study drug (padeliporfin), device, and procedure. AEs were
272 coded and categorised according to the Medical Dictionary for Regulatory Activities
273 (version: 18.0). Haematology, coagulation, serum chemistry, and urinalysis were evaluated
274 every three months. Troponin was measured before discharge and quantitative D-Dimer
275 before anaesthesia, before discharge, and at 7 days post-treatment for subjects who received
276 VTP. Vital signs, electrocardiogram, and physical examination were performed preprocedure
277 and postprocedure for subjects who received padeliporfin VTP. An independent Data Safety
278 Monitoring Board (composed of two urologists, a laser surgery expert, and a statistician)

279 reviewed safety data and SAE reports throughout the study and advised the sponsor on
280 matters of subject safety.

281 ***Outcomes***

282 The prespecified co-primary efficacy endpoints were treatment failure (histological
283 progression of cancer from low to moderate or higher risk over 24 months follow-up) and
284 absence of definitive cancer (absence of any histology result definitively positive for cancer
285 at Month 24). Moderate or higher risk was defined as the observation of one of the following
286 events: more than three cores definitively positive for cancer when considering all
287 histological results available during follow-up in the study, any Gleason primary or
288 secondary pattern of 4 or more, at least one cancer core length >5 mm, PSA > 10 ng/mL in
289 three consecutive measures, any T3 PC, metastasis, PC-related death. The prespecified
290 secondary objective was to determine any differences between the two groups in the
291 following outcomes: total cancer burden in the prostate; rate of additional PC radical therapy;
292 rate of severe PC-related events (cancer extension to T3, metastasis, PC-related death); rate
293 of AEs; rate of incontinence, erectile dysfunction, and urinary symptoms.

294 ***Statistical analysis***

295 The sample size was based on an expected rate of progression from low to moderate or higher
296 risk of $\geq 15\%$ over 2 years in the AS group and 5% in the VTP group. Using these
297 assumptions, the sample size required was 400 subjects (200 subjects per group), and at least
298 40 events (subjects with progression of cancer) needed to be observed for the final analysis to
299 take place.

300 Statistical analyses were conducted using SAS version 9.3. All randomised subjects were
301 analysed for efficacy according to assigned treatment in an intention-to-treat analysis.

302 Treatment failure (progression) was analysed by survival analysis. Times to progression were
303 compared between the two treatment groups using the log-rank test and quantified using a
304 Cox proportional-hazards regression model to derive hazard ratios at Month 24, and
305 treatment group and age, number of positive cores, prostate volume, and disease status at
306 baseline were used as covariates. Absence of definitive cancer (positive biopsy) was analysed
307 as a dichotomous outcome. Proportions of subjects with observed success at Month 24 were
308 compared by 2-sided Pearson's chi-square test, and odds and risk ratios were calculated.
309 Time to initiation of radical therapy was estimated by the Kaplan-Meier method, and the log-
310 rank test was used for comparison. The mean number of positive cores and maximum cancer
311 core length at Months 12 and 24 were compared by Student *t* test. Other efficacy data were
312 summarised descriptively.

313 All subjects randomised to VTP who received any padeliporfin or initiated any study
314 treatment-related procedure and all subjects randomised to AS were analysed for safety by
315 treatment received. IIEF-15, IPSS, and EQ-5D results were analysed by analysis of
316 covariance. Other safety data, including, AEs, were summarised descriptively.

317 The trial is registered at ClinicalTrials.gov (NCT01310894).

318 ***Role of the funding source***

319 The study sponsor and funder, STEBA Biotech S.A., developed the protocol in consultation
320 with the study investigators and the European Medicines Agency (EMA). STEBA performed
321 data management and statistical analysis and provided medical writing support for this report.
322 AAzzouzi and ME had full access to all data in the study. The final decision to submit this
323 report for publication was made jointly by all the authors. The corresponding author (ME)
324 had the final responsibility to submit for publication.

325 **RESULTS**

326 Subjects were recruited from March 8, 2011 to April 30, 2013 and followed for
327 approximately 24 months at 47 university centres at community hospitals in ten European
328 countries (Belgium, Finland, France, Germany, Italy, Netherlands, Spain, Sweden,
329 Switzerland, and the United Kingdom). Tables showing investigational sites, principal
330 investigators, and numbers enrolled at each site and in each country are included in the
331 Appendix (pp.1-2). The study was completed on June 25, 2015, and a total of 413 men were
332 enrolled: 206 randomised to the VTP group and 207 to the AS group. More subjects in the
333 AS group (n=6) than in the VTP group (n=17) withdrew consent before study completion.
334 Although unwillingness to accept randomisation to either group was an exclusion criterion,
335 the sponsor anticipated that subjects randomised to AS might withdraw because they had
336 entered the study to receive active treatment. The percentage of such withdrawals was less
337 than expected. Otherwise, study completion and reasons for withdrawal were similar between
338 the two groups (Figure 1).

339 Demographic and baseline disease characteristics were well balanced between the two groups
340 and fit the profile of low-risk PC patients (Table 1). Of the 206 subjects randomised to VTP,
341 nine did not subsequently start the VTP procedure: three who withdrew consent, three who
342 were excluded because for exclusion criteria (bladder cancer discovered on pretreatment
343 MRI, previous Gleason 3+4 biopsy, history of transurethral prostate resection), one who was
344 discontinued by the investigator because of noncompliance, one who had a myocardial
345 infarction, and one who was claustrophobic so unable to undergo the pretreatment MRI.

346 Of the 197 subjects who started the VTP procedure, one had an anaesthesia reaction before
347 receipt of any padeliporfin or laser treatment. In all, 196 subjects received initial VTP (Figure
348 1). Of these, 62 received subsequent contralateral treatment, 11 received retreatment, and two

349 received both contralateral treatment and retreatment. An LDI ≥ 1 was achieved in 252 (98%)
350 of 254 initial treatments of a lobe. Prostate lobes that were retreated were less likely to
351 achieve an LDI ≥ 1 , although they were exposed to the same energy of 200 J/cm (appendix
352 p.2).

353 All 413 randomised subjects were included in the efficacy analysis (Figure 1). Padeliporfin
354 VTP delayed progression from low-risk to moderate or higher-risk PC and reduced the
355 probability of a positive biopsy results at Month 24 compared to AS (Table 2). Padeliporfin
356 VTP doubled time to progression from 14.1 (95% CI: 12.9 to 23.8) months to 28.3 (95% CI:
357 26.0 to 30.6) months ($p < 0.0001$). The rate of progression over 24 months was reduced to
358 approximately one-third that of AS (adjusted hazard ratio = 0.34; 95% CI: 0.24, 0.46;
359 $p < 0.0001$). The distribution of predefined progression criteria showed that padeliporfin VTP
360 was efficacious against the individual parameters of the composite progression endpoint. The
361 principal determinants of progression were Gleason grade ≥ 4 and increases in number of
362 positive cores and cancer core length, which all showed substantial reduction in the
363 padeliporfin VTP group. The regression coefficients showed no effect of treatment group or
364 baseline characteristics. Padeliporfin VTP also increased the probability of a negative Month
365 24 biopsy by from 13.5% (28 of 207 subjects) to 49.0% (101 of 206 subjects) (adjusted risk
366 ratio: 3.67; 95% CI: 2.53, 5.33); $p < 0.0001$). Eight subjects experienced a severe PC-related
367 event within 24 months, but only one of the subjects who did have such an event (both T3 PC
368 and metastasis) was in the VTP group. This subject was probably under-staged at study entry.
369 His first protocol-required biopsy resulted in a Gleason upgrading that, for the purposes of
370 the study, constituted his first—and therefore reported—progression event. Subsequent
371 investigation revealed a locally advanced PC, and metastasis was detected on further staging
372 investigation. VTP exposure was associated with a reduction in the rate of radical therapy
373 compared to men allocated to AS (12 [5.8%] of 206 subjects versus 60 [29.0%] of 207

374 subjects; $p < 0.0001$) and in time to radical therapy ($p < 0.0001$) (Figure 2). For subjects whose
375 PC did not progress during the study, padeliporfin VTP also produced clinically and
376 statistically significant decrease compared to AS at Month 24 in all mean tumour burden
377 parameters: total number of positive cores (0.9 vs 2.3; $p < 0.0001$), total cancer core length
378 (2.6 vs 6.8 mm; $p < 0.0001$), and maximum cancer core length (1.6 vs 3.4 mm; $p < 0.0001$).
379 Moreover, VTP produced a stable reduction in PSA of about 3 ng/mL over the course of the
380 study.

381 The nine subjects randomised to VTP but who had no treatment-related procedure were
382 excluded from the safety analysis (Figure 1). In the VTP group, IIEF-15 and IPSS
383 assessments showed transient deterioration in erectile and urinary function, but the Month 24
384 result was comparable between the two groups (appendix p.3). Month 24 IPSS was 6.6
385 (standard deviation [SD]: 5.47) for VTP and 8.2 (SD: 6.47) for AS, and Month 24 IIEF-15
386 was 15 (SD: 10.70) for VTP and 16.8 (SD: 11.17) for AS. These results show no significant
387 effect of padeliporfin VTP on genitourinary function compared to AS. The mean EQ-5D
388 questionnaire scores at Month 24 in both the VTP and AS groups were slightly decreased
389 from baseline with no difference in the two groups (82.5 [SD: 12.31] in the VTP group and
390 81.8 [SD: 12.09] in the AS group), indicating no decrease in quality of life associated with
391 VTP at Month 24 (appendix p.2).

392 As expected, both the incidence and severity of AEs and SAEs were higher in the VTP group
393 than in the AS group (Table 3). Most subjects in the VTP group experienced an AE, most of
394 which were mild or moderate in severity and self-limited. The most commonly reported AEs
395 in the padeliporfin VTP group were urinary tract infections (23 AEs in 21 [10.7%] subjects)
396 and AEs in the renal and urinary disorders (280 AEs in 133 [67.5%] of 197 subjects) and
397 reproductive system and breast disorders system organ classes (197 AEs in 121 [61.4%] of
398 197 subjects), and these AEs accounted for the largest differences between the treatment

399 groups. AEs related to the study drug, device, or procedure were common but generally not
400 severe. Most of these related AEs occurred during the procedure or in the days immediately
401 after the procedure and resolved quickly without sequelae. The reporting of pain that was
402 thought to be related to the procedure (due to the transcutaneous needle placement, due to the
403 swelling of the prostate or both) was captured by the term ‘perineal pain’. This was reported
404 by 30 (15%) men allocated to the VTP group and by 1(0.5%) man in the AS group.

405 Three subjects experienced events that were more long-lasting: two with urethral strictures
406 requiring endoscopic dilation and one case of urinary incontinence in a subject who had
407 previously undergone transurethral prostatectomy (TURP). Men with a history of surgery for
408 benign prostatic hypertrophy (including TURP) were subsequently excluded from the study
409 (via protocol amendment 23 October 2012) for safety reasons. All other reports of
410 incontinence were self-limited, were usually urge-related and occurred in the period after
411 catheter withdrawal. Incontinence management was at the discretion of the investigator. The
412 most common related SAE in the VTP group was urinary retention. Typically this event
413 occurred on the first attempt to withdraw the urinary catheter (day-1 post-op). This was
414 managed with immediate recatheterization. The timing of a second attempt at removal of the
415 urinary catheter was left to the discretion of the local investigator. All 15 retention cases
416 resolved within two months. No subject discontinued VTP because of an AE. Three subjects
417 discontinued the study because of AEs. One subject in the AS group developed ureteric
418 cancer. One subject in the VTP group had an anaphylactic reaction to the anaesthesia
419 administered at the start of the VTP procedure; he had received no padeliporfin or VTP. One
420 subject in the VTP group died from a myocardial infarction during mountain climbing
421 approximately eight months after padeliporfin VTP, and the investigator assessed the AE as
422 unrelated to study drug, device, or procedure.

423 An independent Data and Safety Monitoring Board reviewed safety data approximately every
424 3 months throughout the study and advised the study sponsor on matters of subject safety. At
425 all meetings, the members unanimously agreed that no safety issues had emerged in the
426 study.

427

428 **DISCUSSION**

429 VTP doubled time to progression (from 14.1 to 28.3 months), reduced the progression rate to
430 approximately one-third that of AS, and increased the probability of a negative prostate
431 biopsy at 24 months post-treatment from 13.5% to 49.0%. VTP was also safe and well
432 tolerated with only minor and transient deterioration in genitourinary function. Our study has
433 shown that partial-gland ablation by VTP influences the course of PC in the short-to-medium
434 term. First, the proportion of men who transition from a cancer status to cancer-free status
435 was increased. Second, the proportion of men who progress from a histologically defined
436 low-risk status to a higher one is diminished. As a result, fewer men chose to undergo radical
437 therapy during the study period. Moreover, these benefits were achieved safely, efficiently,
438 and without compromising genitourinary function when assessed at 12 and 24 months after
439 VTP.

440 Since this is the first comparative efficacy study of its type, it is important to consider the
441 methodological considerations that were inherent in its design and conduct. The first relates
442 to the population studied. By today's standards this population might be considered low risk.
443 However, whilst the study was in development and being discussed with the EMA, neither
444 AS nor focal therapy were accepted as standard care. The EMA agreed that we could
445 reasonably exclude very-low-risk patients. Therefore, lower and upper thresholds of risk
446 (defined by Gleason pattern and tumour burden) were set, below which and above which men

447 were excluded. This low-risk group was the only one that could have been studied at the time.
448 Were the study designed today, given the changes to risk categorisation, it is likely that men
449 with well characterised PC and low volume secondary Gleason pattern 4 would be included.¹⁶

450 A second limitation relates to rapidly changing practice in risk stratification of PC patients,
451 most significantly the use of MRI in the diagnostic and the re-evaluation phases of both AS
452 and focal therapy.^{17,18} When the study began, few units offered MRI to patients on AS or as
453 part of the work-up for focal therapy. Now it is difficult to imagine using either strategy
454 without MRI. Although only men assigned to VTP had MRI in this study, images were used
455 only for treatment planning, not for detection or staging. The only way in which unilateral
456 use of MRI could have biased subjects' allocation was the detection of colorectal or bladder
457 cancer, which would have triggered a study withdrawal. If the study were repeated today,
458 MRI would play an important role in subject selection and risk stratification for both
459 interventions.¹⁹

460 A third concern is discriminating true progression from reclassification. When using a
461 biopsy-based strategy to refine the risk stratification at given intervals in AS, upgrading
462 (transition from an exclusive Gleason pattern 3 status to one with elements of Gleason pattern
463 4 or 5) occurs. Determining whether the observed increase in the Gleason pattern is a
464 correction of inherent diagnostic imprecision or the product of true disease progression has
465 proved challenging. Whilst no universal definition of clinical significance exists, recently
466 published MRI studies have used the presence of Gleason pattern 4 as the minimum
467 definition of clinically significant PC.^{17,18} Physicians have recommended treatment upon
468 upgrading irrespective of its underlying cause. This strategy appears prudent given that
469 recently published data from two mature AS series have identified higher risk groups (within
470 the risk profile suitable for AS) that are at greater risk of progression.^{2,20,21}

471 The final issue relates to the efficacy endpoints evaluated. If endpoints such as progression to
472 metastases or death had been used, the natural history of low-risk PC would have required a
473 very large study conducted over two decades. Some experts advocate prioritizing of shorter-
474 term, relevant outcomes that are important to patients to support patients and their physicians
475 in their clinical decision-making.²²

476 This multicentre study has demonstrated that padeliporfin VTP can be implemented widely
477 and delivered effectively and safely. The latter issue deserves some qualification. Exposure to
478 VTP resulted in an increase in the frequency of SAEs from 1 in 10 men on AS to 1 in 3 men
479 who received VTP. Most of the events were expected, genitourinary in nature, and self-
480 limited. The most important of these events was failure to void on catheter removal (urinary
481 retention). The event was managed by replacement of the urethral catheter and extension of
482 the period of dependent urinary drainage.

483 It is worth noting that most study sites had no prior experience in delivering focal therapy, let
484 alone VTP. Study recruitment was timely over a large geographical area, a scenario that
485 contrasts with the many previous attempts to undertake randomised, comparative studies of
486 early PC treatment, which either failed to recruit completely or closed because of poor
487 recruitment.²³ Feasibility is an important attribute for surgical interventions, and our results
488 demonstrate that VTP can be taught, learned, and delivered by a range of health care
489 providers and systems. This study was performed at a large number of centres and in a
490 variety of healthcare systems, few of which had any previous experience with VTP, and yet
491 we managed to achieve a very low rate of permanent urinary toxicity. Since our
492 understanding and management of early PC have changed so much in the last few years, it is
493 worth speculating on how padeliporfin VTP might be used with current diagnostics and risk
494 stratification, which are unrecognizable from those at the time of study design. Adoption of
495 MRI and targeted biopsy into the clinical pathway has created more precise risk stratification,

496 allowing a more nuanced approach to men with a new PC diagnosis. Given that MRI is now
497 widely used within the diagnostic pathway but was not used for diagnosis or risk stratification
498 in our study, it is worth speculating on how the diagnostic process may be influenced by the
499 results of this study. First, it is likely that a pathway based on MRI—because of its role as a
500 triage test between an elevated PSA and biopsy—will result in a reduction of the number of
501 men biopsied and in the proportion of men receiving the diagnosis of clinically insignificant
502 PC. In contrast, men with an MRI abnormality will undergo targeted biopsy (something that
503 was not possible without MRI), resulting in a greater sensitivity for clinically significant
504 disease. It is very likely that the men with clinically significant isolated lesions will be the
505 candidates for focal prostate therapy. Men who do not need treatment should not have it. Men
506 who require whole-gland treatment because of bilateral clinically significant disease should
507 be offered it. Men with locally advanced disease should be offered multimodality therapy.
508 However, men who have low-risk, localised disease can now choose, on the basis of the
509 evidence that our study has generated, how to approach tissue preservation.

510 More research is needed to address unanswered questions, the principal one being the long-
511 term effect of tissue-preserving treatment on PC control rates. One unknown element is the
512 efficacy of padeliporfin VTP in eradicating cancers of different grades within the target
513 volume. A study in men with Gleason pattern 4 (NCT01875393) has been submitted for
514 publication. Another uncertainty relates to the stability of the tissue that lies beyond the
515 treatment zone. This question requires long-term follow-up, which has been initiated in the
516 men from Study CLIN1001 PCM301.

517 **CONTRIBUTORS**

518 The sponsor, STEBA Biotech S.A., developed the study design in consultation with the study
519 investigators and the EMA. BA performed the statistical analysis and interpretation on behalf

520 of the sponsor. AAzzouzi, SV, EB, AC, FK, HVP, CGS, JR, GS, ES, AAAlcaraz, TTT, DJR,
521 FGV, GA, ME, and the PCM301 Study Group conducted the study and collected the data.
522 FMJD chaired the Data Safety Monitoring Board and GF and CG served on the Outcomes
523 Review Panel. ME prepared the first draft of the manuscript and with Anne McDonough, a
524 professional medical writer funded by the sponsor. All authors contributed to the final data
525 interpretation and final draft of the report and approved submission for publication.

526

527 **DECLARATION OF INTEREST**

528 AAzzouzi, SV, EB, AC, FK, HGV, CGS, JR, GS, ES, AAlcaraz, TTT, DJR, FGV, GA, and
529 ME received payment from STEBA as investigators on this study. AA and ME have also
530 acted as consultants and proctors for STEBA. FMJD, GF, and CG received payment from
531 STEBA for other roles on the study (Data Safety Monitoring Board, Outcomes Review
532 Panel). BA is a statistical consultant to STEBA. FB and BG are employees of STEBA. FGV
533 reports receipt of funding for research from Astellas Pharma and acting as a paid proctor for
534 Intuitive Surgical, Inc. AAlcaraz reports payment for speaking engagements from several
535 companies (Astellas Pharma, Janssen Pharmaceutica, Sanofi, Bayer, STEBA Biotech S.A.,
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537 Pharmaceuticals, Orion Corporation, and Bayer and receiving institutional funding from
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539 ME reports acting as a principal/co-investigator in a number of PC studies supported by
540 SonaCare Medical, Sophiris Bio Inc, and TROD Medical and as a consultant/advisor to GSK
541 and Sanofi-Aventis, being a founding partner of London Urology Associates, and
542 shareholdings in Nuada Medical Ltd.

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622 therapy in prostate cancer? *Nat Rev Clin Oncol.* 2014; **11**: 482–91.

624 Table 1. Demographic and baseline prostate cancer characteristics

Characteristic	Padeliporfin VTP N = 206	Active surveillance N = 207	Total N = 413
Age (years)			
Mean (SD)	64.2 (6.7)	62.9 (6.7)	63.5 (6.7)
Range: minimum, maximum	45, 85	44, 79	44, 85
Race			
Caucasian, n (%)	202 (98.1)	206 (99.5)	408 (98.8)
Other, n (%)	4 (2.9)	1 (0.5)	5 (1.2)
Body mass index (kg/m ²)			
Mean (SD)	26.5 (3.3)	27.3 (4.0)	26.9 (3.7)
Range: minimum, maximum	18.8, 38.6	18.8, 44.8	18.8, 44.8
Time since diagnosis (months)			
Mean (SD)	6.3 (8.5)	6.0 (7.9)	6.2 (8.2)
Range: minimum, maximum	0.2, 54.2	0.2, 47.4	0.2, 54.2
TNM staging			
T1a, n (%)	1 (0.5)	0	1 (0.2)
T1c, n (%)	177 (85.9)	180 (87.0)	357 (86.4)
T2a, n (%)	28 (13.6)	27 (13.0)	55 (13.3)
PSA (ng/mL)			
Mean (SD)	6.2 (2.1)	5.9 (2.0)	6.1 (2.1)
Range: minimum, maximum	0.1, 10.0	0.5, 10.0	0.1, 10.0
Estimated prostate volume (cc)			
Mean (SD)	42.5 (12.5)	42.5 (11.8)	42.5 (12.1)
Unilateral disease, n (%)	157 (76.2)	163 (78.7)	320 (77.5)
Bilateral disease, n (%)	49 (23.8)	44 (21.3)	93 (22.5)
Total number of pretreatment biopsy cores			
Mean (SD)	13.6 (3.3)	13.6 (3.6)	13.6 (3.4)
Range: minimum, maximum	10, 25	10, 26	10, 26
Total number of pretreatment biopsy cores with cancer			
Mean (SD)	2.1 (0.7)	2.0 (0.7)	2.1 (0.7)
Range: minimum, maximum	1, 3	1, 3	1, 3
1 core, n (%)	39 (18.9)	52 (25.1)	91 (22.0)
2 cores, n (%)	110 (53.4)	100 (48.3)	210 (50.8)
3 cores, n (%)	57 (27.7)	55 (26.6)	112 (27.1)
Total cancer core length (mm)			
Mean (SD)	4.3 (2.3)	3.8 (2.4)	4.1 (2.4)
Range: minimum, maximum	0 ^a , 14	0 ^a , 11	0, 14

SD = standard deviation; TNM = tumour, nodes, metastasis; VTP = vascular-targeted photodynamic therapy.
^a Some of the subjects included on the basis of two biopsies at the beginning of the study had one of those two biopsies negative.

Table 2. Co-primary efficacy endpoints

Endpoint ^a	Padeliporfin VTP N = 206 n (%)	Active surveillance N = 207 n (%)	Padeliporfin VTP vs active surveillance	
			Ratio (95% CI)	p value
Progression	58 (28.2)	120 (58.0)	Adjusted ^b hazard ratio 0.34 (0.24, 0.46)	<0.001 ^c
Criteria for progression ^d				
More than three cores positive	23 (11.2)	58 (28.0)	NC	<0.001 ^e
Gleason ≥4	49 (23.8)	91 (44.0)	NC	<0.001 ^e
Cancer core length >5 mm	25 (12.1)	51 (24.6)	NC	0.001 ^e
PSA >10 ng/mL in three consecutive measures	3 (1.5)	14 (6.8)	NC	0.007 ^e
Any T3 prostate cancer	0	4 (1.9)	NC	NA
Metastasis	0	0	NC	NA
Prostate cancer-related death	0	0	NC	NA
Negative Biopsy at Month 24	101 (49.0)	28 (13.5)	Adjusted ^f risk ratio 3.67 (2.53, 5.33)	<0.001 ^e

CI = confidence interval; NA = not applicable; NC = not calculated; VTP = vascular-targeted photodynamic therapy.

^a The Hochberg procedure was used to adjust for multiplicity of the two co-primary endpoints.

^b Cox proportional-hazards model with treatment as fixed effect and baseline age, number of cores positive, prostate volume, and disease status (unilateral/bilateral) as covariates.

^c From the log-rank test of equality of survival curves across treatment groups Cox proportional-hazards model with treatment as fixed effect and baseline age, number of cores positive, prostate volume, and disease status (unilateral/bilateral) as covariates.

^d A subject might have met > 1 criterion for progression.

^e From Pearson's chi-square test for observed success.

^f Logistic regression model with treatment as fixed effect and baseline age, number of cores positive, prostate volume, and disease status (unilateral/bilateral) as covariates.

Table 3. Adverse events

AE category	Padeliporfin VTP N = 197*		Active surveillance N = 207	
	Subjects n (%)	Events n	Subjects n (%)	Events n
All AEs	187 (94.9)	939	114 (55.1)	307
Drug, device, or VTP procedure-related AE	155 (78.7)	551	NA	NA
All SAEs	60 (30.5)	88	21 (10.1)	25
Drug, device, or VTP procedure-related SAE	30 (15.2)	39	NA	NA
AE leading to study discontinuation	2 (1.0)	2	1 (0.5)	1
AE leading to death	1 (0.5)	1	0	0
Adverse Events Occurring in ≥ 10% of Subjects in Either Group				
System Organ Class Preferred Term	Subjects n (%)		Subjects n (%)	
Infections and infestations				
Urinary tract infection	21 (10.7)		9 (4.3)	
Renal and urinary disorders				
Dysuria	54 (27.4)		5 (2.4)	
Haematuria	56 (28.4)		6 (2.9)	
Micturition urgency	21 (10.7)		2 (1.0)	
Pollakiuria	20 (10.2)		6 (2.9)	
Urinary retention	32 (16.2)		2 (1.0)	
Reproductive system and breast disorders				
Erectile dysfunction	74 (37.6)		24 (11.6)	
Perineal pain	30 (15.2)		1 (0.5)	
Adverse Events by Severity				
AE Grade System Organ Class Preferred Term	Subjects n (%)		Subjects n (%)	
Grade 1 (mild)	49 (24.9)		42 (20.3)	
Grade 2 (moderate)	94 (47.7)		52 (25.1)	
Grade 3 (severe)	40 (20.3)		19 (9.2)	
Blood and lymphatic disorders				
Thrombocytopenia	1 (0.5)		0	
Cardiac disorders				
Atrial fibrillation	1 (0.5)		0	
Myocardial infarction	1 (0.5)		2 (1.0)	
Endocrine disorders				
Hypothyroidism	1 (0.5)		0	
Gastrointestinal disorders				
Abdominal pain	1 (0.5)		0	
Gastrointestinal haemorrhage	0		1 (0.5)	
Inguinal hernia	2 (1.0)		0	
Rectal haemorrhage	1 (0.5)		0	
General disorders and administration site conditions				
Device failure	1 (0.5)		0	
Pyrexia	0		1 (0.5)	
Immune system disorders				
Drug hypersensitivity	2 (1.0)		0	
Infections and infestations				
Epididymitis	1 (0.5)		0	
Orchitis	1 (0.5)		0	
Otitis externa	0		1 (0.5)	
Staphylococcal infection	0		1 (0.5)	
Urinary tract infection	2 (1.0)		2 (1.0)	
Injury, poisoning and procedural complications				
Accident	1 (0.5)		0	
Cranio-cerebral injury	1 (0.5)		0	
Procedural pain	0		1 (0.5)	
Investigations				
Fibrin D dimer increased	2 (1.0)		0	
Musculoskeletal and connective tissue disorders				
Arthralgia	1 (0.5)		0	
Osteoarthritis	0		1 (0.5)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)				
Ear neoplasm	0		1 (0.5)	
Neuroendocrine carcinoma	1 (0.5)		0	
Prostate cancer	1 (0.5)		0	
Tongue cancer recurrent	0		1 (0.5)	
Tonsillar neoplasm	1 (0.5)		0	
Ureteric cancer metastatic	0		1 (0.5)	

Ureteric cancer regional	0	1 (0.5)
Nervous system disorders		
Cerebrovascular accident	1 (0.5)	0
Headache	1 (0.5)	0
Transient ischaemic attack	0	1 (0.5)
Psychiatric disorders		
Depression	1 (0.5)	1 (0.5)
Renal and urinary disorders		
Dysuria	3 (1.5)	0
Haematuria	1 (0.5)	0
Urinary incontinence	2 (1.0)	1 (0.5)
Urinary retention	3 (1.5)	1 (0.5)
Reproductive system and breast disorders		
Ejaculation failure	2 (1.0)	0
Erectile dysfunction	2 (1.0)	3 (1.4)
Perineal pain	1 (0.5)	0
Prostatic pain	1 (0.5)	0
Prostatitis	3 (1.5)	1 (0.5)
Skin and cutaneous tissue disorders		
Purpura	1 (0.5)	0
Surgical and medical procedures		
Aortic valve replacement	0	1 (0.5)
Cataract operation	1 (0.5)	0
Facial operation	1 (0.5)	0
Knee arthroplasty	1 (0.5)	0
Vascular disorders		
Phlebitis	0	1 (0.5)
Thrombosis	0	1 (0.5)
Grade 4 (life-threatening)	3 (1.5)	1 (0.5)
Cardiac disorders		
Angina unstable	1 (0.5)	0
Myocardial infarction	0	1 (0.5)
Immune system disorders		
Anaphylactic reaction	1 (0.5)	0
Respiratory, thoracic and mediastinal disorders		
Bronchospasm	1 (0.5)	0
Grade 5 (death)	1 (0.5)	0
Cardiac disorders		
Myocardial infarction	1 (0.5)	0
AE = adverse event; SAE = serious adverse event; VTP = vascular-targeted photodynamic therapy.		
* The nine subjects randomised to VTP but who had no treatment-related procedure were excluded from analysis of safety.		

FIGURE LEGENDS (IN-TEXT)

Figure 1. Disposition of subjects by treatment group

Figure 2. Time to initiation of radical therapy by treatment group – Kaplan-Meier analysis