ZOLADEX® Clinical Study Report	
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A Multi-centre, Prospective, Observational Study on Effectiveness and Safety of ZOLADEX® (goserelin acetate implant) 10.8 mg and ZOLADEX® (goserelin acetate implant) 3.6 mg in Chinese Patients with Localized or Locally Advanced Hormonal Treatment-naïve Prostate Cancer

Study Dates: First subject enrolled: 19 September 2017

Last subject last visit: 30 December 2019

The analyses presented in this report are based on a clinical database lock date of 27 August 2021.

Phase of Development: Therapeutic use (IV)

This study was performed in compliance with International Council for Harmonisation (ICH) Good Clinical Practice, including the archiving of essential documents.

Study population

A total of 35 study centres were selected. Six study centres did not recruit any subject due to the failure of the negotiation, and 29 study centres recruited at least one subject.

Overall, a total of 330 subjects were screened, 23 subjects of which were screen failure, and the other 307 subjects were enrolled. Among the 307 enrolled subjects, 1 subject who was enrolled but not dosed and 12 subjects who were dosed but did not meet inclusion or meet exclusion criteria were excluded from the FAS. Therefore, only 294 subjects were included in the FAS. Among 307 enrolled subjects, 203 subjects completed the study, 104 subjects early discontinued the study due to withdrawal by other (79 subjects, 25.7%), withdrawal by subject (16 subjects, 5.2%), lost to follow-up (4 subjects, 1.3%), death (2 subjects, 0.7%), physician decision (2 subjects, 0.7%), and AEs (1 subject, 0.3%; PT: sexual dysfunction; SOC: reproductive system and breast disorders). Among 79 subjects with the reason of "other", 65 (21.2%) subjects were categorized as "no visit data since last treatment visit date to week 26 visit date"; 12 (3.9%) subjects were categorized as "does not meet the inclusion criteria/meet the exclusion criteria"; and 2 (0.7%) subjects were categorized as "no drug".

In the FAS, 135 subjects were diagnosed as localized prostate cancer while 159 subjects were diagnosed as locally advanced prostate cancer. A total of 287 subjects received Zoladex® 10.8 mg treatment, in which, 182 subjects received Zoladex® 10.8 mg as adjuvant therapy while 105 subjects were received Zoladex® 10.8 mg as first line treatment, and 7 subjects received Zoladex® 3.6 mg as first line treatment.

The mean (SD) age of FAS population was 70.2 (7.72) years old. The means (SD) of height, weight and BMI were 167.76 (6.342) cm, 66.75 (9.938) kg and 23.7369 (3.2840) kg/m^2, respectively. The demographic of subjects in FAS were well balanced in age, height, weight, and BMI across all subgroups by Zoladex® dosage, by disease status, by RP status and by different exposure. More than 90% of subjects for all subgroups had ECOG performance status score of 0 or 1, except for 3.6 mg group by Zoladex® dosage, and 3.6 mg first line group by different exposure with 1 (14.3%) subject having ECOG performance status score of 2. By Zoladex® dosage, the baseline pathology at diagnosis characteristics was balanced between the 2 subgroups.

Summary of efficacy results

In overall, after Zoladex® initiation, there was an obvious trend that the serum PSA level and serum testosterone level greatly decreased from baseline and the same trend can be observed for all subgroups (by Zoladex® dosage, disease status, RP status, different exposure, combination of Casodex [or not] with or without RP status).

In overall, the mean (SD) serum PSA level at baseline was 36.7384 (88.7702) ng/mL with the median as 5.2400 ng/mL with 281 available subjects. After drug administration, the minimum mean (SD) serum PSA level was 0.5070 (2.3585) ng/mL at analysis visit 6 with 136 available subjects, with the median as 0.0100 ng/mL and the mean (SD) change from baseline as -35.4188 (104.3942) ng/mL. The difference (95% CI) between baseline and analysis visit 6 was -35.4188 (-53.4635, -17.3741) ng/mL.

In overall, the mean (SD) serum testosterone level at baseline was 448.4719 (315.8730) ng/dL and the median was 373.0000 ng/dL with 261 available subjects. After drug administration, the minimum mean (SD) serum testosterone level was 20.7342 (13.6624) ng/dL at analysis visit 5

with 28 available subjects, with the median as 17.5744 ng/dL and the mean (SD) change from baseline as -381.2946 (217.6451) ng/dL, while the number of subjects with serum testosterone level <50 ng/dL was 26 (92.9%) subjects. The difference (95% CI) between baseline and analysis visit 6 was -400.9720 (-462.4778, -339.4661) ng/dL.

The number (percentage) of subjects with serum testosterone level < 50 ng/dL from the first injection to the second injection was 169 (86.7%) with 195 available subjects. The number (percentage) of subjects with serum testosterone level < 50 ng/dL between 28 and 84 days after the first injection was 97 (90.7%) with 107 available subjects. The number (percentage) of subjects with serum testosterone level < 50 ng/dL after the second injection was 117 (91.4%) with 128 available subjects. The number (percentage) of subjects with serum testosterone level < 50 ng/dL between 28 and 84 days after the second injection was 69 (87.3%) with 79 available subjects. In overall, after Zoladex® initiation, there was an obvious trend that the serum testosterone level greatly decreased, more than 90% subjects had at least one of serum testosterone level <50 ng/dL during the study period.

This study was an observational study in a "real-world" clinical practice setting. The subject's treatment was based on the physicians' personal and each visit was not mandatory so that the number of subjects at each visit was vary. In addition, the test of serum testosterone level and PSA levels was not mandatory at each visit. In order to better evaluate the efficacy of Zoladex® and ensure the robustness of the results, combined with correlation between visit and administration, the serum PSA level were calculated from 107 subjects who completed all the 3 visits i.e. baseline visit, analysis visit 3 and 6; the serum testosterone levels were calculated from 80 subjects who completed all the 3 visits i.e. baseline visit, analysis visit 3 and 6.

In 107 subjects who completed all the 3 visits i.e. the baseline visit, analysis visit 3 and 6, the mean (SD) serum PSA level at baseline was 39.4536 (116.3993) ng/mL with the median as 2.1800 ng/mL. After drug administration, the mean (SD) serum PSA level at analysis visit 3 was 0.6991 (3.2191) ng/mL with the mean (SD) change from baseline as -38.7545 (113.8271) ng/mL; the mean (SD) serum PSA level at analysis visit 6 was 0.4794 (2.4498) ng/mL with the mean (SD) change from baseline as -38.9742 (114.6796) ng/mL. In the 107 subjects, 10 subjects received 1 injection of 10.8 mg Zoladex® and 97 subjects received 2 injections of 10.8 mg Zoladex®.

In all 80 subjects who completed all the 3 visits i.e. baseline visit, analysis visit 3 and 6, the mean (SD) serum testosterone level at baseline was 392.2423 (169.8105) ng/dL with the median as 362.6951 ng/dL. After drug administration, the mean (SD) serum testosterone level at analysis visit 3 was 29.5995 (22.5774) ng/dL with the mean (SD) change from baseline as -362.6428 (173.1174) ng/dL; the mean (SD) serum testosterone level at analysis visit 6 was 27.2762 (23.3600) ng/dL with the mean (SD) change from baseline as -364.9661 (172.9032) ng/dL. In the 80 subjects, 1 subject received 1 injection of 10.8 mg Zoladex® and 79 subjects received 2 injections of 10.8 mg Zoladex®. The number (percentage) of subjects with serum testosterone level < 50 ng/dL after 2 injections of 10.8 mg Zoladex® was 74 (93.7%).

Summary of safety results

In the study, there were 287 subjects received the Zoladex® 10.8 mg and 7 subjects received Zoladex® 3.6 mg as the initial dosage. The mean (SD) of total exposure was 23.48 (8.407) mg with the range of 10.8-32.4 mg for Zoladex® 10.8 mg group, while the mean (SD) of total exposure was 19.54 (8.011) mg with the range of 3.6-25.2 mg for Zoladex® 3.6 mg group. The

mean (SD) of duration of exposure and the mean (SD) proportion of days covered (PDC) were comparable between two treatment groups.

A total of 117 (39.8%) subjects in FAS population experienced 324 AEs, 109 (37.1%) subjects experienced 301 TEAEs, 22 (7.5%) subjects experienced 37 ADRs, 30 (10.2%) subjects experienced 44 SAEs, and also 30 (10.2%) subjects experienced 43 TESAEs. Considering events with CTCAE grade ≥ 3, 32 (10.9%) subjects experienced 43 AEs with CTCAE grade ≥ 3, 31 (10.5%) subjects experienced 42 TEAEs with CTCAE grade ≥3. Treatment-related TESAEs, TEAEs leading to death, TEAEs leading to treatment discontinuation and TEAEs leading to study withdrawal were all with only 1 (0.3%) subject. None of the subjects experienced ADRs leading to study withdrawal, ADRs leading to treatment discontinuation, and AESI (cardiovascular related AE, sexual related AE) during the study.

In this study, a total of 22 (7.5%) subjects experienced 37 ADRs, and all of them received Zoladex® 10.8 mg. The most common ADRs by PT with incidence rate > 1.0% in either group was anaemia (6 subjects, 2.1%), followed by hot flush (4 subjects, 1.4%).

All the TEAEs with CTCAE grade ≥ 3 by SOC and PT were contributed by subject from 10.8 mg group. In the 3.6 mg group, no subject experienced TEAEs with CTCAE grade ≥ 3 in the study. Most of TEAEs with CTCAE grade ≥ 3 recovered/resolved after treatment. Most of TEAEs with CTCAE grade < 3 recovered/resolved or were recovering/resolving without any treatment.

For laboratory test results (including hematology and chemistry), the results in most subjects were normal or abnormal non-clinically significant, and the results in a few subjects were abnormal clinically significant.

Conclusion(s)

The serum testosterone and PSA levels in Chinese patients with localized or locally advanced hormonal treatment-naïve prostate cancer are greatly decreased from baseline and achieved castrate levels after treatment with Zoladex®. The same trend was observed for all subgroups (by Zoladex® dosage, disease status, RP status, different exposure, combination of Casodex [or not] with or without RP status).

No new clinically significant safety concerns related to treatment with Zoladex® emerged from this study. The incidence of ADR in this study was similar or even lower than the safety profile in Zoladex® label, suggesting a good overall safety profile of Zoladex® in the Chinese patients with localized or locally advanced hormonal treatment-naïve prostate cancer.