3 REPORT SUMMARY

3.1 Sponsor identification

IPSEN PHARMA, S.A.
Torre Realia – Plaza Europa 41-43, Planta 7
08908 L'Hospitalet de Llobregat (Barcelona)
Tel.: PPD
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3.2 Title

Post-marketing observational study to prospectively evaluate the prevalence of cognitive changes in patients suffering of PCa before starting and after six months of treatment with LHRH analogues (ANAMEM study).

3.3 Code

IPS-TRI-2010-02

3.4 Principal investigator

Dr. Juan Morote
Hospital Vall d'Hebron
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3.5 Centres

Dr. Juan Pablo Sanz – Hospital de Donostia, San Sebastián; Dr. Juan Pablo Ciria – Hospital de Donostia, San Sebastián; Dr. José Luis Álvarez-Ossorio – Hospital U. Puerta del Mar, Cádiz; Dr. Adolfo Vergez – Hospital Torrecárdenas – Almería; Dr. Ángel José Tabernero – Hospital U. La Paz, Madrid; Dr. Javier Angulo – Hospital de Getafe, Madrid; Dr. Carlos Llorente – Fundación Hospital Alcorcón, Madrid; Dr. Carlos Olivier – Hospital La Princesa, Madrid; Dra. Almudena Zapatero – Hospital La Princesa, Madrid; Dra. Ana María Pérez – Fundación Jiménez Díaz, Madrid; Dr. Manuel Fernández – Hospital de Henares, Madrid; Dr. Víctor Macías – Hospital U. de Salamanca, Salamanca; Dr. Ramón La Iglesia – Hospital Rafael Méndez, Murcia; Dr. Francisco Javier López – Hospital Virgen de la Arrixaca, Murcia; Dr. Bernardino Miñana – Hospital Morales Meseguer, Murcia; Dr. Carlos Gutiérrez – Hospital Son Llàtzer, Palma de Mallorca; Dr. Jesús Romero – Hospital San Juan de Alicante, Alicante; Dr. Eduardo Solsona – IVO, Valencia; Dr. Antonio Benedicto – Hospital La Ribera de Alzira, Valencia; Dr. José Martínez – Hospital Clínico U. de Valencia, Valencia; Dr. José Luis Gutiérrez – Hospital Marqués de Valdecilla, Santander; Dr. Josep Campá – Hospital de Navarra, Pamplona; Dra. Blanca Tirapuer – Hospital Virgen del Camino, Pamplona; and Dr. Manuel Sánchez – Hospital Príncipe de Asturias, Madrid.

3.6 Ethics Committees

The study was submitted for evaluation and approval to the Ethics Committees of Hospital Vall d'Hebron.

3.7 Objectives

The objective of this study was to assess the proportion of patients suffering from prostate cancer (PCa) who underwent cognitive changes before and after a six-month treatment with LHRH analogues.

The secondary objective was the assessment of such changes, both at the baseline visit and after 6 months, with the following parameters:

- Basic clinical data record:
  - Demographic data
  - Gleason score
  - TNM staging
  - Specific previous PCa therapies
  - Significant clinical history
  - Prior and concomitant medication
  - Safety (related adverse events)
- Treatment efficacy according to:
  - PSA levels
  - Testosterone levels

3.8 Design

ANAMEM was a post-marketing, observational, prospective, multicentre, open-label study for evaluating which proportion of patients with prostate cancer (PCa) were suffering from cognitive changes before and after six months of treatment with LHRH analogues.

3.9 Disease or disorder under study

Male patients with prostate cancer.

3.10 Medicinal product

The patients included in this study received treatment with LHRH analogues.

The LHRH analogues currently commercialized in our country are:

- Buserelin (9.45 mg quarterly implant; SC injection)
- Goserelin (10.8 mg quarterly implant; SC injection)
- Leuprorelin (22.5 mg quarterly injection; SC injection)
- Leuprorelin (45 mg six-monthly injection; SC injection)
- Leuprorelin (22.5 mg quarterly injection; IM injection)
- Triptorelin (11.25 mg quarterly injection; IM injection)

- Triptorelin (22.5 mg six-monthly injection; IM injection)

3.11 Study Population and Sample Size

Male adults with prostate cancer diagnosis histologically confirmed who received a LHRH analogue therapy and who had given their written consent to participate in the study or represented by someone who had given said consent in their name in accordance with local recommendations/requirements.

The sample size calculation was driven by the primary objective that was to say the estimation of the proportion of patients with cognitive changes after six months of treatment with LHRH analogues (which was defined in a first step as subjects having at least one cognitive test with relevant change from baseline to M6 according to the methodology). A sample size of 385 patients would allow to estimate this proportion with a precision of at most 5% (assuming the proportion to be 50%).

In order to allow for subgroup analyses while keeping a rather good precision, this sample size was increased to 500 patients (indeed, the precision would be at most 10% for subgroup of 100 patients). Considering a 10% dropout rate, the final sample size was 500/0.9=556 subjects.

3.12 Study Calendar

Inclusion of the first patient was made on 17 December 2010, and completion of the last patient's follow-up on 25 February 2013. The statistical tables and the report were completed on Q1 of 2014.

3.13 Financial Source of the Study

As the sponsor of the study, IPSEN PHARMA, S.A met all expenses originated by the same.

3.14 Summary -Conclusions

The study screened 404 patients from 17 December 2010 to 25 November 2011. Out of 404 patients screened and included, 384 (95.1%) were treated with LHRH analogues injections (334 (87.0%) with Triptorelin, 41 (10.7%) with Leuprorelin, 5 (1.3%) with Goselerin, 3 (0.8%) with Histrelin and 1 (0.2%) with a medication not reported. Thirty-six (8.9%) of the treated patients did not complete the study (1 of the patients withdrew consent, 23 patients were lost to follow-up, and 12 patients withdrew for other reasons (not specified in the CRF)). Additionally 60 patients were excluded from the primary analysis set for the following reasons: 37 patients did not have at least one assessment of the tests done, 2 patients did not have a histologically-confirmed prostate cancer, 4 patients were simultaneously on treatment or had been on treatment with LHRH analogues over the past 6 months, 36 patients were castrated at baseline visit, and 26 patients had deviations in time visit windows (it should be noted that patients could have multiple reasons for exclusion) and accordingly the completer population, no major protocol deviations detected included 308 (80.2%) patients.

Mean age of patients was 71.31 years old (SD 8.01) with a mean time from diagnosis of 1.76 years (SD 3.10). A total of 261 patients had a Gleason score rated at baseline between 5 – 7 points and 163 patients had localized prostate cancer. Bicalutamide was the most frequently concomitant medication reported in 240 patients and 162 patients reported at least one prior prostate cancer treatment.

Results

Regarding safety population, at 6 months of androgen suppression treatment, a total of 312 (81.3%) patients did not experience significant cognitive changes in any of the five neuropsychological tests, while 68 (17.7%) patients showed a significant improvement in 1 of the cognitive tests, and 5 (1.0%) patients showed a significant improvement in 2 of the cognitive tests. In addition, there was a significant correlation between the baseline period and after 6 months of treatment with LHRH analogues for the 5 neuropsychological tests.

The same happened when additional subgroups were analysed (patients younger vs older than 70 years old; patients using or not androgen blockade treatment during the study; patients using or not anti-aggregating/anti-coagulating therapies during the study; and patients previous treated with LHRH analogues or not treated), where more than the 80% of patients did not show any significant changes in the cognitive neuropsychological tests.

After 6 months of treatment with LHRH analogues, patients significantly reduced their values in prostatic specific antigen and testosterone.

Conclusions

In conclusion, the main goal of this study pretended to clarify the existing controversy on the changes of the cognitive performance of patients treated with anti-androgen therapy, and with this study it could be concluded that after 6 months of treatment with LHRH analogues no significant cognitive changes in the performance tests have been found.

Date of report

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