ANNEX IV

SCIENTIFIC CONCLUSIONS

Scientific conclusions

Yondelis is an anti-cancer medicinal product with two indications:

1. treatment of patients with advanced *soft-tissue sarcoma*, after failure of anthracyclines and ifosfamide, or who are unsuited to receive these agents;

2. in combination with pegylated liposomal doxorubicin (PLD), Yondelis is indicated for the treatment of patients with relapsed platinum-sensitive *ovarian cancer*.

After the indication in ovarian cancer was authorised in the EU, trial OVC-3006 was started. It was a randomised, open-label, multicentre phase 3 study evaluating the efficacy and safety of trabectedin in combination with PLD in patients with advanced, relapsed ovarian cancer who had received two previous lines of platinum-based chemotherapy, compared to PLD alone and with overall survival (OS) as primary endpoint.

Following a review of results of a second interim analysis for futility, the Independent data Monitoring Committee recommended discontinuation of the study due to lack of survival superiority in the trabectedin in combination with PLD arm over PLD alone arm. The study failed to achieve both the primary endpoint of OS and the secondary endpoint of progression-free survival (PFS).

On 21 February 2020 the European Commission therefore triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and requested the CHMP to assess study 3006 and its impact on the benefit-risk balance of Yondelis and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation

The marketing authorisation for Yondelis was first issued on 17 September 2007 for the soft tissue sarcoma indication. The ovarian cancer indication was authorised in 2009 based mainly on study OVA-301, a randomised, open-label, multicentre phase 3 trial to evaluate the efficacy and safety of trabectedin in combination with pegylated liposomal doxorubicin (PLD) in 645 patients with relapsed ovarian cancer. The trial showed superiority of trabectedin with PLD compared to PLD alone in terms of progression-free survival (PFS, primary endpoint): 21% risk reduction for disease progression (HR=0.79, CI: 0.65-0.96, p=0.02)-. Also, overall response rates were higher with trabectedin combined with PLD (27.6% vs. 18.8% with PLD alone). Results for overall survival were compatible with a risk reduction for death with a 95% CI 0.72-1.02, but without significance. On the basis of this study, the following indication was granted: “Yondelis in combination with pegylated liposomal doxorubicin (PLD) is indicated for the treatment of patients with relapsed platinum-sensitive ovarian cancer”.

Yondelis in combination with pegylated liposomal doxorubicin (Yondelis + PLD) is indicated for the treatment of patient relapsed platinum-sensitive ovarian cancer. Study ET743-OVA-301 (Study 301), a randomised phase 3 study of 672 patients who received either trabectedin (1.1 mg/m^2) and PLD (30 mg/m^2) every 3 weeks or PLD (50 mg/m^2) every 4 weeks, was the basis for this approval. In this study, patients had been previously treated for ovarian carcinoma (80% previously received taxanes) but had only 1 platinum-based chemotherapy regimen and had experienced either recurrence or progression after more than 6 months from the beginning (first dose) of the platinum-based chemotherapy for ovarian cancer. The study included patients with platinum-resistant disease (platinum-free interval from the end of platinum treatment less than 6 months) and patients with platinum-sensitive disease (platinum-free interval from the end of platinum treatment ≥6 months) who were not expected to benefit from or who were ineligible for or who were not willing to receive retreatment with platinum-based chemotherapy. The primary endpoint was PFS and patients were stratified based on platinum sensitive vs. platinum resistant.

Subsequently Janssen conducted study ET743-OVC-3006 (Study 3006). No EU scientific advice had been sought for study 3006. This study was a phase 3, randomized, open-label, multicenter study designed to evaluate the efficacy and safety of trabectedin+PLD as a third-line chemotherapy in subjects with advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer. *Study participants were required to be platinum sensitive (PFI ≥ 6 months) following their first platinum-containing regimen and have a complete or partial response to a second line platinum-based chemotherapy (without PFI restrictions) meaning that these patients could be either platinum-sensitive (PFI ≥ 6 months) or platinum-resistant (PFI < 6 months) following their second platinum-containing regimen.* Women were allocated randomly 1:1 to Yondelis + PLD or PLD alone with randomization stratified by ECOG PS (0 vs 1), PFI following first-line platinum-based chemotherapy (6 to 12 months, >12 to 24 months, >24 months), BRCA1/2 germline status (mutation vs. no mutation), and use of prior PLD (yes vs. no). The primary objective of the study was to compare OS after treatment with Yondelis + PLD vs. PLD monotherapy. Secondary objectives were PFS, ORR, PK and safety. One non-binding interim futility analysis for OS was conducted after 170 events corresponding to 33% of the pre-specified number of events required for the final analysis (514 events). Following the data review at this first interim analysis, the IDMC requested an additional futility analysis at 45% of events (232 events); this analysis was not planned in the protocol. It showed a HR=0.96 for OS, which crossed the boundary of 0.93 for futility of the study to show that Yondelis + PLD would improve OS compared with PLD monotherapy. The study was subsequently discontinued after the IDMC concluded to recommend discontinuation of the trial for 2 main reasons: a) futility of the primary analysis (OS) and b) excessive risk based on imbalance of AE not in favour of the experimental regimen arm.

The observed data cannot be used for testing the statistical hypothesis related to the hypothesis in the study protocol (i.e. Yondelis + PLD will improve OS compared with PLD monotherapy in the treatment of subjects with platinum-sensitive advanced-relapsed epithelial ovarian, primary peritoneal, or fallopian tube cancer who received 2 previous lines of platinum-based chemotherapy), and the observed data are deemed to lack the strength and level of evidence that would have been obtained had the study been completed as planned.

Moreover, differences between the two trials (Study 301 and study 3006) hinder an appropriate comparison of populations and outcomes. The main difference is with regards to the number of prior lines of therapy. Study 301 included patients previously treated with one line of platinum-based chemotherapy, while study 3006 included patients failing a second-line platinum-containing chemotherapy). *Furthermore, a post hoc analysis determined that 42% of subjects enrolled in study 3006 were platinum-resistant (PFI < 6 months) following their last platinum-containing regimen while* Yondelis is only approved in patients with platinum sensitive disease.

With respect to outcomes for primary endpoints, Study 301 found a difference in terms of median PFS of 1.5 months with Yondelis+PLD, whereas Study 3006 was powered to detect a difference in median OS of 4.5 months.

The MAH argued that post-hoc analyses of Study 3006 showed a trend towards improved PFS combined with a significant improvement in ORR among the subset of patients who were platinum-sensitive following their last line of platinum-containing therapy. However, as discussed previously, the study failed to meet its primary objective, to evaluate Yondelis with the assumption that Yondelis + PLD will improve OS compared with PLD monotherapy. Only if study 3006 had been completed as planned and was positive for OS, the submitted ad hoc comparison of study 301 and 3006 (data not shown) might have been considered for the post-hoc defined subgroup of patients in Study 3006 with platinum-sensitive disease after their last line of platinum-containing therapy; however, limitations of comparisons across trials in different patient populations still would have been a high concern.

Even though BRCA and PFI were stratification factors, OS and PFS as a function of BRCA status or of PFI were exploratory endpoints and were not adjusted for multiplicity. As a consequence of the

methodological shortcomings, the results for these endpoints and in subgroups defined by these factors are much more likely to be spurious in magnitude and direction and cannot be used for regulatory decision-making.

In light of the above, data from Study 3006 do not permit to conclude on the effects of Yondelis + PLD in third line platinum-sensitive ovarian cancer.

With regards to safety, there was a difference between the two treatment arms in study 3006 in terms of number of AEs, severity and seriousness. Approximately 85% of patients in the Yondelis + PLD experienced a Grade 3-4 AE compared to 63.8% in the control arm. The greatest difference is seen in terms of Grade 4 AEs, 44.1% vs. 10.3%. Looking at SOCs a clear difference is seen in "blood and lymphatic system disorder", 56.6% vs. 27.7%, and "investigations" (neutropenia, leukopenia, thrombocytopenia, etc.) 51.7% vs. 10.6%. However, there were significantly fewer Grade 3-4 AEs in terms of skin and subcutaneous tissue disorders in the Yondelis + PLD arm compared to doxorubicin alone, 3.8% vs. 14.5%, which is somewhat puzzling, because trabectedin is given in study 3006 as add-on treatment to doxorubicin.

There were slightly more deaths in the Yondelis + PLD arm with regards to "death within 60 days of initiation of study drug" in the Yondelis + PLD arm and in "death within 30 days from the last dose". AEs leading to death was 10 (3.5%) vs. 5 (1.8%) in favour of the doxorubicin monotherapy arm.

Patients in the Yondelis + PLD arm discontinued treatment to a much higher degree compared with the control arm and as expected dose-reductions had to be made in half of the patients in the Yondelis + PLD arm compared to one third in the control arm.

Overall, the number of SAEs was considerably higher (41.3% in the combination arm vs 20.6% in PLD arm) and a considerable difference in overall rate of Grade 3-4 AEs was observed (85% in the combination arm vs 63.8% in the control arm). This is not unexpected when comparing a combination treatment with monotherapy in patients who have already received several lines of treatment.

The CHMP noted and endorsed the PRAC request in *EMEA/H/C/PSUSA/00003001/201909* for the MAH to submit a variation to update section 4.8 of the SmPC with pooled data from the ovarian cancer phase 3 clinical studies.

Yondelis has been authorised in combination with PLD based on a positive trial rendering a favourable benefit-risk balance in patients with relapsed platinum-sensitive ovarian cancer (study 301). The new study 3006 failed to provide evidence against the statistical hypothesis that OS is the same with Yondelis + PLD and PLD. In addition, results of study 3006 also do not provide a level and strength of clinical evidence that would allow to conclude there are no clinically relevant favourable effects of Yondelis + PLD in terms of OS and PFS in third line platinum-sensitive ovarian cancer.

The positive benefit-risk balance established for the ovarian cancer indication on the basis of the well-conducted phase III trial 301, showing favourable effects of Yondelis + PLD in terms of PFS in patients with a relapsed platinum-sensitive ovarian cancer, therefore remains unchanged.

Furthermore, the CHMP recommended that the marketing authorisation of this product should be varied so that section 5.1 of the SmPC reflects the results from Study 3006.

Grounds for the CHMP opinion

Whereas

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Yondelis;
- The Committee reviewed the clinical study report on study ET743-OVC-3006, a phase 3, randomized, open-label, multicenter study designed to evaluate the efficacy and safety of trabectedin in combination with pegylated liposomal doxorubicin as a third-line chemotherapy in patients with advanced-relapsed epithelial ovarian, primary peritoneal, or Fallopian tube cancer.
- The Committee noted that following a first unplanned interim futility analysis, the Independent Data Monitoring Committee (IDMC) for study 3006 requested an additional futility analysis at 45% of events (232 events). This analysis, which was not planned in the protocol, led to an IDMC recommendation to discontinue the trial for futility of the primary endpoint (OS) and excessive risk based on imbalance of adverse events not in favour of the experimental arm, after which the sponsor prematurely terminated study 3006.
- The Committee further noted that there are differences between study 3006 and study 301 (pivotal study for the authorisation of the ovarian cancer indication) in terms of number of prior lines of therapy, platinum sensitivity status and primary endpoint hampering an appropriate comparison of populations and outcomes. These differences between studies hinder an appropriate comparison of populations and outcomes.
- Overall, the Committee considered that data from the prematurely terminated study 3006 do not provide the level and strength of clinical evidence necessary to conclude on the absence of favourable effects in third line platinum-sensitive ovarian cancer patients.
- The Committee noted that overall, in study 3006, the safety profile of Yondelis +PLD appears consistent with the known safety profile for this combination. While patients in the Yondelis + PLD arm of the study experienced more adverse events than those in the PLD arm, this is not unexpected when comparing a combination treatment with monotherapy.
- The Committee therefore concluded that the positive benefit-risk balance of Yondelis in the ovarian cancer indication, that was established on the basis of the well-conducted phase III trial 301 showing favourable effects of Yondelis in combination with pegylated liposomal doxorubicin in terms of progression-free survival (PFS) in patients with relapsed platinum-sensitive ovarian cancer, remains unchanged.
- The Committee recommended that study 3006 be reflected in section 5.1 of the summary of product characteristics.

The Committee, as a consequence, concluded that the benefit-risk balance of Yondelis remains favourable subject to changes to the agreed amendments to the product information.