Annex

Scientific conclusions

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Lartruvo was granted a conditional marketing authorisation under Article 14(7) of Regulation (EC) No. 726/2004, valid throughout the European Union, on 9 November 2016. The therapeutic indication of Lartruvo is:

'*in combination with doxorubicin, for the treatment of adult patients with advanced soft tissue sarcoma who are not amenable to curative treatment with surgery or radiotherapy and who have not been previously treated with doxorubicin*'.

Lartruvo was authorised based on a single open-label, randomised phase 1b/2 clinical trial which enrolled doxorubicin-naïve subjects with advanced soft tissue sarcoma not amenable to treatment with surgery and radiotherapy (study JGDG). In this trial, treatment with olaratumab in combination with doxorubicin resulted in an improvement in progression-free survival (PFS) (8.2 vs. 4.4 months according to independent assessment; 6.6 vs. 4.1 months, hazard ratio (HR) 0.672 [95% CI: 0.442, 1.021], p = 0.0615 according to investigator assessment) and overall survival (OS) (26.5 months vs. 14.7 months, HR = 0.463; p = 0.0003).

In order to confirm the efficacy and safety of olaratumab, the marketing authorisation holder was required to submit as specific obligation, by January 2020, the clinical study report of a phase III randomised double-blind confirmatory study comparing doxorubicin plus olaratumab versus doxorubicin in patients with advanced or metastatic soft tissue sarcoma (Study I5B-MCJGDJ [JGDJ]; ANNOUNCE), including exploratory biomarker data.

In January 2019, the marketing authorisation holder communicated to the European Medicines Agency high level preliminary results of the JGDJ study. In total, 509 patients were randomised to treatment either with Lartruvo + doxorubicin (followed by Lartruvo monotherapy until progression) or with placebo + doxorubicin (followed by placebo monotherapy until progression).

The study gave rise to concerns about lack of efficacy, because it did not meet the primary objective to prolong survival in the overall population or in the leiomyosarcoma sub-population. Furthermore, there was no clinical benefit in key secondary efficacy endpoints.

On 25 January 2019 the European Commission (EC) triggered a procedure under Article 20 of Regulation (EC) No 726/2004, and requested the CHMP to assess the above concerns and their impact on the benefit-risk balance of Lartruvo. The EC requested the CHMP to give its opinion on whether the marketing authorisation for this product should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation

Favourable effects

ANNOUNCE (I5B-MC-JGDJ) was a randomized, double-blind, placebo-controlled, phase 3 trial of olaratumab plus doxorubicin versus placebo plus doxorubicin in patients with locally advanced or metastatic soft tissue sarcoma. It was designed to confirm the OS benefit previously shown in the smaller phase 1b/2 study JGDG. The latter showed an unexpected survival gain in patients with advanced/metastatic STS recruited in the United States. Even though the primary endpoint of that study (PFS) did not reveal a clear delay in the tumour progression for the experimental arm, the longer survival associated with the olaratumab combination treatment supported the granting of a conditional marketing authorisation. The ANNOUNCE (JGDJ) study was then requested as a specific obligation to confirm the efficacy and safety of olaratumab in same population for whom Lartruvo is currently indicated.

Overall, 509 adult patients with advanced or metastatic soft tissue sarcoma not amenable to treatment with surgery or radiotherapy with curative intent (of those 234 were leiomiosarcoma, LMS) were

randomized 1:1, stratified by number of prior systemic therapies for advanced/metastatic disease, histological tumour type, and ECOG PS, to the investigational arm (n=258; LMS n=119) with olaratumab plus doxorubicin or the control arm (n=251; LMS n=114) with placebo plus doxorubicin. Doxorubicin was administered for a maximum of 8 cycles every 3 weeks, along with olaratumab/placebo which was continued after 8 cycles until PD, unacceptable toxicity, death, or other withdrawal criteria. Compared to the currently recommended posology of olaratumab (15 mg/kg on days 1 and 8 of each 3 week cycle), a loading cycle of 20 mg/kg on day 1 and day 8 of cycle 1 was used, to minimize the number of patients exposed to sub-therapeutic olaratumab serum levels without an increased risk of toxicity, based on PK and matched case-control analysis by exposure quartiles results. Baseline patient and disease characteristics appeared overall well balanced.

The primary endpoint for this study was OS in the ITT population and in the LMS population. In the ITT population, the median OS was 20.37 months in the investigational arm and 19.75 months in the control arm (HR=1.047 [95% CI: 0.841, 1.303]; p=0.69), and the OS KM curves are completely overlapping, indicating that adding Lartruvo to doxorubicin had no favourable effect on OS. Further OS analyses showed that in most subgroups HR estimates ranged from 0.9 to 1.1, consistent with the overall OS results. No difference was seen in OS in the LMS population either.

There was a significant difference in PFS in the ITT population based on investigator assessment, but in favour of the control arm. The median PFS was 5.42 months in the investigational arm and 6.77 months in the control arm (HR=1.231 [95% CI: 1.009, 1.502]; p=0.042). No significant difference in PFS between the treatment arms in the LMS population was found.

No statistically significant difference in ORR or DCR in the ITT population was observed between the investigational arm and control arms, and both rates favoured the control arm. In the LMS population, ORR was in favour of the control arm (no statistical significance) and DCR was statistically significant in favour of the control arm.

No difference was observed in any of the other secondary endpoints analysed in the ITT population. The analyses of ANNOUNCE study showed that PDGFR-α status did not have any predictive role of the response to olaratumab in terms of OS or PFS, and that PDGFR-α was a poor prognostic factor, consistently with literature data. With regard to PDGFR-β, no significant association was found between PDGFR-β status and response to olaratumab in terms of OS or PFS. PDGFR-β did not seem to have a clear prognostic role in STS either.

Unfavourable effects

The results of the ANNOUNCE study confirmed the safety profile seen in the previous phase II study.

The rate of TEAE was overall similar in both treatment arms (98.1% vs 99.2%). Nausea, neutropenia and fatigue were the most frequently reported TEAEs. The rate of haematological toxicities (neutropenia, thrombocytopenia, anaemia and febrile neutropenia) and gastrointestinal toxicities (nausea, vomiting and diarrhoea) was balanced between the treatment arms. In addition, the rate of (consolidated) musculoskeletal pain was similar between the 2 treatment arms.

Infusion related reactions, cardiac arrhythmia and cardiac dysfunction are considered events of special interest for olaratumab. The rate of potential immediate (i.e. occurring on the day of infusion) hypersensitivity reactions was higher in the investigational arm for all grade events (11.7% vs. 7.2%) and Grade ≥3 events (2.3% vs 0.8%) but no fatal events were reported. Overall, 6 patients in the investigational vs none in the control arm developed an anaphylactic reaction. All anaphylactic reactions occurred during the first olaratumab infusion. Immediate non-anaphylactic reactions were reported in 9.3% patients and were grade 1/2 in severity.

Cardiac arrhythmia events were more commonly reported in the investigational arm (any grade 12.8% vs 9.6%; grade >=3 2.7% vs 0.8%).

The incidence for all grades of events in the cardiac dysfunction AESI category was 18.3% in the investigational arm and 13.7% in the control arm, the majority being events of peripheral oedema (13.2 vs 9.2%) and oedema (1.2% vs 0%). When excluding the event of oedema not associated with an AE suggestive of cardiac dysfunction or a significant decrease in left ventricular function, the true incidence of cardiac dysfunction was 9.3% in the investigational arm and 6.8% in the control arm. However, this remains higher in the investigational arm.

Few more SAE (38.9% vs 34.9%) occurred in the investigational arm than in the control arm. Febrile neutropenia was the most frequently SAE occurring with similar frequency in both arms (12.8% vs 13.3%). No data on AE adjusted by exposure are available. There are also no data regarding the toxicity observed in subjects in the investigational arm when treated with olaratumab maintenance.

Frequency of patients with TEAE leading to treatment discontinuation was similar in both arms (4.3% vs 4.4%).

A total of 170 (66.1%) vs 158 (63.5%) of patients died in the investigational vs control arm, respectively, mostly attributed to study disease (63.4% vs 61%). Deaths due to adverse events were overall similar in both arms (7[2.7%] vs 6 [2.4%]). Death due to AEs on therapy or within 30 days from the last dose of study drug were 5 (1.9%) vs 3 (1.2%) (investigational arm: pulmonary embolism in 2 subjects, acute respiratory failure, aspiration and pneumonia in one patient each; control arm: cerebrovascular accident, ischemic stroke and sepsis, each in one patient). Of those, 2 TEAE leading to deaths were considered related to study treatment in the investigational arm (pneumonia and aspiration) vs none in the control arm.

Safety analysis by age category (<65 vs >=65 years) showed higher toxicity in older subjects, although this occurred equally in both arms.

The different exposure to doxorubicin between investigational arm and the control group was noted. According to the protocol, doxorubicin 75 mg/m^2 was to be administered (after olaratumab or placebo) on day 1 of cycles 1 to 8 (of 3 weeks each). However, the median duration of doxorubicin treatment was 18 weeks and 23 weeks for the investigational and control groups, respectively. The median of the number of cycles received were higher in the control arm (6 vs 7) and the median of cumulative dose per body surface area (mg/m^2) was also higher for the control group (409 vs 483). These data seem to suggest a different tolerability to doxorubicin depending on the group, which appears to be different from that observed in the previous phase II trial, where the exposure to doxorubicin was higher for patients in the investigational group as compared to the control group (7 vs 4).

Benefit-risk assessment and discussion

In summary, no benefit of adding Lartruvo to doxorubicin in patients with advanced STS was observed in the ANNOUNCE study.

The sample size, conduct of the study, endpoints, statistical methods or randomisation do not seem to explain the discrepancy between ANNOUNCE and the phase II JGDG. The patient disposition of the ANNOUNCE trial does not indicate major differences between arms in reasons for treatment discontinuation. The baseline characteristics appear to be evenly balanced, both in histology and disease at randomization.

All the sensitivity analyses carried out in the ANNOUNCE study, both in the ITT population an in the LMS group, point in the same direction (no favourable effect of olaratumab). The Kaplan-Meier curves for OS are overlapping. The subgroup analyses do not reveal any subgroup of interest where there could be some benefit. Even the post-discontinuation therapy is balanced. The only significant

difference found in PFS was in the ITT population, but in favour of the control arm. Neither the exploratory analysis of PDGFR-α expression nor the immunogenicity appear to explain the absence of benefit.

No new safety concerns arose from the ANNOUNCE study.

It seems no single reason can explain the discrepancy in results between phase II JGDG and phase III ANNOUNCE studies. ANNOUNCE as the confirmatory trial was specifically designed to show differences in OS. The strength of the evidence from the phase III ANNOUNCE study is necessarily higher due to higher patient numbers and the blinded design with no cross-over. The heterogeneity could also play a role in the two studies. STS is a disease which encompasses a wide range of different tumour histologies, some of them with different prognosis and specific treatments. It is plausible that a different rate of several histologies between the two studies could have had an impact in the dissimilar efficacy observed.

Overall, the results of the ANNOUNCE study are mature and robust to draw the conclusion that the study showed lack of therapeutic efficacy associated with olaratumab treatment in the authorised indication. Even though no new safety concerns arose from the ANNOUNCE study, any safety concerns associated with olaratumab render the benefit-risk balance of Lartruvo negative in view of the lack of therapeutic efficacy observed in the study. Consequently, as the ANNOUNCE study was imposed as a specific obligation to confirm the efficacy and safety of olaratumab in the authorised indication, the conditional marketing authorisation for Lartruvo should be revoked.

CHMP opinion

Whereas

- The Committee considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Lartruvo.
- The Committee reviewed the results of the ANNOUNCE (JGDJ) study, which was conducted to fulfil the specific obligation with a view to confirming a favourable benefit-risk balance for the conditional marketing authorisation for Lartruvo, pursuant to Article 14-a of Regulation (EC) No 726/2004.
- The Committee noted that no benefit was observed from adding Lartruvo to doxorubicin in the treatment of patients with advanced soft tissue sarcoma, when compared to doxorubicin alone.
- The Committee, as a consequence, concluded that Lartruvo lacks therapeutic efficacy and that the benefit-risk of Lartruvo is not favourable.

Therefore, pursuant to Article 116 of Directive 2001/83/EC, the Committee recommends the revocation of the marketing authorisation for Lartruvo.