Annex II

Scientific conclusions

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The United States (US) Food and Drug Administration (FDA) recently concluded that all clinical and bioanalytical studies conducted by Synchron Research Services, a contract research organisation (CRO) located in Ahmedabad, Gujarat, India, were "not acceptable because of data integrity concerns", and that "the studies must be repeated", on the ground that inspections and analyses of study data indicated that the company was "responsible for the creation of false data" and that all studies conducted at that CRO were therefore "unacceptable"[1]. More concretely, the US-FDA recommendation is based on combination of the following:

- Outcome of US-FDA GCP inspection (18-22 November 2019):
  - The site failed to demonstrate that the analytical method used in an in vivo bioavailability or bioequivalence study, is accurate and of sufficient sensitivity to measure the actual concentration of the active drug in the body.
  - Significant pharmacokinetic (PK) data anomalies were observed across multiple studies conducted at the site.
- Analysis of study data generated at Synchron (pre- and post- GCP inspection):
  - multiple pairs of subjects with overlapping time-concentration profiles;
  - distinct groups of subjects where the T/R ratio for Cmax, AUC0-t, or AUC0-∞, among other parameters, for most subjects in the subgroups is above or below 1; or
  - study data having both the above concerns.
- Lack of adequate CRO responses to explain the study data and observations.

Similar concerns have been previously identified further to two EU inspections in 2005 and 2009, which, at the time, were treated as isolated non-compliance and data from the studies concerned were rejected.

The available information and data raise serious concerns related to the suitability of the quality management system and the overall reliability of data generated at Synchron and submitted to support marketing authorisation (applications) in EU Member States (MS).

Between 11th and 14th January 2022 Belgium, Denmark, Finland, The Netherlands, and Sweden therefore triggered a referral under Article 31 of Directive 2001/83/EC, and requested the CHMP to assess the impact of the above concerns on the benefit-risk balance of the medicinal products which have been authorised by the EU Member States on the basis of relevant trials performed at Synchron Research Services sites, as well as for pending procedures, and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

Overall summary of the scientific evaluation

In applications for generic medicinal products under Article 10(1) of Directive 2001/83/EC, the concept of bioequivalence is fundamental. The purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutics quality between the generic medicinal product and a reference medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the reference medicinal product.

[1] Further information about FDA's action, including letters sent to Synchron are available on FDA's website.

Where the bioequivalence is not established, safety and efficacy cannot be extrapolated from the EU reference medicinal product to the generic medicinal product as the bioavailability of the active substance between the two medicinal products may not be within acceptable predefined limits. These limits are set to ensure comparable *in-vivo* performance, i.e. similarity in terms of safety and efficacy. If the bioavailability of the generic product is higher than the predefined upper limit, i.e. the bioavailability of the reference medicinal product, it may result in a higher than intended exposure of patients to the active substance, leading potentially to an increase in the incidence or severity of adverse effects. If the bioavailability of the generic product is lower than the predefined lower limit, i.e. the bioavailability of the reference medicinal product, it may result in a lower than intended exposure to the active substance, leading potentially to a decrease in efficacy, a delay or even a lack of therapeutic effect.

In applications for hybrid medicinal products under Article 10(3) of Directive 2001/83/EC and for well established-used medicinal products under Article 10a of Directive 2001/83/EC, the need for bioequivalence studies is determined on a case-by-case basis. However, where it was fundamental to demonstrate equivalence with a reference medicinal product or with the medicinal product referred in the scientific literature submitted in order to allow bridging of preclinical tests and of clinical trials associated with the reference medicinal product or to the scientific literature submitted, the same principles apply.

The severity and the extent of the findings identified in relation to data generated at Synchron, raised serious concerns related to the suitability of the quality management system and the overall reliability of data generated at Synchron and submitted to support marketing authorisation (applications) in EU MS.

In the absence of reliable data demonstrating bioequivalence with a EU reference medicinal product or, where applicable, with the medicinal product referred in the scientific literature demonstrating that the active substance of the medicinal product concerned has been in well-established medicinal use, the benefit-risk balance of the products either authorised or seeking a marketing authorisation based only on data generated at Synchron Research Services to demonstrate the bioequivalence could not be considered positive, as the possibility of safety/tolerability or efficacy issues cannot be excluded.

Although it is acknowledged that audits or inspections carried out in the past at Synchron Research Services, India, may have had positive outcomes, the findings identified in relation to data generated at Synchron are considered to reflect broader problems concerning the suitability of the quality management system and the overall reliability of all data generated at Synchron and no review or audit of unreliable data can be used to address the concerns. Indeed, although the findings relate to the bioanalytical part of the studies, given the failure of the quality management system to prevent and detect their occurrences, failures in other areas of the trials (including clinical parts) cannot be excluded. It should also be noted that upper management is common to clinical and bioanalytical activities. Because of their nature, these issues are either difficult to identify or not possible to detect during an inspection. It is considered that any other inspection performed at the site would not provide enough reassurance since they may not have detected serious GCP violations, even if present. Considering that the concerns raised by the FDA, taken together with the observations in previous EU inspections of the site (2005 and 2009 inspections, which led to the rejection of the concerned studies), point towards a CRO system issue rather than isolated findings/cases, an at-risk period could not be defined. Therefore, it is considered that those arguments do not demonstrate that the said studies can be relied upon. In addition, the CHMP is of the opinion that the absence of the identification of any pharmacovigilance signals does not provide sufficient reassurance because it is not established that the pharmacovigilance activities may be designed to detect such a signal. The CHMP cannot rule out beyond reasonable doubt that critical GCP violations at the site have affected the said studies and

is of the opinion that the studies cannot be relied upon to establish bioequivalence vis-à-vis the EU reference medicinal product.

Alternative data were submitted to demonstrate the bioequivalence of Almiden, Amlodipine Accord, Rexazon, Varcodes, Tianeptine Mylan, Tianesan, Neluptin, Nobixal, Tramadol / Paracetamol Mylan, Tramadol/Paracetamol EG, Tramadol/Paracetamol Stada, Tramylpa, Xymel and Tramadol/Paracetamol Alter to an EU reference medicinal product. Having assessed the alternative study, the CHMP recommends the maintenance of the marketing authorisations for Almiden, Amlodipine Accord, Rexazon, Varcodes, Tianeptine Mylan, Neluptin, Nobixal, Tramadol / Paracetamol Mylan, Tramadol/Paracetamol EG, Tramadol/Paracetamol Stada, Tramylpa, Xymel and Tramadol/Paracetamol Alter, and concludes that, with regards to the Tianesan marketing authorisation application, bioequivalence has been demonstrated vis-à-vis the EU reference medicinal product using alternative data.

Alternative bioequivalence studies were referred to as the pivotal evidence to demonstrate the bioequivalence of Amlodipin Jubilant, Azithromycin Heumann, Dorzolamid Heumann, Zormid, Rozemib, Aurozeb and Torasemida Stada, and of the ongoing marketing authorisation application for Arrox plus and rosuvastatina/ezetimiba Alter to an EU reference medicinal product, and not the studies performed at Synchron. Having assessed the information provided, the CHMP concluded that the benefit-risk balance of Amlodipin Jubilant, Azithromycin Heumann, Dorzolamid Heumann, Zormid, Rozemib, Aurozeb and Torasemida Stada were not affected by the concerns related to the studies performed by Synchron and recommended the maintenance of the marketing authorisations. Likewise, the CHMP concluded that the benefit-risk balance of Hydrokortison Orifarm was not affected by the concerns related to the studies performed by Synchron and recommended the maintenance of the marketing authorisation. Having assessed the information provided, the CHMP also concluded that the benefit-risk balance of Arrox plus and rosuvastatina/ezetimiba Alter was not affected by the concerns related to the studies performed by Synchron and recommended that the evaluation of this application may continue at national level.

Results of bioequivalence studies conducted outside the EU, with non-EU reference products have been provided. According to Article 10 of Directive 2001/83/EC, the bioequivalence needs to be established vis-à-vis an EU reference medicinal product. Results from bioequivalence studies using non-EU reference medicinal products can therefore not be accepted for demonstrating said bioequivalence.

In the absence of the demonstration of bioequivalence vis-à-vis the EU reference medicinal product, or in the absence of demonstration that the active substance of the medicinal product has been in well-established medicinal use, the requirements of Article 10 or 10a of Directive 2001/83/EC cannot be considered fulfilled, the efficacy and safety of the concerned medicinal products cannot be established and therefore, the benefit-risk balance cannot be considered positive. The CHMP therefore considers that all concerned marketing authorisation applications not listed in the above paragraph of this section do not currently fulfil the criteria for authorisation and recommended the suspension of the marketing authorisations for all concerned medicinal products not listed in the above paragraph of this section (those concerned marketing authorisation applications and marketing authorisations are listed in annex IB).

The Committee recommends that these marketing authorisations (annex IB) should be suspended unless the medicinal product is considered critical by the relevant national competent authorities.

For marketing authorisation(s) of a medicinal product considered critical, the suspension may be deferred in the relevant EU Member State(s) for a period which shall not exceed 24 months from the Commission Decision. Should during this period the EU Member State(s) consider a medicinal product not critical anymore, the suspension of the concerned marketing authorisation shall apply. For these medicinal products considered critical by EU Member States, the marketing authorisation holders shall

submit a bioequivalence study conducted vis-à-vis the EU reference medicinal product within 12 months following Commission Decision. An authorised medicinal product listed in Annex IB may be considered critical by the EU Member State(s) based on the evaluation of the potential unmet medical need, considering the availability of suitable alternative medicinal products in the respective EU Member State(s) and, as appropriate, the nature of the disease to be treated.

Re-examination procedure

Following the adoption of the CHMP opinion in May 2022, the MAHs AbZ Pharma GmbH, Pliva, Teva and Ratiopharm requested a re-examination of the CHMP opinion on the Article 31 referral for Synchron Research Services according to Article 32(4) of Directive 2001/83/EC for their affected torasemide-containing products (i.e. Diuver, Torasemide Teva, Torasemid-ratiopharm, Torasemide, Torasemid AbZ and Torasemide Teva Italia). Detailed grounds for re-examination of the CHMP recommendation have been submitted by the MAHs on 18 July 2022.

CHMP discussion on grounds for re-examination

The CHMP considered the detailed grounds as submitted by the MAHs within this re-examination procedure and the scientific data underlying these grounds.

The CHMP reiterated that the findings identified in relation to data generated at Synchron reflect broad problems concerning the suitability of the quality management system and the overall reliability of all data generated at Synchron. The CHMP maintained that it cannot rule out beyond reasonable doubt that critical GCP violations at the site have affected the said studies and is of the opinion that the studies cannot be relied upon to establish bioequivalence vis-à-vis the EU reference medicinal product. In addition, the CHMP reiterated its opinion that the absence of the identification of any pharmacovigilance signals does not provide sufficient reassurance to conclude on a positive benefit-risk balance in the absence of the demonstration of bioequivalence with the EU reference medicinal product because it is not established that the pharmacovigilance activities may be designed to detect such a signal.

The CHMP considered that the scientific justification provided for the lack of incurred sample reanalysis (ISR) supported the following:

- Metabolic back conversion is not an issue for torasemide as the metabolites of torasemide appear to be stable and back conversion into parent during storage is unlikely. Moreover, due to a difference in molecular weight, in case that metabolites are eluted at the same time as the parent drug, it would not interfere with the detection of torasemide by the tandem mass spectrometry (MS/MS) detector. For the same reason, co-medication with ibuprofen would not have influenced the results, as it has a different molecular weight. In addition, long term stability data did not indicate an issue with possible back-conversion. The CHMP considered the bioanalytical method sufficiently sensitive to be able to detect the analyte and its internal standard without any interference.
- Acceptable data on repeat analysis (based on QC sample analysis) is available.
- Comparison of the pharmacokinetic data obtained in study B034601 with literature data showed these were comparable.
- The 90% CI observed in study B034601 are well within the 80 – 125% limits and therefore the probability of a false positive outcome due to ISR problems is low.

Therefore, whilst no ISR data available using the same bioanalytical method in the same laboratory, the data provided support the validity of the analytical method and a false positive outcome of this bioequivalence study is considered unlikely. The CHMP considered the lack of ISR data sufficiently justified in line with point 1.3 of the EMA Q&A on Clinical pharmacology and pharmacokinetics.

In addition, within-run and between-run accuracy and precision were tested on torasemide quality control (QC) sample concentrations at 25, 250, 2500 and 6000 ng/ml during validation. In principle for the newly added high QC concentration (i.e. 6000 ng/ml), stability should have been shown, however the data obtained at 25, 250 and 2500 ng/ml is considered sufficient to support the conclusion on stability.

Matrix effect was evaluated using matrices from 4 different lots/donors. While, the internal standard normalised matrix factor was not applied, the new ICH guideline M10 on bioanalytical method validation (EMA/CHMP/ICH/172948/2019) does not include this requirement. Therefore, the CHMP agreed that the matrix effect was sufficiently evaluated.

Selectivity was considered demonstrated in processed blank plasma samples from 6 different sources in line with the requirements of the EMA Guideline on bioanalytical method validation. Haemolysed samples and/or lipemic samples were not evaluated, however this is not a requirement in this case.

Subject samples were obtained in tubes with EDTA as anticoagulant. The same EDTA human plasma was used for both study sample analysis and method validation. Hence, whilst it is noted that the counter-ion was not mentioned (e.g. K2 or K3), CHMP considered that from an analytical perspective it is very unlikely that use of K2 instead of K3-EDTA (or vice versa) would have an impact on the accuracy and precision, or on the stability of torasemide and therefore no additional matrix-anticoagulant testing was considered required.

The CHMP noted that the following stability experiments were performed: room temperature stability, in-process stability and storage stability of extracted samples in refrigerator. The results showed that torasemide was stable for at least forty-eight (48) hours during sample processing at room temperature and therefore it can be extrapolated that the stability remains at colder temperatures. The results also showed that torasemide was stable for at least forty-eight (48) hours during storage in the refrigerator. Based on this experiment, autosampler stability is considered demonstrated (same temperature as in the refrigerator). Working solution stability experiment was not conducted, however, prepared working solution were used for spiking of calibration and quality control samples.

Overall, the CHMP, concluded that the analytical method of study B034601 is sufficiently sensitive, accurate and precise for the analysis of torasemide in plasma.

The CHMP noted that the MAHs of Torasemid AL and Torasemid STADA (Aliud Pharma GmbH and Stadapharm GmbH, respectively) had also referred to study B034601 as alternative evidence of bioequivalence. Taking this into consideration, the above considerations for study B034601 are also applicable to these marketing authorisations.

The CHMP further noted that at time of initial authorisation of those medicinal products, the conduct of a further bioequivalence study for the 5 mg strength had been waived, based on the 10 mg batch used in the Synchron study. The same 10 mg batch was used in the Synchron study and in study B034601, therefore results of the latter study can be extrapolated to the 5 mg strength.

In conclusion, having assessed the alternative study B034601, the CHMP considered that it supports the bioequivalence of the torasemide-containing products Diuver, Torasemide Teva, Torasemid-ratiopharm, Torasemide, Torasemid AbZ, Torasemide Teva Italia, Torasemid AL and Torasemid STADA to the EU reference medicinal product or, for well-established use products, with the medicinal product referred in the scientific literature.

The CHMP also noted the further grounds for re-examination submitted by the MAHs and summarised under points 1 and 3 in the above section, however, in view of their non-scientific nature and the above conclusion, those are no longer relevant and are therefore not discussed here.

Based on the totality of the data available, including the information submitted during the initial assessment procedure and the detailed grounds for re-examination put forward by the MAHs, the CHMP recommends the maintenance of the marketing authorisations for Diuver, Torasemide Teva, Torasemid-ratiopharm, Torasemide, Torasemid AbZ, Torasemide Teva Italia, Torasemid AL and Torasemid STADA.

Grounds for CHMP opinion

Whereas,

- The CHMP considered the procedure under Article 31 of Directive 2001/83/EC for marketing authorisations and marketing authorisation applications for medicinal products for which the clinical and/or bioanalytical parts of the bioequivalence studies were performed at Synchron Research Services, a contract research organisation (CRO) located in Ahmedabad, Gujarat, India, since the set-up of the site under the name Synchron Research Services.
- The CHMP reviewed available data and information provided in writing and in an oral explanation by the MAHs and applicants, as well as information provided by Synchron Research Services. The CHMP considered that Synchron Research Services did not provide any new information that changed the conclusions laid out in the notifications for this procedure.
- The CHMP also considered the grounds for re-examination submitted by the MAHs in writing.
- The CHMP concluded that, for the marketing authorisations and marketing authorisation applications referred to in annex IA, there was alternative data to establish bioequivalence vis-à-vis the EU reference medicinal product, or to demonstrate that the active substance of the medicinal product has been in well-established medicinal use.
- The Committee concluded that the particulars supporting the marketing authorisation/marketing authorisation application are incorrect and that the benefit-risk balance is considered not favourable for:
    - Authorised medicinal products for which alternative bioequivalence data or a justification was submitted but considered insufficient by the CHMP to establish bioequivalence vis-à-vis the EU reference medicinal product, or, for well-established use products, with the medicinal product referred in the scientific literature, or for which no alternative bioequivalence data or a justification was submitted (annex IB);
    - Marketing authorisation applications for which no alternative bioequivalence data or a justification was submitted (annex IB).

Therefore, in accordance with Articles 31 and 32 of Directive 2001/83/EC, the CHMP concludes that:

a. Marketing authorisations for medicinal products for which the bioequivalence vis-à-vis the EU reference medicinal product has been established or for which it has been demonstrated that the active substance of the medicinal product has been in well-established medicinal use (annex IA) should be maintained, as the benefit risk balance of these marketing authorisation is considered favourable.

b. Bioequivalence vis-à-vis the EU reference medicinal product has been established for Tianesan and may continue to be assessed by the relevant national competent authorities for Arrox plus and rosuvastatina/ezetimiba Alter listed in annex IA.

c. Marketing authorisations for medicinal products for which bioequivalence data or justification were not submitted or considered insufficient by the CHMP to establish bioequivalence vis-à-vis the EU reference medicinal product/medicinal product referred in the scientific literature (Annex IB) should be suspended, as the particulars supporting the marketing authorisations are incorrect and the benefit-risk balance of these marketing authorisations is considered not favourable pursuant to Article 116 of Directive 2001/83/EC.

   For the suspension of the marketing authorisations to be lifted the MAHs shall provide evidence that bioequivalence vis-à-vis an EU reference medicinal product has been demonstrated, based on relevant data, in accordance with the requirements of Article 10 of Directive 2001/83/EC (e.g. a bioequivalence study conducted vis-à-vis the EU reference medicinal product) or, when applicable for well-established use products, bioequivalence vis-à-vis the medicinal product referred in the scientific literature has been demonstrated.

   Some of these authorised medicinal products may be considered critical by the individual EU Member States on the evaluation of the potential unmet medical need, considering the availability of suitable alternative medicinal products in the respective EU Member State(s) and, as appropriate, the nature of the disease to be treated. Where on the basis of these criteria the relevant national competent authorities of the EU Member States consider that a medicinal product is critical, the suspension of the concerned marketing authorisation(s) may be deferred by the period for which the medicinal product is considered critical. This period of deferral shall not exceed 24 months from the Commission Decision. Should during this period the EU Member State(s) consider a medicinal product not critical anymore, the suspension of the concerned marketing authorisation(s) shall apply. For these medicinal products considered critical by EU Member State(s), the marketing authorisations holders shall submit a bioequivalence study conducted vis-à-vis the EU reference medicinal product/medicinal product referred in the scientific literature within 12 months from the Commission Decision.

d. Marketing authorisation applications for which bioequivalence data or justification were not submitted or considered insufficient by the CHMP to establish bioequivalence vis-à-vis the EU reference medicinal product (Annex IB) do not satisfy the criteria for authorisation, as the particulars supporting the marketing authorisations are incorrect and the benefit-risk balance of these marketing authorisation is considered not favourable pursuant to Article 26 of Directive 2001/83/EC.