I

The totality of the efficacy and safety data show a positive benefit-risk assessment and support approval of the use of trastuzumab deruxtecan at a dose of 5.4 mg/kg Q3W for the treatment of patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2-based regimens. Trastuzumab deruxtecan demonstrated substantial antitumor activity, with clinically meaningful and durable responses in extensively pretreated patients. The clinical benefit from high response rates associated with durable responses was reflected by a prolonged PFS, which is expected to translate into a survival benefit. These results, associated with a manageable and tolerable safety profile, represent a clinically meaningful improvement over available therapies in the proposed patient population who has no clearly preferential treatment options after having received 2 or more prior anti-HER2-based regimens, addressing an unmet medical need and potentially changing the treatment paradigm.

The totality of the data provides compelling evidence for a positive benefit/risk profile supporting the use of trastuzumab deruxtecan in patients with unresectable or metastatic HER2-positive breast cancer who have received 2 or more prior anti-HER2-based regimens.

II

The development of the lanadelumab pre-filled syringe drug product and manufacturing process is detailed in the various subsections of Section 3.2.P.2 Pharmaceutical Development PFS. Information is provided regarding the development studies performed to establish the dosage form, formulation, manufacturing process, container closure system, microbiological attributes, and comparability between the vial and pre-filled syringe presentation.

The components of the pre-filled syringe drug product and the compatibility of the active ingredient lanadelumab with manufacturing processes and excipients are discussed in Section 3.2.P.2.1 Components of the Drug Product PFS.

The lanadelumab pre-filled syringe drug product formulation is identical to the commercial vial drug product formulation. The suitability of the drug product formulation for subcutaneous injection has been established previously through several formulation screening and optimization studies that evaluated the impact of pH, buffer species, excipients, and the protein and polysorbate 80 (PS80) concentrations on the stability of lanadelumab. The robustness of the formulation and the performance of drug product were also evaluated by varying the formulation components from the selected target formulation. These studies are described in the drug product vial Section 3.2.P.2.2 Drug Product. Additionally, the potential impact of various concentrations of PS80 on product quality of pre-filled syringes was assessed by a worst-case simulated shipping study. The results of the simulated shipping study are summarized and discussed in Section 3.2.P.2.2 Drug Product PFS.

III

In most cases, the PPQ study needs to be completed successfully and a high degree of assurance in the process achieved before commercial distribution of a product. In special situations, the PPQ protocol can be designed to release a PPQ batch for distribution before complete execution of the protocol steps and activities, i.e., concurrent release. FDA expects that concurrent release will be used rarely.