Vocabria

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
IB/0025	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	22/01/2025		SmPC	
II/0022	Extension of indication to include, in combination with rilpivirine injection, the treatment of adolescents	12/12/2024	13/01/2025	SmPC and PL	Please refer to Scientific Discussion 'Vocabria-H-C-004976-II-0022'

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	(at least 12 years of age and weighing at least 35 kg) for Vocabria, based on interim results from study 208580. This is an ongoing Phase 1/Phase 2 multicentre, open-label, non-comparative study evaluating the safety, acceptability, tolerability, and pharmacokinetic of oral and long-acting injectable cabotegravir and long-acting injectable rilpivirine in virologically suppressed HIV-infected adolescents 12 to <18 years of age and weighing at least 35 kg who are receiving stable combination antiretroviral therapy consisting of 2 or more drugs from 2 or more classes of antiretroviral drugs. Consequently, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.3 of the RMP has also been adopted. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor editorial changes and to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.4. The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
PSUSA/10900 /202403	Periodic Safety Update EU Single assessment - cabotegravir (for treatment of human immunodeficiency virus type 1 (HIV-1)	17/10/2024	12/12/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUSA/10900/202403.
IB/0024/G	This was an application for a group of variations. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	10/09/2024	n/a		
WS/2608/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	18/04/2024	n/a		

	B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size				
II/0019	Update of section 4.2 of the SmPC in order to update administration instructions to mitigate product leakage related to the correct use of the vial adapter, based on Human Factor studies. The Package Leaflet (Instructions for Use) is updated accordingly.	08/02/2024	12/12/2024	SmPC and PL	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0021	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	21/12/2023	n/a		
IB/0018/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	04/12/2023	n/a		
PSUSA/10900 /202303	Periodic Safety Update EU Single assessment - cabotegravir (for treatment of human immunodeficiency virus type 1 (HIV-1)	26/10/2023	n/a		PRAC Recommendation - maintenance

II/0016/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.b.4.d - Change in the batch size (including batch size ranges) of the finished product - The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes	31/08/2023	n/a		
PSUSA/10900 /202203	Periodic Safety Update EU Single assessment - cabotegravir (for treatment of human immunodeficiency virus type 1 (HIV-1)	10/11/2022	10/01/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10900/202203.
IA/0015	A.7 - Administrative change - Deletion of manufacturing sites	16/12/2022	n/a		
II/0012	Update of sections 4.2 and 5.1 of the SmPC in order to describe data regarding oral bridging using other suppressive regimens than oral bridging with cabotegravir and rilpivirine based on studies 201584 (FLAIR), 207966 (ATLAS-2M), 200056 (LATTE 2) and 201585 (ATLAS). In addition, the MAH is also taking this opportunity to introduce editorial changes in the SmPC and Package Leaflet.	15/09/2022	10/01/2023	SmPC and PL	Section 4.2. Missed monthly injection […] Limited data is available on oral bridging with other fully suppressive antiretroviral therapy (ART) (mainly INI-based), see section 5.1. […] Missed 2 month injection […] Limited data is available on oral bridging with other fully suppressive antiretroviral therapy (ART) (mainly INI-based), see section 5.1. […]

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Oral dosing for missed injections of cabotegravir […] Limited data is available on oral bridging with other fully suppressive antiretroviral therapy (ART) (mainly INI-based), see section 5.1. […] Section 5.1. Oral bridging with other ART In a retrospective analysis of pooled data from 3 clinical studies (FLAIR, ATLAS-2M, and LATTE-2/study 200056), 29 subjects were included who received oral bridging for a median duration of 59 days (25th and 75th percentile 53-135) with ART other than Vocabria plus rilpivirine (alternative oral bridging) during treatment with Vocabria plus rilpivirine long-acting (LA) intramuscular (IM) injections. The median age of subjects was 32 years, 14% were female, 31% were non-white, 97% received an integrase inhibitor (INI)-based regimen for alternative oral bridging, 41% received an NNRTI as part of their alternative oral bridging regimen (including rilpivirine in 11/12 cases), and 62% received an NRTI. Three subjects withdrew during oral bridging or shortly following oral bridging for non-safety reasons. The majority (≥96%) of subjects maintained virologic suppression (plasma HIV-1 RNA <50 c/mL). During bridging with alternative oral bridging and during the period following alternative oral bridging (up to 2 Vocabria plus rilpivirine injections following oral bridging), no cases of CVF (plasma HIV-1 RNA ≥200 c/mL) were observed. For more information, please refer to the Summary of Product Characteristics.

II/0008	Update of sections 4.4 and 5.1 of the SmPC in order to update efficay ad safety information based on week 96 results from the clinical study 207966 (ATLAS-2M). This is a open-label, randomized, Phase IIIb trial to demonstrate non-inferior antiviral activity and safety of CAB + RPV Q8W compared with CAB + RPV Q4W. Supporting Cabotegravir (CAB) Long-acting Injectable (LA) + Rilpivirine (RPV) LA every 2 months (Q8W) dosing regimen for the treatment of HIV-1 infection. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/09/2022	10/01/2023	SmPC	Section 4.4. Baseline factors associated with virological failure Available data suggest that virologic failure occurs more often when these patients are treated according to the every 2 month dosing regimen as compared to the monthly dosing regimen. Section 5.1. Every 2 months dosing Patients virologically suppressed (stable on prior ART for at least 6 months) The efficacy results at Week 96 are consistent with the results of the primary endpoint at Week 48. Vocabria plus rilpivirine injections administered every 2 months is non-inferior to Vocabria and rilpivirine administered every month. The proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 96 in Vocabria plus rilpivirine every 2 months dosing (n=522) and Vocabria plus rilpivirine monthly dosing (n=523) was 2.1% and 1.1% respectively (adjusted treatment difference between Vocabria plus rilpivirine every 2 months dosing and monthly dosing [1.0; 95% CI: -0.6, 2.5]). The proportion of subjects having plasma HIV-1 RNA <50 c/mL at Week 96 in Vocabria plus rilpivirine every 2 months dosing and Vocabria plus rilpivirine monthly dosing was 91% and 90.2% respectively (adjusted treatment difference between Vocabria plus rilpivirine every 2 months dosing and monthly dosing [0.8; 95% CI: -2.8, 4.3]). The efficacy results at Week 152 are consistent with the results of the primary endpoint at Week 48 and at Week 96. Vocabria plus rilpivirine injections administered every 2 months is non-inferior to Vocabria and rilpivirine

					administered every month. In an ITT analysis, the proportion of subjects having plasma HIV-1 RNA ≥50 c/mL at Week 152 in Vocabria plus rilpivirine every 2 months dosing (n=522) and Vocabria plus rilpivirine monthly dosing (n=523) was 2.7% and 1.0% respectively (adjusted treatment difference between Vocabria plus rilpivirine every 2 months dosing and monthly dosing [1.7; 95% CI: 0.1, 3.3]). In an ITT analysis, the proportion of subjects having plasma HIV-1 RNA <50 c/mL at Week 152 in Vocabria plus rilpivirine every 2 months dosing and Vocabria plus rilpivirine monthly dosing was 87% and 86% respectively (adjusted treatment difference between Vocabria plus rilpivirine every 2 months dosing and monthly dosing [1.5; 95% CI: -2.6, 5.6]). Post-hoc analyses Multivariable analyses of pooled phase 3 studies (ATLAS through 96 weeks, FLAIR through 124 weeks and ATLAS-2M through 152 weeks) examined the influence of various factors on the risk of CVF. The baseline factors analysis (BFA) examined baseline viral and participant characteristics and dosing regimen; and the multivariable analysis (MVA) included the baseline factors and incorporated post-baseline predicted plasma drug concentrations on CVF using regression modelling with a variable selection procedure. Following a total of 4291 person-years, the unadjusted CVF incidence rate was 0.54 per 100 person-years; 23 CVFs were reported (1.4% of 1651 individuals in these studies). The BFA demonstrated rilpivirine resistance mutations (incidence rate ratio IRR=21.65, p<0.0001), HIV-1 subtype A6/A1 (IRR=12.87, p<0.0001), and body mass index

					IRR=1.09 per 1 unit increase, p=0.04; IRR=3.97 of ≥30 kg/m2, p=0.01) were associated with CVF. Other variables including Q4W or Q8W dosing, female gender, or CAB/INSTI resistance mutations had no significant association with CVF. A combination of at least 2 of the following key baseline factors was associated with an increased risk of CVF: rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI□30 kg/m2. In patients with at least two of these risk factors, the proportion of subjects who had a CVF was higher than observed in patients with none or one risk factor, with CVF identified in 6/24 patients [25.0%, 95%CI (9.8%, 46.7%)] treated with the every 2 months dosing regimen and 5/33 patients [15.2%, 95%CI (5.1%, 31.9%)] treated with the monthly dosing regimen.
IG/1531	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/08/2022	10/01/2023	SmPC and PL	
PSUSA/10900 /202109	Periodic Safety Update EU Single assessment - cabotegravir (for treatment of human immunodeficiency virus type 1 (HIV-1)	22/04/2022	21/06/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10900/202109.
II/0011	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/04/2022	n/a		
PSUSA/10900 /202103	Periodic Safety Update EU Single assessment - cabotegravir (for treatment of human immunodeficiency virus type 1 (HIV-1)	14/10/2021	16/12/2021	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10900/202103.
IB/0009	B.I.d.1.a.4 - Stability of AS - Change in the re-test	15/12/2021	n/a		

	period/storage period - Extension or introduction of a re-test period/storage period supported by real time data				
II/0004	Update of section 4.2 (to change posology recommendations) and sections 4.4, 4.8, 5.1 and 5.2 of the SmPC (to update safety and efficacy information) based on week 124 results from the FLAIR study. This is a Phase III, randomized, open-label study to evaluate the efficacy, safety and tolerability of the combined treatment Cabotegravir and Rilpivirine. The Package Leaflet has been updated accordingly. Editorial changes and corrections have been carried out throughout the PI. The RMP version 2 has also been submitted. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet to bring the PI in line with the latest QRD template version 10.2. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/09/2021	19/10/2021	SmPC and PL	SmPC new text 4.2 Posology and method of administration […] The healthcare provider and patient may decide to use cabotegravir tablets as an oral lead-in prior to the initiation of Vocabria injection to assess tolerability to cabotegravir (see Table 1) or may proceed directly to Vocabria injections (see Table 2 for monthly and Table 3 for every 2 month dosing recommendations). […] 4.8 Undesirable effects […] The overall safety profile at Week 96 and Week 124 in the FLAIR study was consistent with that observed at Week 48, with no new safety findings identified. In the extension phase of the FLAIR study, initiating the Vocabria and rilpivirine injection regimen with Direct to Injection did not identify any new safety concerns related to omitting the oral lead-in phase (see section 5.1). [..] 5.1 Pharmacodynamic properties Week 124 FLAIR Direct to Injection vs Oral Lead-in. In the FLAIR study, an evaluation of safety and efficacy was performed at Week 124 for patients electing to switch (at Week 100) from abacavir/dolutegravir/lamivudine to Vocabria plus rilpivirine in the Extension Phase. Subjects were given the option to switch with or without an oral lead-in phase, creating an oral lead-in (OLI) group (n=121)

					and a direct to injection (DTI) group (n=111). At Week 124, the proportion of subjects with HIV-1 RNA ≥50 copies/mL was 0.8% and 0.9% for the oral lead-in and direct to injection groups, respectively. The rates of virologic suppression (HIV-1 RNA <50 c/mL) were similar in both OLI (93.4%) and DTI (99.1%) groups. For more information, please refer to the Summary of Product Characteristics.
II/0007	Update of section 4.8 of the SmPC in order to update the adverse reactions section, adding information regarding events of pyrexia have a close temporal association with injections. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to include minor typographical updates. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	30/09/2021	16/12/2021	SmPC and PL	Based on data submitted, the adverse drug reactions section has been updated, by including the information regarding events of pyrexia have a close temporal association with injections. Accordingly the package leaflet has been updated as well. For more information, please refer to the Summary of Product Characteristics.
IB/0005	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	18/06/2021	19/10/2021	SmPC and PL	
IB/0002	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	16/03/2021	n/a		
IB/0001	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	16/03/2021	n/a		

IA/0003	A.7 - Administrative change - Deletion of manufacturing sites	19/02/2021	19/10/2021	SmPC, Annex II and PL	