

**7.03 CABOTEGRAVIR/CABOTEGRAVIR AND RILPIVIRINE,
Tablet containing cabotegravir 30 mg,
Vocabria[®],
Pack containing 1 injection of cabotegravir 600 mg in
3 mL and 1 injection of rilpivirine 900 mg in 3 mL,
Cabenuva[®],
ViiV Healthcare Pty Ltd**

1 Purpose of Application

- 1.1 The standard re-entry resubmission requested a Section 100 (Highly Specialised Drugs Program – Community Access), Authority Required (STREAMLINED) listing for cabotegravir (CAB) long-acting (LA) injection and rilpivirine (RPV) LA injection (combination pack with the tradename Cabenuva), and CAB tablets (trade name Vocabria) for treatment of human immunodeficiency virus (HIV) in virologically suppressed patients (at initiation). This was the first resubmission for CAB LA + RPV LA and oral CAB, with the previous submission considered at the March 2021 PBAC meeting.
- 1.2 Listing was requested on the basis of a cost-utility analysis (CUA) against a basket of oral antiretroviral therapies (ART) based on the resubmission's claim of noninferior effectiveness but providing additional benefits to patients who have an unmet need for an alternative to daily oral ART.

Table 1: Key components of the clinical issue addressed by the resubmission

Component	Description
Population	Treatment of HIV infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) and switching therapy.
Intervention	<ul style="list-style-type: none"> • Oral lead in: CAB 30 mg PO once daily and RPV 25 mg PO once daily for ONE month • Initiation injection: CAB 600 mg (3 mL) IM and RPV 900 mg (3 mL) IM at separate gluteal sites • Continuation injection: one month following initiation injection: CAB 600 mg (3 mL) IM and RPV 900 mg (3 mL) IM at separate gluteal sites then every TWO months
Comparator	Weighted basket of fixed dose combination ART including (BIC/FTC/TAF Biktarvy®, DTG/ABC/3TC Triumeq®, ELV/c/FTC/TAF Genvoya®, RPV/FTC/TAF Odefsey®, DTG/RPV Juluca® and DTG/3TC Dovato®)
Outcomes	<p>Primary:</p> <ul style="list-style-type: none"> • Proportion of subjects with HIV-1 RNA ≥50 copies/mL at Week 48 <p>Secondary:</p> <ul style="list-style-type: none"> • Proportion of participants with Plasma HIV-1 RNA <50 copies/mL at Week 48 • Incidence and severity of adverse events <p>Patient-reported outcomes: Treatment satisfaction using the HIV Treatment Satisfaction Questionnaire; SF-12; preference question; SF-6D</p>
Clinical claim	<ul style="list-style-type: none"> • CAB LA + RPV LA is noninferior in terms of effectiveness in comparison to ART for the treatment of HIV infection in treatment-experienced patients. • CAB LA + RPV LA has an acceptable safety profile for the treatment of HIV infection. • CAB LA + RPV LA provides additional benefits to patients who have an unmet need for an alternative to daily oral ART (QoL impacts such as anxiety and worry due to the requirement to adhere to daily treatment, stigma and associated reminder of disease, fear of unintentional disclosure, patient preference, convenience, less frequent dosing and medical conditions affecting oral dosing) as demonstrated by a QoL gain compared to the ART treatment arm (based on SF-6D analysis)

Source: Table 3, p15 of the resubmission.

ABC = abacavir; AIDS = acquired immunodeficiency syndrome; ART = antiretroviral; BIC = bicitgravir; CAB = cabotegravir; DTG = dolutegravir; ELV/c = elvitegravir/cobicistat; FTC = emtricitabine, HIV = Human Immunodeficiency Virus; HIVSTQ = HIV treatment satisfaction questionnaire, IM = intramuscular; LA = long-acting; RNA = ribonucleic acid; RPV = rilpivirine; PO = by mouth; SF-12 = 12-Item Short Form Health Survey; SF-6D = Short-Form six-dimension; TAF = tenofovir alafenamide; 3TC = lamivudine; QoL = quality of life

2 Background

Registration status

2.1 CAB 600 mg/3 mL + RPV 900 mg/3 mL (the two monthly/every eight-weekly dosage) and CAB 400 mg/2 mL + RPV 600 mg/2 mL (the one monthly/every four-weekly dosage) were approved by the TGA on 23 February 2021 for the following indication:

- “CABENUVA (cabotegravir long-acting intramuscular injection and rilpivirine long-acting intramuscular injection) is indicated for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies per mL) and have no known or suspected resistance to either cabotegravir or rilpivirine.”

2.2 Additionally, the oral CAB tablets were approved by the TGA for the following indication:

- “VOCABRIA tablets are indicated in combination with rilpivirine tablets for the short-term treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults

who are virologically suppressed (HIV-1 RNA <50 copies/mL) and have no known or suspected resistance to either cabotegravir or rilpivirine for:

- oral lead in to assess tolerability of cabotegravir prior to administration of cabotegravir prolonged-release suspension for injection plus rilpivirine prolonged-release suspension for injection.
- oral therapy for adults who will miss planned dosing with cabotegravir prolonged-release suspension for injection.”

Previous PBAC consideration

2.3 The PBAC previously considered CAB LA + RPV LA for patients with virologically suppressed HIV-1 infection at the March 2021 PBAC meeting.

2.4 The key matters of concern regarding the previous submission and how the resubmission has addressed these concerns are summarised in Table 2.

Table 2: Summary of outstanding matters of concern

Component	Matter of concern	How the resubmission addresses it
Quality of life benefit for CAB LA + RPV LA	The PBAC considered the presented evidence did not support a conclusion that CAB LA + RPV LA offered advantages in terms of quality of life, reduced anxiety or worry associated with daily oral therapy (ART) (paragraph 7.1, 7.7, cabotegravir-rilpivirine PSD, March 2021 PBAC meeting).	A <i>post hoc</i> analysis utilising the SF-12 individual patient data in the ATLAS and FLAIR trials was utilised to generate SF-6D results. The analysis showed a statistically significant utility gain of 0.02 in CAB LA + RPV LA arm vs oral ART arm. (paragraphs 6.19 to 6.40).
Economic evaluation modelling	The PBAC considered the economic analysis, which relied on a cost-benefit analysis rather than a formal cost-utility analysis (CUA) was uninformative for decision making as it did not capture or allow exploration of the factors for which advantages over daily oral ART were claimed (paragraph 7.1, cabotegravir-rilpivirine PSD, March 2021 PBAC meeting).	A new economic analysis (CUA) incorporating the utility data was provided to determine the incremental cost per QALY gained of including CAB LA + RPV LA as a treatment option for persons who consider the benefits of a long-acting treatment will provide an improvement in their QoL (paragraphs 6.48 to 6.52).
Unmet need for alternative to oral ART	The PBAC noted that Australian epidemiological data indicated diagnosis and treatment rates in Australia were high and did not indicate an unmet need in the overall HIV population (paragraph 7.3, cabotegravir-rilpivirine PSD, March 2021 PBAC meeting).	Not addressed specifically. Sponsor requested the PBAC to reconsider entirety of presented evidence as well as the consumer comments submitted to the March 2021 submission by NACCHO, NAPWHA, Thorne Harbour Health Group (Vic) and the sponsor hearing presented at the PBAC meeting in March 2021. Additional sponsor hearing and consumer comments were also received for the resubmission.

Source: Table 1-1, p19 of the resubmission

CAB = cabotegravir; LA = long-acting; NACCHO = National Aboriginal Community Controlled Health Organisation; NAPWHA = National Association for People Living with HIV; PSD = public summary document; QALY = quality adjusted life years; RPV = rilpivirine; SF-12 = 12-Item Short Form Health Survey; SF-6D = Short-Form six-dimension.

For more detail on PBAC’s view, see section 7 PBAC outcome.

3 Requested listing

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
Cabotegravir 30 mg, oral tablets	30	0	\$ [REDACTED]	Vocabria®	ViiV Healthcare Pty Ltd
Cabotegravir and Rilpivirine long-acting suspension for injection	One 3 mL single-dose vial CAB 600 mg + one 3 mL single-dose vial RPV 900 mg = 1 pack	5	\$ [REDACTED] ^a effective price \$2,827.78 published price	Cabenuva®	ViiV Healthcare Pty Ltd

a. Price offered in Pre-PBAC Response.

Requested restriction cabotegravir tablets

Episodicity:	Chronic
Condition:	HIV infection
Treatment phase:	Initial
Restriction: Section 100 Highly Specialised Drugs Program (Community Access)	<input checked="" type="checkbox"/> Streamlined
Treatment criteria:	Patient must be virologically suppressed on a stable antiretroviral regimen for at least 6 months AND Treatment must be prescribed in combination with rilpivirine tablets Patient must intend to commence intramuscular administration of antiviral treatment.

Source: Table1-7, p44 of the resubmission.

Requested restriction cabotegravir long-acting and rilpivirine long-acting injection

Episodicity:	Chronic
Condition:	HIV infection
Treatment phase:	Continuing
Restriction: Section 100 Highly Specialised Drugs Program (Community Access)	<input checked="" type="checkbox"/> Streamlined
Treatment criteria:	Patient must have previously received PBS-subsidised therapy for this condition. AND Patient is recommended to have previously received one-month treatment with oral cabotegravir and rilpivirine AND The treatment must be the sole PBS-subsidised therapy for this indication.

Source: Table1-8, p37 of the submission.

- 3.1 A special pricing arrangement was proposed for CAB LA + RPV LA. The requested price of CAB LA + RPV LA was based on a CUA compared to a basket of oral ARTs. The Pre-PBAC Response offered a reduced price for CAB LA + RPV LA (from a DPMQ of \$ [REDACTED] to \$ [REDACTED]).
- 3.2 The requested price for the oral tablet was the same as an equivalent pack size of dolutegravir, consistent with that proposed in the March 2021 submission.
- 3.3 The only change in the requested restriction compared to the previous submission was a change in the wording of 'must have' to 'recommended to have' previously received oral lead in with CAB and RPV tablets for the maintenance injections. The

sponsor had previously suggested that prior treatment with CAB and RPV tablets should not be a mandatory requirement of the CAB LA + RPV LA PBS listing (paragraph 2.2, cabotegravir-rilpivirine Public Summary Document (PSD), March 2021 PBAC meeting). The approved TGA PI states that a 28-day oral lead-in phase is recommended to assess the tolerability of cabotegravir and rilpivirine. As with the previous submission, the Secretariat suggested amendments to improve clarity and meet the electronic requirements for listing.

- 3.4 The requested listing was broadly aligned with the TGA indication, although the proposed PBS listing for CAB tablets did not include patients who have a planned missed dose of CAB LA + RPV LA.
- 3.5 The ESC noted the Cabenuva Implementation Report 2020 and additional information presented in section 5 of the submission, which explored options for service delivery and support for healthcare professionals and patients. The ESC and PBAC considered it was likely in practice that CAB LA + RPV LA would be administered at nominated two-monthly intervals after the loading doses (consistent with the TGA Product Information) and clinics would likely manage patients and schedule appointments in this manner.

For more detail on PBAC's view, see section 7 PBAC outcome.

4 Population and disease

- 4.1 HIV is an enveloped single-stranded RNA retrovirus that infects cells of the immune system by attaching to CD4 receptors on the surface of lymphocytes, destroying or impairing their function. As the infection progresses, the immune system becomes weaker and the infected person becomes more susceptible to infections. HIV infection can progress to acquired immunodeficiency syndrome (AIDS), which leads to complications, opportunistic infections and death.
- 4.2 Currently, all ART for the suppression of HIV are administered orally on a daily basis. The resubmission claimed a long-acting injectable (LAI) treatment may provide a viable treatment alternative to the current daily oral regimen for people living with HIV (PLHIV) experiencing physical, emotional or psychosocial challenges in relation to daily oral ART. The resubmission claimed that HIV patients suitable for LAI include those who:
 - Experience quality of life (QoL) impact and emotional challenges with oral ART due to fear of disclosure, adherence anxiety and psychological burden;
 - Need to improve suboptimal adherence;
 - Need confidentiality; or
 - Need non-oral alternatives such as those with malabsorption and gastrointestinal conditions, dysphagia and pill aversion, or with neurocognitive impairment and mental health disorders.

- 4.3 Consumer comments from the National Association for People Living with HIV (NAPWHA), the National Aboriginal Community Controlled Health Organisation (NACCHO) and Thorne Harbour Health (Vic) were considered by the PBAC for the previous submission. In March 2021, the PBAC noted that NAPWHA commented that anxiety, stigma and fear of unintentional disclosure of HIV status were a real concern for many PLHIV and has direct impact on mental health and QoL. Also, NACCHO noted the fear of unintentional disclosure was an additional mental health issue for Aboriginal and/or Torres Strait Islander peoples who may face additional discrimination and rejection by their community if their HIV status were disclosed in such a way; however, the PBAC considered it needed more detail from NACCHO regarding the suggestion that there is a component of the Aboriginal and/or Torres Strait Islander population that would choose LAIs and two monthly visits, including information on remote access. The PBAC also noted that Thorne Harbour Health (Vic) highlighted potential advantages of LAIs for older patients with neurocognitive impairments or drug problems (paragraph 6.2, cabotegravir-rilpivirine PSD, March 2021 PBAC meeting).
- 4.4 The PBAC had previously noted that Australian epidemiological data indicated diagnosis and treatment rates in Australia were high and did not indicate an unmet need in the overall HIV population, although the PBAC accepted that a LAI option such as CAB LA + RPV LA may offer advantages in communities where HIV transmission and treatment adherence are of concern. At the same time, it noted that no evidence was presented to show that the availability of the long-acting injections would alleviate adherence issues (paragraph 7.3, cabotegravir-rilpivirine PSD March 2021 PBAC meeting). The Pre-PBAC Response claimed that even though most PLHIV are suppressed on daily oral ART, this does not represent optimal care for all patients, given the issues that remain in some PLHIV around stigma, treatment fatigue, adherence anxiety, fear of unintentional disclosure of HIV status due to daily treatment and the effect on psychological wellbeing of the daily reminder of their HIV status.

For more detail on PBAC's view, see section 7 PBAC outcome.

5 Comparator

- 5.1 The resubmission nominated a weighted basket of ART as the main comparator, with weightings based on the proportion of market share (Table 3).

Table 3: Summary of weighted basket of FDC ARTs (Main Comparator in resubmission)

FDC or other combination components	Abbreviations	Tradename	DPMQ (June 2021)	Proportion of market share*
Bictegravir / emtricitabine / tenofovir alafenamide	BIC/FTC/TAF	Biktarvy®	\$1848.46	49%
Dolutegravir / abacavir / lamivudine	DTG/ABC/3TC	Triumeq®	\$1707.84	22%
Elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide	ELV/c/FTC/TAF	Genvoya®	\$1963.90	14%
Rilpivirine / emtricitabine / tenofovir alafenamide	RPV/FTC/TAF	Odefsey®	\$1963.90	10%
Dolutegravir / rilpivirine	DTG/RPV	Juluca®	\$1732.64	3%
Dolutegravir / lamivudine	DTG/3TC	Dovato®	\$1443.34	2%
Weighted	-	-	\$1832.50	100%

Source: Table 1.5, p40 of the resubmission and Attachment H to the resubmission

* PBS script data April 2020 to April 2021

- 5.2 In the previous submission, the dolutegravir (DTG)/RPV fixed dose combination (FDC) (Juluca®) was nominated as the main comparator. The PBAC had considered this was reasonable, however it also considered that relevant alternatives may include other single tablet fixed-dose combinations such as those containing TAF, DTG/ABC/3TC and DTG/3TC (paragraph 7.4, cabotegravir-rilpivirine PSD, March 2021 PBAC meeting). The PBAC did not specify that a basket of comparators would be appropriate.
- 5.3 The resubmission considered that an alternative approach to a basket of comparators would be to nominate the pharmacological analogue that is prescribed on the PBS for the largest number of patients in the target population (consistent with *PBAC Guidelines* section 1.1.3), which would be BIC/FTC/TAF (Biktarvy®).
- 5.4 The Pre-PBAC Response considered that DTG/RPV was an appropriate comparator and proposed a revised DPMQ for CAB LA + RPB LA (\$██████), which it claimed would be cost-effective compared with this regimen (DPMQ: \$1732.64).
- 5.5 If treatment with CAB LA + RPV LA is substantially more costly than an alternative therapy or alternative therapies, the PBAC can only recommend listing if it is satisfied that CAB LA + RPV LA provides, for some patients, a significant improvement in efficacy or reduction of toxicity over the alternative therapy or therapies (*National Health Act 1953*, Section 101(3B)) (paragraph 5.3, cabotegravir-rilpivirine PSD, March 2021 PBAC Meeting). For the requested population, the following PBS-listed medicines are less costly than CAB LA + RPV LA (requested effective DPMQ: \$██████; Pre-PBAC Response: DPMQ \$██████) and could be replaced in practice: DTG/3TC FDC (Dovato®) DPMQ: \$1,443.34; DTG/ABC/3TC (Triumeq®) DPMQ: \$1,707.84; and DTG/RPV (Juluca®) DPMQ: \$1,732.64.

For more detail on PBAC's view, see section 7 PBAC outcome.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item. The clinician stated there was a clinical need for alternatives to daily oral ART therapy as the requirement for medication to be kept and taken daily for a lifetime was a barrier to a large minority of people in

vulnerable populations, such as those in circumstances of poverty, unstable housing, incarceration, culturally and linguistically diverse backgrounds, rural/remote location, mental illness, drug/alcohol addiction or other medical comorbidities. (It was estimated that in one state-based program, incomplete viral suppression due to non-adherence was around 10% at any one time). The clinician highlighted the substantial resources involved in implementing existing targeted, case-based multidisciplinary clinical care programs involving medical, nursing and social work collaboration, in order to deliver “direct observed therapy” to vulnerable populations. It was stated that a LAI option would reduce the need for much of this activity, and improved viral suppression would have flow-on implications for resources used to manage additional HIV transmissions, viral resistance, and acute health care episodes. The clinician also held the strong view that the LAI option will likely lead to adherence benefits for some patients. Specifically, the clinician highlighted evidence from a planned phase IV study of CAB LA + RPV LA, where screening activities had already indicated that vulnerable patients with a history of poor adherence can be supported to maintain a short-term regimen of oral ART to achieve an undetectable viral load, knowing that this will make them eligible for CAB LA + RPV LA over the long term.

Consumer comments

6.2 The PBAC noted and welcomed the input from an individual (1) and health care professionals (17) via the Consumer Comments facility on the PBS website. The comments described a range of benefits of treatment with a LAI option for the management of HIV in terms of quality of life and improved adherence, especially for people in complex living circumstances where the risk of disclosure of HIV status and stigma negatively impact mental health and sometimes physical safety as well. For one clinician in far north Queensland treating many Aboriginal and/or Torres Strait Islander people, this was considered to represent up to 16% of patients. The comments also highlighted the aging cohort of PLHIV and the expected adherence challenges as some patients face HIV-related neurocognitive decline and age-related health issues. Some of the circumstances outlined in the comments also related to patient choice and convenience factors. The comments also highlighted there were subgroups of the HIV population with known adherence issues and stated that there may be adherence benefits for these groups as treatment is administered by a health care professional. Overall, clinicians highlighted the diversity of the Australian population living with HIV and considered that the availability of CAB LA + RPV LA on the PBS would allow clinicians to offer the most suitable therapy according to patients’ particular needs.

Clinical trials

6.3 No head-to-head trials comparing CAB LA + RPV LA every two months (Q2M) and oral ART were identified. Instead, an indirect treatment comparison (ITC) using the Bucher method was used to assess the comparative virological effectiveness and safety of CAB

LA + RPV LA every eight weeks (Q8W) (as a proxy for Q2M) against oral ART, using CAB LA + RPV LA every four weeks (Q4W) as the common comparator.

- 6.4 The resubmission was based on three randomised CAB LA + RPV LA trials:
- Study 201584 (hereafter referred to as "FLAIR", n=566): following oral induction with oral DTG/ABC/3TC FDC in ART naïve individuals, randomised patients either continue treatment with oral DTG/ABC/3TC FDC (n=283) or CAB LA + RPV LA Q4W injections (n=283);
 - Study 201585 (hereafter referred to as "ATLAS", n=616): patients were randomised to CAB LA + RPV LA Q4W (n=310) or treatment with an oral INSTI-, NNRTI-, or protease inhibitor (PI)-based antiretroviral regimen (n=308) in virologically suppressed individuals; and
 - Study 207966 (hereafter referred to as "ATLAS-2M", n=1,049): patients were randomised to be treated with the Q4W regimen for CAB LA + RPV LA (n=525) or with the Q8W regimen (n=524) in virologically suppressed individuals.
- 6.5 The results of FLAIR and ATLAS were pooled in the ITCs. These trials were considered by the PBAC in the previous submission. Two DTG/RPV trials (SWORD 1 & SWORD 2) included in the previous submission were excluded in the resubmission, given the change in nominated comparator.
- 6.6 Details of the trials presented in the resubmission are provided in Table 4.

Table 4: Trials and associated reports presented in the resubmission

Trial ID	Protocol title/ Publication title	Publication citation
CAB LA + RPV LA trials		
FLAIR	Orkin, C. et al. Long-acting Cabotegravir and Rilpivirine after oral induction for HIV-1 infection.	<i>New England Journal of Medicine</i> 2020; 382(12): 1124-1135.
	Orkin, C. et al. Long-acting Cabotegravir and Rilpivirine for HIV-1 treatment: FLAIR Week 96 results. Conference on Retroviruses and Opportunistic infections; March 8-11, Boston, MA	March 2020
	D'Amico et al. Safety and efficacy of Cabotegravir + Rilpivirine long-acting with and without oral lead-in: FLAIR Week 124 results.	<i>Journal of the International AIDS Society</i> 2020 23:SUPPL 7.
	ViiV Healthcare. A randomised, multicenter, open label study evaluating the efficacy, safety and tolerability of LA IM Cabotegravir and Rilpivirine for maintenance of virologic suppression in HIV naive adults: Week 96/100 results.	96 Week CSR 2020
	ViiV Healthcare. A phase II, randomised, multicenter, parallel-group, open-label study evaluating the efficacy, safety, and tolerability of long-acting intramuscular cabotegravir and rilpivirine for maintenance of virologic suppression following switch in HIV naive adults.	48 Week CSR 2019
ATLAS	Swindells, S. et al. Long-acting Cabotegravir and Rilpivirine for maintenance of HIV-1 suppression.	<i>New England Journal of Medicine</i> 2020; 382(12): 1112-1123.
	Swindells, S. et al. Cabotegravir + Rilpivirine long-acting as HIV-1 maintenance therapy: ATLAS Week 96 results.	<i>Journal of the International AIDS Society</i> 2020 23:SUPPL 7.
	ViiV Healthcare. A Phase III, randomised, multicenter, parallel-group, non-inferiority, open-label study evaluating the efficacy, safety, and tolerability of switching to long-acting rilpivirine from current ART in HIV-1 infected adults who are virologically suppressed.	CSR 2019
POOLED ATLAS + FLAIR	Rizzardini, G., Overton, E., Orkin, C., Swindells, S et al. Long-acting injectable Cabotegravir + Rilpivirine for HIV maintenance therapy: Week 48 Pooled analysis of phase 3 ATLAS and FLAIR trials.	<i>Journal of Acquired Immune Deficiency Syndromes</i> 2020; 85(4): 498-506.
	Chounta et al. Subgroup analysis of patient-reported outcomes among participants in two phase III clinical trials of long-acting cabotegravir and rilpivirine (ATLAS and FLAIR).	<i>Journal of the International AIDS Society</i> 2020 23:SUPPL 7.
	Murray et al. Patient-Reported Outcomes in ATLAS and FLAIR Participants on Long-Acting Regimens of Cabotegravir and Rilpivirine Over 48 Weeks.	<i>AIDS and Behaviour</i> 2020; 24(12): 3533-3544.
ATLAS-2M	Overton, E. et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study.	<i>Lancet</i> 2020; 396(10267):1994-2005
	Jaeger, H. et al. Week 96 Efficacy and Safety of Cabotegravir + Rilpivirine Every 2 months: ATLAS-2.	Conference on Retroviruses and Opportunistic Infections 2021
	ViiV Healthcare. Phase IIIb, randomized, multicenter, non-inferiority, open-label study evaluating the efficacy, safety and tolerability of LA Cabotegravir plus LA rilpivirine administered every 8 weeks or every 4 weeks in HIV-1 infected adults virologically suppressed.	CSR 2019

Source: Table 2-4, p49 of the resubmission.

Shaded cells indicate publications identified in previous submission

6.7 The key features of the direct randomised trials are summarised in Table 5. These remained unchanged from the previous submission. Overall, all trials had a low risk of

bias, as although they were open-label, the primary outcome of HIV RNA copies per mL was objective. The outcomes of virological failure (HIV-RNA ≥ 50 copies/mL) and virological success (HIV-RNA < 50 copies/mL) were used by the resubmission to determine the noninferiority of CAB LA + RPV LA Q8W, compared to oral ART.

Table 5: Key features of the included evidence

Trial, N	Trial Design	Interventions	Population	Main Outcomes
FLAIR N=566 ^a	Phase III, OL, RCT, noninferiority	<p><u>Induction Phase (20 weeks)</u> Oral DTG/ABC/3TC FDC (NRTI substitution allowed)</p> <p><u>Maintenance phase (100 weeks)</u> CAB LA + RPV LA group: <ul style="list-style-type: none"> • Oral CAB 30 mg + RPV 25 mg OD for 4 weeks, then • IM CAB LA 600 mg + RPV LA 900 mg (loading dose), then • IM CAB LA 400 mg + RPV LA 600 mg every 4 weeks </p> <p>Control group: Oral DTG/ABC/3TC FDC daily (or alternative DTG + 2NRTIs)</p>	<p>HIV-1 infected, ≥ 18 years of age, ART-naïve</p> <p>Subjects who had an HIV-1 RNA < 50 copies/mL at the Week –4 Visit (i.e. 16 weeks after induction phase starts) were eligible to enter the maintenance Phase.</p>	
ATLAS N=616	Phase III, OL, RCT, noninferiority	<p><u>Maintenance phase (52 weeks)</u> CAB LA + RPV LA group: <ul style="list-style-type: none"> • Oral CAB 30 mg + RPV 25 mg OD for 4 weeks, then • IM CAB LA 600 mg + RPV LA 900 mg (loading dose), then • IM CAB LA 400 mg + RPV LA 600 mg every 4 weeks </p> <p>Control group: Current anti-retroviral. 2 NRTIs + an INSTI or an NNRTI or PI</p>	HIV-1 infected, ≥ 18 years of age, ART-experienced, virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable ART regimen containing 2 NRTIs + an INSTI, NNRTI or PI	Proportion of participants with virological failure (HIV-RNA ≥ 50 copies/mL) as per FDA Snapshot algorithm at Week 48
ATLAS-2M N=1,045	Phase IIIb, OL, RCT, noninferiority	<p><u>Maintenance phase (52 weeks)</u> Patients receiving ART prior to trial: Q4W: Oral CAB 30 mg + RPV 25 mg OD for 4 weeks, then IM CAB LA 600 mg + RPV LA 900 mg (loading dose), then IM CAB LA 400 mg + RPV LA 600 mg every 4 weeks Q8W: Oral CAB 30 mg + RPV 25 mg OD for 4 weeks, then IM CAB LA 600 mg + RPV LA 900 mg (loading dose) at week 4 and 8, then IM CAB LA 400 mg + RPV LA 600 mg every 8 weeks</p> <p>Patients receiving CAB LA + RPV LA Q4W prior to trial: Q4W: IM CAB LA 400 mg + RPV LA 600 mg every 4 weeks Q8W: IM CAB LA 400 mg + RPV LA 600 mg every 8 weeks</p>	HIV-1 infected, ≥ 18 years of age, ART-experienced, virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable ART regimen	

Source: Table 2-5-2-7, pp52-53 of the resubmission.

ABC = abacavir; ART = antiretroviral therapy; CAB = cabotegravir; DTG = dolutegravir; FDA = US Food and Drug Administration; FDC = fixed dose combination; HIV-1 = human immunodeficiency virus-1; IM = intramuscular; INSTI = integrase strand transfer inhibitor; LA = long-acting; NRTI = nucleoside reverse transcriptase inhibitor; NNRTI = non-nucleoside reverse transcriptase inhibitor; OD = once daily; OL = open label; PI = protease inhibitor; RCT = randomised controlled trial; RNA = ribonucleic acid; RPV = rilpivirine; Q4W = every four weeks; Q8W = every eight weeks; 3TC = lamivudine

a. 631 patients were enrolled in the induction phase, but only 566 patients met the criteria (HIV RNA < 50 copies/mL) at 16 weeks after induction and randomised to a treatment in the maintenance phase.

6.8 Additionally, patient-reported outcomes were a key focus of the CAB LA + RPV LA trials. Patient satisfaction with treatment was reported using the HIV Treatment Satisfaction Questionnaire (HIVTSQ) in all trials. QoL data in FLAIR and ATLAS was reported using the 12-item short form health survey (SF-12) health survey, a shorter alternative to the 36-item short form health survey (SF-36). A *post hoc* analysis of QoL using the pooled SF-12 data from FLAIR and ATLAS converted to short-form six-dimension (SF-6D) was also presented in the resubmission. The *post hoc* analysis was used by the resubmission as new evidence to support its claim of QoL gain in patients receiving CAB LA + RPV LA, compared to patients receiving oral ART.

Comparative effectiveness

Virologic response outcomes

6.9 The results for the primary outcome of the CAB LA + RPV LA trials of virological failure (confirmed viral load ≥ 50 copies/mL or discontinued due to lack of efficacy or other reason while not below threshold) are presented in Table 6. Pooled FLAIR and ATLAS results informed the ITC.

Table 6: Results for the proportion of subjects with plasma HIV-1 RNA ≥ 50 copies/mL at Week 48

Trial ID	ART	CAB LA + RPV LA Q4W	CAB LA + RPV LA Q8W	RD % (95% CI)	Adjusted RD% ^a (95% CI)
ART vs CAB+RPV Q4W^b					
FLAIR	7/283 (2.5)	6/283 (2.1)	-	0.4 (-2.1, 2.8)	0.4 (-2.1, 2.8)
ATLAS	3/308 (1.0)	5/308 (1.6)	-	-0.6 (-2.4, 1.1)	-0.6 (-2.5, 1.2)
Pooled FLAIR & ATLAS	10/591 (1.7)	11/591 (1.9)	-	-0.2 (-1.7, 1.3)	-0.2 (-1.7, 1.4)
CAB+RPV Q4W vs CAB+RPV Q8W					
ATLAS-2M ITT-E	-	5/523 (1.0)	9/522 (1.7)	0.8 (-0.6, 2.2)	0.8 (-0.6, 2.2)
ATLAS-2M w/exposure	-	0/196 (0)	4/195 (2.1)	2.1 (0.1, 5.2)	NA
ATLAS-2M w/o exposure	-	5/327 (1.5)	5/327 (1.5)	0.0 (-2.2, 2.2) ^c	NA
Indirect analysis (CAB+RPV Q8W ITT-E vs ART)				0.9 (-1.1, 3)	1.0 (-1.1, 3.1)
<i>Indirect analysis (CAB + RPV Q8W w/exposure vs ART)</i>				2.3 (-0.7, 5.3)	NA
Indirect analysis (CAB+RPV Q8W w/o exposure vs ART)				0.2 (-2.5, 2.9) ^c	NA

Source: Table 2.5.2, p63 of the previous commentary & Table 2-22, 2-39 & 2-41, pp83, 112 & 113 of the resubmission.

Grey shaded cells indicate values previously considered by the PBAC

CAB = cabotegravir; CI = confidence interval; NA = not applicable; RD = risk difference; RPV = rilpivirine; Q4W = four weekly dosing of CAB + RPV; Q8W = eight weekly dosing of CAB + RPV; w/exposure = previous exposure to CAB + RPV; w/o exposure = without previous exposure to CAB + RPV

a. Adjusted: Based on Cochran-Mantel Haenszel stratified analysis adjusting to baseline viral load and Gender for FLAIR; adjusting to 3rd ART class and Gender for ATLAS; and adjusting to 10 strata for pooled analysis. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1-24 weeks, >24 weeks) for ATLAS-2M.

b. The risk difference reported differed from the previous submission where results were reported as CAB+RPV Q4W vs ART (rather than ART vs CAB+RPV; i.e. values were reversed).

c. Updated during the evaluation to RD of 0 (-2.2, 2.2) (from ATLAS-2M CSR, p 97). The resubmission presented a RD of 0 (-1.9, 1.9) and the resultant RD for the indirect comparison of 0.2% (-2.2%, 2.6%).

Text in italics indicate values calculated or extracted during evaluation

6.10 The results of the indirect comparison between CAB LA + RPV LA Q8W and oral ART in the Intent-to-Treat Exposed (ITT-E) population (RD = 0.9%, 95% CI: -1.1%, 3%) and when excluding patients with prior CAB LA + RPV LA exposure (RD = 0.2%, 95% CI: -2.5%, 2.9%) both met the noninferiority margin for virological failure of 4% in ATLAS-

2M. For completeness, an indirect comparison between CAB LA + RPV LA Q8W with oral ART in patients with prior exposure to CAB LA + RPV LA in ATLAS-2M was performed during the evaluation, which found that this did not meet the proposed noninferiority margin (RD = 2.3%, 95% CI: -0.7%, 5.3%) as the upper 95% CI exceeded the noninferiority margin of 4%.

- 6.11 For the outcome of virological success (Table 7), the results of the indirect comparison between CAB LA + RPV LA and oral ART in the ITT-E population (RD = -0.6%, 95% CI: -4.6%, 3.4%) met the specified non-inferiority margin of 10%. Results from the subgroup of patients with and without prior exposure to CAB LA + RPV LA also met the specified margin.

Table 7: Results for the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48

Trial ID	ART	CAB LA + RPV LA Q4W	CAB LA + RPV LA Q8W	RD (95% CI)	Adjusted RD ^a (95% CI)
ART vs CAB+RPV Q4W^b					
FLAIR	264/283 (93.3)	265/283 (93.6)	-	-0.4 (-4.4 to 3.7)	-0.4 (-4.4 to 3.7)
ATLAS	294/308 (95.5)	285/308 (92.5)	-	2.9 (-0.8 to 6.7)	3.0 (-0.7 to 6.7)
Pooled FLAIR & ATLAS	558/591 (94.4)	550/591 (93.1)	-	1.4 (-1.4 to 4.1)	1.4 (-1.4 to 4.1)
CAB+RPV Q4W vs CAB+RPV Q8W					
ATLAS-2M ITT-E	-	489/523 (93.5)	492/522 (94.3)	0.8 (-2.2 to 3.7)	0.8 (-2.1 to 3.7)
ATLAS-2M w/exposure	-	189/196 (96.4)	186/195 (95.4)	-1.0 (-5.5 to 3.3)	NA
ATLAS-2M w/o exposure	-	300/327 (91.7)	306/327 (93.6)	1.8 (-2.3 to 6.0) ^c	NA
Indirect analysis (CAB+RPV Q8W ITT-E vs ART)				-0.6% (-4.6%, 3.4%)	-0.6 (4.6, 3.4)
Indirect analysis (CAB+RPV Q8W w/exposure vs ART)				-2.4% (-7.5%, 2.8%)	NA
Indirect analysis (CAB+RPV Q8W w/o exposure vs ART)				0.4% (-4.6%, 5.4%) ^c	NA

Source: Table 2.5.4, p66 of the previous commentary & Table 2-23 & 2-42, p85 & 113 of the resubmission.

Grey shaded cells indicate values previously considered by the PBAC

CAB = cabotegravir; CI = confidence interval; NA = not applicable; RD = risk difference; RPV = rilpivirine; Q4W = four weekly dosing of CAB + RPV; Q8W = eight weekly dosing of CAB + RPV; w/exposure = previous exposure to CAB + RPV; w/o exposure = without previous exposure to CAB + RPV

a. Based on Cochran-Mantel Haenszel stratified analyses adjusting to baseline viral load and sex at birth for FLAIR; adjusting to 3rd ART class and sex at birth for ATLAS; and adjusting to 10 strata for pooled analysis. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following baseline stratification factor: prior exposure to CAB + RPV (0 weeks, 1-24 weeks, >24 weeks) for ATLAS-2M.

b. The risk difference reported differed from the previous submission where results were reported as CAB+RPV Q4W vs ART (rather than ART vs CAB+RPV; i.e. values were reversed).

c. Updated during the evaluation to RD of 1.8 (-2.3, 6.0) (from ATLAS-2M CSR, p 101). The resubmission presented a RD of 1.8 (-2.2, 5.8) and a resultant RD for the indirect comparison of 0.2% (-2.2%, 2.6%).

Text in italics indicate values calculated or extracted during evaluation

- 6.12 The resubmission also presented longer-term trial data not reported in the previous submission. However, these results did not compare effectiveness between CAB LA + RPV LA and ART.

- 6.13 Overall, similar trends were noted in the results between the resubmission and the previous submission, noting that the comparator and trials included in the ITC used differed from the previous submission. Noninferiority margins were met for virological failure in the ITT-E population and those without prior exposure to CAB LA + RPV LA, Comparatively, the ITT-E population as well as the subgroups of patients with and without prior exposure to CAB LA + RPV LA met the noninferiority margins for virological success.

Patient-reported outcomes

- 6.14 The HIVTSQ was identified by the resubmission as an important measure, designed to assess satisfaction with patients' current antiretroviral therapy. The results for the HIVSTQ were unchanged from the previous submission. As in the previous submission, a distribution-based approach was used to determine the minimal clinically important difference (MCID) for HIVTSQ based on the standard deviation (SD) and the within treatment group mean change in score such that the MCID threshold corresponded to half the SD of the within-group mean.
- 6.15 Using the resubmission's methodology, the MCID threshold for HIVSTQ would not have been met by the CAB LA + RPV LA Q4W arm of FLAIR at Week 44 or ATLAS-2M at Week 48, even though it was met in the same treatment arm in ATLAS at Week 44, suggesting that there may be uncertainty with the results.
- 6.16 The pooled FLAIR/ATLAS data at Week 44 reported a statistically significantly higher (RD = 3.4, 95% CI: 2.5, 4.3, $P < 0.001$) HIVTSQ improvement in patients treated with CAB LA + RPV LA Q4W (+3.9) compared to patients treated with ART (+0.5). While it was unclear if the MCID from within group should apply to this comparison, the lower 95% CI of 2.5 would not have met any of the proposed within group MCIDs. The magnitude of difference between treatment arms was numerically small.
- 6.17 The PBAC previously considered the nominated MCID for HIVTSQ to be an arbitrary measure and was likely inappropriate, and it was unclear if the trials were powered to detect meaningful difference in HIVTSQ given they were not primary outcomes (paragraph 6.29, cabotegravir-rilpivirine PSD, March 2021 PBAC meeting). Moreover, patients who chose to enrol in the open-label CAB LA + RPV LA trials were more likely to favour treatment with LA injections, which biased any patient-reported outcomes (paragraph 6.40, cabotegravir-rilpivirine PSD, March 2021 PBAC meeting).
- 6.18 The resubmission also presented the SF-12 results measured at baseline, Week 24 and Week 48 in the FLAIR and ATLAS trials. Results demonstrated no significant differences between treatment arms in the change from baseline in SF-12 mental component score (MCS) and physical component score (PCS) at any timepoint. In ATLAS, patients receiving LA therapy had a mean adjusted treatment difference from baseline of 0.64 (95% CI: -0.64, 1.91; $p = 0.327$) in the MCS domain and 0.70 (95% CI: -0.11, 1.51; $p = 0.092$) in the PCS domain at 48 weeks. In FLAIR, patients receiving LA therapy had a mean adjusted treatment difference from baseline of 1.10 (95% CI: -0.25, 2.45; $p = 0.109$) in the MCS domain and -0.17 (95% CI: -0.99, 0.66; $p = 0.689$) in the PCS domain at 48 weeks. The resubmission also included SF-12 data pooled from ATLAS and FLAIR *post hoc* which showed an improvement in the CAB LA + RPV LA arm compared to the oral ART arm, although no statistical analysis was carried out.
- 6.19 The results from the newly presented *post hoc* analysis of SF-6D health-state utility values derived from the SF-12 pooled data set from ATLAS and FLAIR, which were used to support the resubmission's claim of QoL gain, are summarised in Table 8. The SF-6D health-state utility values were mapped from the SF-12 pooled within-trial data set

using a proprietary algorithm based on methods derived from Brazier and Roberts 2004. This methodology was opaque and was unable to be independently verified.

Table 8: Pooled ATLAS and FLAIR SF-6D utility analysis results

Treatment	Baseline		Week 24		Week 48	
	CAB +RPV	Oral ART	CAB + RPV	Oral ART	CAB + RPV	Oral ART
N	591	591	591	591	591	591
n	500	548	535	546	500	548
Adjusted Mean (SF-6D score)	0.832	0.827	0.836	0.817	0.839	0.821
95% CI of adjusted mean	0.822, 0.842	0.817, 0.838	0.824, 0.847	0.805, 0.828	0.828, 0.851	0.810, 0.832
Adjusted difference in SF-6D score	0.00		0.02		0.02	
95% CI of treatment difference	-0.010, 0.020		0.002, 0.035		0.002, 0.035	
P value for model	0.533		0.024		0.030	

Source: Table 3.3, p133 of the resubmission

ART = antiretroviral therapy; CAB = cabotegravir; CI = confidence interval; LA = long-acting; RPV = rilpivirine

6.20 The SF-6D analysis from the pooled ATLAS and FLAIR study reported no difference at baseline ($p=0.533$) but an adjusted benefit of 0.02 (95% CI: 0.002, 0.035, $p=0.024$) at Week 24 and 0.02 (95% CI: 0.002, 0.035 $p=0.030$) at Week 48. The resubmission claimed that this met a minimal important difference (MID) “best estimate” of 0.01-0.048 reported by Walters and Brazier 2003. These differences based on the Week 48 results were used to inform the economic evaluation. This may not have been appropriate as:

- The resubmission used an incremental utility benefit of 0.02 derived by rounding up to two decimal places, which increased the assumed quality adjusted life year (QALY) gain by 10% (i.e. from $0.839-0.821 = 0.018$ at Week 48 to 0.02) and favoured CAB LA + RPV LA;
- It was unclear if the MID range reported in Walters and Brazier 2003 would be applicable to HIV, given the MID ranges were based on analyses of other conditions. The lower bound of 0.01 was based on a non-significant result for patients with Chronic Obstructive Pulmonary Disease (MID reported 0.01, 95% CI: -0.019, 0.043), and several other MID ranges from other disease areas also had confidence intervals which included zero. Walters and Brazier 2003 also reported a mean MID of 0.033 (95% CI: 0.029, 0.037) which was likely a more reasonable value for the MID (if one was to be accepted at all), in which case the benefit of 0.02 (rounded up from 0.018) presented by the resubmission would not meet the MID in Walters and Brazier 2003; and
- The magnitude of benefit from the analysis of SF-12 data, converted to SF-6D, was uncertain as it was a *post hoc* analysis of results which were originally not statistically significant (see paragraph 6.18) and reported a benefit with methodology which biased in favour of CAB LA + RPV LA in various manners, and was 10 times higher than the incremental QALY gain reported in the EVA-29155 report provided in the resubmission (see paragraph 6.36).

- 6.21 The Pre-Sub-Committee Response (PSCR) disagreed with the issues raised in the evaluation and argued:
- There have been no SF-6D MID publications specifically for HIV, however such an MID should be disease-agnostic as the SF-6D is a generic instrument.
 - The difference of 0.002 in the EVA-29155 report showed there is no difference in utility between a single daily tablet and injections every two months, for those patients who see no benefit in LAI. However, for the sub-population of patients who have a reason to prefer LAI over oral, which is the intended use of LAI, the utility benefit is 0.02. The ESC noted that the use of the 0.02 value may not be consistent with the population enrolled in FLAIR, ATLAS, or ATLAS-2M, which did not enrol patients specifically based on preference for LAI. It further noted the claimed 0.02 value was highly selective and based on a group of patients who have expressed a preference for an LAI. The ESC considered this methodology was unconventional for assessing such a utility gain and therefore considered the 0.002 in the general analysis may be a closer representation of the likely impact on utility.
- 6.22 The results of the *post hoc* SF-6D analysis and the EVA-29155 report are discussed further in paragraphs 6.48 to 6.52.
- 6.23 In its consideration of the previous submission, the PBAC considered that although for some patients the option of a LAI for control of HIV may be a preference, the results of the patient-reported outcomes in the clinical trials did not support a conclusion that treatment with CAB LA + RPV LA was associated with improvements in QoL (paragraph 7.7, cabotegravir-rilpivirine PSD, March 2021 PBAC Meeting).
- 6.24 The ESC considered the resubmission's claim that CAB LA + RPV LA offers advantages in terms of QoL over daily oral ART remained highly uncertain given the claimed utility benefit was very small, with unclear MID, and from a *post hoc* analysis.
- 6.25 The ESC also noted that no direct causal relationship was demonstrated given the complexities in separating patient preference and convenience factors from stigma, anxiety and fear of unintentional disclosure. The Pre-PBAC Response acknowledged the complexities in distinguishing between the various factors within the claimed utility benefit, however reiterated the view that the utility gain was robust and driven by genuine QoL benefits. The Pre-PBAC Response noted that the SF-12 is a validated HR-QoL measure that does not measure convenience, and it also considered that the SF-6D would be unlikely to detect convenience benefits. The PBAC agreed with the ESC and considered the claimed utility benefit likely included an element of patient convenience or preference and therefore considered the claimed utility gain to be uncertain in terms of health benefits and overall unreliable for decision making.
- 6.26 The ESC considered that treatment with CAB LA + RPV LA may offer additional (but difficult to quantify) benefits for some patients in terms of reduced dosing frequency and the potential for some patient groups to experience an adherence benefit due to the long acting nature of CAB LA + RPV LA and the need for healthcare professionals

to administer doses. The ESC noted the consumer comments submitted for the March 2021 consideration of CAB LA + RPV LA indicated some populations, such as Aboriginal and/or Torres Strait Islander peoples, or those with neurocognitive impairments may experience adherence benefits with the availability of a LAI option for the management of HIV infection. The ESC considered the proposed administration in clinics at set dates every two months may assist with this, if these patients can access clinics.

Comparative harms

6.27 Table 9 presents a summary of adverse events (AEs) across the randomised trials. The AEs reported in FLAIR, ATLAS and ATLAS-2M remained unchanged from the previous submission. The PBAC had previously considered that the evidence supported a conclusion that overall, CAB LA + RPV LA was likely to be noninferior in comparative safety to daily oral ART therapy (paragraph 7.8, cabotegravir-rilpivirine PSD, March 2021 PBAC meeting).

Table 9: Summary of key adverse events in the randomised trials at Week 48

Outcome, n (%)	FLAIR		ATLAS		ATLAS-2M	
	CAB+ RPV (283)	ART (283)	CAB+ RPV (308)	ART (308)	Q8W (522)	Q4W (523)
Any AE	267 (94)	225 (80)	294 (95)	220 (71)	473 (91)	482 (92)
Any AE, excluding ISRs	246 (87)	225 (80)	264 (86)	220 (71)	403 (77)	441 (84)
ISR, n (%)	239 (86)	NA	250 (83)	NA	392 (75)	390 (75)
Any Grade 3 to 5 AEs	31 (11)	11 (4)	35 (11)	24 (8)	41 (8)	49 (9)
Any Grade 3 to 5 AEs, excluding ISRs	22 (8)	11 (4)	25 (8)	24 (8)	29 (6)	30 (6)
Any drug-related AE	236 (83)	28 (10)	255 (83)	8 (3)	400 (77)	399 (76)
Any drug-related AE, excluding ISRs	79 (28)	28 (10)	88 (29)	8 (3)	109 (21)	125 (24)
AEs leading to withdrawal	9 (3)	4 (1)	10 (3)	1 (<1)	12 (2)	13 (2)
Any SAE	18 (6)	12 (4)	13 (4)	14 (5)	27 (5)	19 (4)
SAEs related to study treatment	1 (<1)	0	0	1 (<1)	3 (<1)	1 (<1)
Fatal SAEs	0	0	0	1 (<1)	1 (<1)	0
Drug related fatal SAEs	0	0	0	0	0	0

Source: Table 2-31 & 2-32, p101-102 of the resubmission; Table 30, p 114 FLAIR CSR; Table 23, p 100 of ATLAS CSR; and Table 33, p 123 of ATLAS-2M CSR

Grey shaded cells indicate values previously considered by the PBAC

ART = antiretroviral therapy; AE = adverse event; CAB = cabotegravir; ISR = injection site reaction; NA = not applicable; RPV = rilpivirine; SAE = serious adverse event; Q4W = four weekly dosing of CAB + RPV; Q8W = eight weekly dosing of CAB + RPV

6.28 There were more drug-related AEs, excluding injection site reactions (ISRs), in the LAI arms compared to the oral ART arms. An indirect comparison of any drug-related AE, excluding ISRs, between CAB LA + RPV LA Q8W and oral ART was conducted during the evaluation and indicated that a statistically significantly higher proportion of patients treated with CAB LA + RPV LA Q8W reported any drug-related AE, excluding ISRs, compared to patients treated with oral ART. The reason for this difference was not entirely transparent and could potentially be related to the open-label nature of the included trials. The evaluation noted that the incidence of drug-related AEs in the

oral ART arm in FLAIR was higher than ATLAS due to FLAIR recruiting treatment-naïve patients whereas ATLAS recruited treatment-experienced patients (who would have continued optimised oral ART). In the previous submission, a similar pattern was observed in the SWORD 1&2 trials where the intervention (DTG/RPV) had a higher rate of any drug-related AE (97/513, 19%) compared to other oral ARTs (9/511, 2%).

Benefits/harms

6.29 A comparison of benefits and harms for CAB LA + RPV LA Q8W and oral ART is presented in Table 10.

Table 10: Comparative harms for CAB LA + RPV LA Q8W and oral ART at Week 48

Benefits							
SF-6D Quality of life							
	CAB LA + RPV LA Q8W			Oral ART			Mean difference: (95% CI)
	N	Value at week 48	95% CI	N	Value at week 48	95% CI	
Pooled FLAIR + ATLAS	500	0.839	0.828, 0.851	548	0.821	0.810, 0.832	0.018 (0.002, 0.035)
Harms							
	CAB LA + RPV LA Q8W n/N	Oral ART n/N	RR (95% CI)	Event rate/100 patients		RD (95% CI)	
				CAB LA + RPV LA	Oral ART		
ISRs							
ITC	392/522	NA	NA	75	0	-0.75 (-0.71, -0.79)	
Any drug-related AE, excluding ISRs							
ITC	109/522	36/591	0.21 (0.05, 0.81) ^a	21	6	-0.19 (-0.33, -0.045) ^a	

Source: Compiled during evaluation

Text in italics indicate values calculated during evaluation

ART = antiretroviral therapy; CAB = cabotegravir; CI = confidence interval; ISR = injection site reactions; ITC = indirect treatment comparison; RD = risk difference; RPV = rilpivirine; RR = risk ratio; Q8W = eight weekly dosing

^a Result of indirect comparison, and as such did not line up directly with event rate/100 patients reported for CAB LA + RPV LA Q8W in ATLAS-2M and for oral ART in pooled FLAIR + ATLAS.

6.30 On the basis of the *post hoc* analysis of SF-12 data converted to SF-6D presented by the resubmission, the comparison of CAB LA + RPV LA and oral ART resulted in:

- Approximately 0.018 gain in utility (out of a scale of 0 to 1.00) per patient per year.

6.31 On the basis of indirect evidence presented by the resubmission, for every 100 patients treated with CAB LA + RPV LA in comparison to oral ART and over a 48-week duration:

- Approximately 75 additional patients would experience any ISRs; and
- Approximately 19 additional patients would have drug-related AE, excluding ISRs.

Clinical claim

6.32 The resubmission described CAB LA + RPV LA Q8W as noninferior in terms of effectiveness in comparison to oral ART for the treatment of HIV infection in treatment-experienced patients. The PBAC had previously considered that CAB LA + RPV LA either given once every four weeks or once every eight weeks, was of

noninferior comparative effectiveness to oral ART regimens in terms of virological response (paragraph 7.6, cabotegravir-rilpivirine PSD, March 2021 PBAC meeting). Given the similarity of the evidence base in the resubmission (continuing to rely on ITC involving FLAIR, ATLAS and ATLAS-2M), the evaluation considered that the same conclusion was likely reasonable.

- 6.33 The resubmission claimed that CAB LA + RPV LA Q8W has an acceptable safety profile for the treatment of HIV infection. This claim remained unchanged from the previous submission, and the PBAC had previously considered this claim was reasonable (paragraph 6.43, cabotegravir-rilpivirine PSD, March 2021 PBAC meeting).
- 6.34 The ESC reaffirmed its previous view (and that expressed by the PBAC at its March 2021 meeting) that CAB LA + RPV LA is likely of noninferior comparative effectiveness in terms of virological suppression to daily oral ART and noninferior safety.
- 6.35 The resubmission claimed that CAB LA + RPV LA provides additional benefits to patients who have an unmet need for an alternative to daily oral ART (QoL impacts such as anxiety and worry due to the requirement to adhere to daily treatment, stigma and associated reminder of disease, fear of unintentional disclosure, patient preference, convenience, less frequent dosing and medical conditions affecting oral dosing) as demonstrated by a QoL gain compared to the ART treatment arm (based on the SF-6D *post hoc* analysis).
- 6.36 The evaluation considered this claim was inadequately supported as:
- It was unclear if the MID range (0.01-0.048) reported in Walters and Brazier 2003 would be applicable to HIV, given the MIDs were based on analyses of other conditions.
 - The point estimate for the utility difference between LAI and oral ART calculated from the SF-6D analysis was ten times higher than the EVA-29155 report which reported results from a time trade off (TTO) study in 201 UK patients with HIV (0.02, $p=0.030$ in SF-6D analysis, 0.002, $p=0.7884$ in the EVA-29155 report).
- 6.37 The PBAC had previously considered that the claim that CAB LA + RPV LA provides additional benefits to patients who have an unmet need for an alternative to daily oral ART was not adequately supported as the results of the HIVTSQ were uncertain and the SF-12 results from ATLAS and FLAIR did not report any statistically significant differences between treatment arms in either the PCS or MCS domains, and that while some patients may prefer the option of a LAI, the results of patient-reported outcomes from the clinical trials did not support a conclusion that treatment with CAB LA + RPV LA was associated with improvements in quality of life (paragraph 7.7, cabotegravir-rilpivirine PSD, March 2021 PBAC meeting).
- 6.38 The ESC considered the resubmission's claim of additional benefits for patients who have an unmet need for an alternative to daily oral ART was highly uncertain and difficult to clearly distinguish from convenience-based preferences for reasons discussed in paragraphs 6.20 and 6.21 above.

- 6.39 The PBAC reiterated its view expressed at the March 2021 consideration that the claim of noninferior comparative effectiveness (in terms of virological suppression) and safety to daily oral ART was reasonable.
- 6.40 The PBAC considered the claim of additional benefits for patients with a need for an alternative to daily oral ART was plausible, but difficult to quantify reliably. The Committee considered the claimed utility gain of 0.02 was unreliable given the results of the *post hoc* SF-6D analysis were difficult to clearly distinguish from convenience-based preferences. However, the PBAC considered, based on the input from consumers and clinicians, that there was an unmet need for an alternative to daily oral ART for a small portion of the population, who may realise QoL and/or adherence benefits with the availability of a LAI option administered in a clinical setting.

Economic analysis

6.41 The type of economic evaluation presented in the resubmission was a stepped cost-utility analysis (CUA) that was conducted to determine the incremental cost per QALY gained for patients who were stabilised on ART and chose to switch their treatment to CAB LA + RPV LA versus continuing oral ART. The steps of the stepped economic evaluation are described in Table 14.

6.42 Table 11 provides a summary of the model structure and key inputs.

Table 11: Summary of model structure and rationale

Component	Summary
Time horizon	A 10-year time horizon was chosen. The stepped analysis assumed a time horizon of 2 years (within trial).
Outcomes	Quality adjusted life years gained for 10-year base case model and stepped analysis
Method used to generate results	Cohort expected value
Health states	Alive and dead. All alive patients receive ART: <ul style="list-style-type: none"> • CAB LA + RPV LA, or • Oral ART
Cycle length	Monthly
Transition probabilities	Switching from CAB LA + RPV LA to oral ART: Year 1: 93.10% Year 2 onwards: 95.05% from ATLAS-2M Mortality from ABS data.

Source: Table 3-1, p123, Table 3.7, p144 and Table ES.8, page ES.11 of the resubmission.

Abbreviations: ABS = Australian Bureau of Statistics; ART= antiretroviral therapy; CAB= cabotegravir; LA = long-acting; RPV = rilpivirine

6.43 The economic evaluation presented in the resubmission differed to the previous submission where a cost benefit analysis (CBA) was presented as the primary analysis. The PBAC previously considered that a CBA, rather than a formal CUA, was uninformative for decision making as it did not capture or allow exploration of the factors for which advantages over daily oral ART were claimed, and that based on its assessment that CAB LA + RPV LA is of noninferior effectiveness and safety compared with daily oral ART, the most appropriate basis for a listing would be if it were cost

minimised to the least costly alternative (paragraphs 7.1 and 7.10, cabotegravir-rilpivirine PSD, March 2021 PBAC Meeting). A cost minimisation analysis (CMA) was not presented as part of the resubmission.

- 6.44 A decision tree structure was used in the economic analysis. The model started with a cohort of 1,000 patients who were all stabilised on their current ART and chose to switch HIV therapy to either CAB LA + RPV LA or continue oral ART. Over time patients may continue CAB LA + RPV LA or oral ART, or switch to another oral ART. The only health states used were alive and dead.
- 6.45 For patients switching to CAB LA + RPV LA, the analysis incorporated the cost of the oral lead-in CAB and RPV tablets, a loading dose of CAB LA +RPV LA and increased administration costs compared with oral ART.
- 6.46 Patients discontinued treatment in the CAB LA + RPV LA arm based on trial withdrawal rates in ATLAS-2M. These patients were assumed to switch treatment to another oral ART as all patients were assumed to remain on some form of ART treatment. Patients who remain on treatment with CAB LA + RPV LA were assumed to derive a utility benefit of 0.02 per annual cycle (see paragraph 6.19 and 6.20). No patients in the oral ART arm discontinued their assigned treatment. As such, patients in the oral ART arm were either alive and on treatment, or dead. No utility adjustments were made for patients who discontinued treatment with CAB LA + RPV LA and switched to oral ART.
- 6.47 The key drivers of the model are presented in Table 12.

Table 12: Key drivers of the model

Description	Method/Value	Impact
Comparator	The weighted basket of ARTs was used as the comparator in the model. This was inconsistent with the PBAC considerations in the previous submission (paragraph 5.2).	High, favoured CAB LA + RPV LA. Using only less expensive ARTs as comparator changed ICER from dominant to \$ ¹ - ² /QALY
Utilities	The economic model assumed an incremental utility gain of 0.02 for patients treated with CAB LA + RPV LA compared to patients treated with oral ART (based on an SF-6D analysis). There were a range of issues that made the application of this utility gain uncertain (see paragraphs 6.20 and 6.21).	High, favoured CAB LA + RPV LA.
Dosing frequency	The clinical trial evidence was for CAB LA + RPV LA administered once every eight weeks whereas the stepped economic evaluation assumed CAB LA + RPV LA was administered once every two months.	High, favoured CAB LA + RPV LA. Moving from eight weekly dosing to two monthly dosing resulted in a 79% decrease in the ICER.
Time horizon	The stepped economic evaluation used a time horizon of 2 years and then extrapolated to a 10-year time horizon.	Moderate, favoured CAB LA + RPV LA. Shortening time horizon to two years changed the base case ICER from dominant to \$ ³ /QALY

ART = antiretrovirals; CAB = cabotegravir; ICER = incremental cost effectiveness ratio; RPV = rilpivirine; QALY = quality-adjusted life year; SF-12 = 12-Item Short-Form Survey; SF-6D = Short-Form Six-Dimension

Source: Compiled during the evaluation from Section 3 of the resubmission and calculations undertaken during the evaluation.

The redacted values correspond to the following ranges:

¹ \$35,000 to < \$45,000

² \$95,000 to < \$115,000

³ \$5,000 to < \$15,000

- 6.48 As discussed in paragraph 6.20, the resubmission claimed that a *post hoc* analysis of pooled SF-6D utility data derived from the SF-12 instrument used in the ATLAS and FLAIR trials demonstrated that there was a mean utility difference of 0.02 between daily oral therapy and CAB LA + RPV LA. The resubmission claimed that the incremental benefit of 0.02 derived from the SF-6D analysis met the MID proposed by Walters and Brazier 2003 (range 0.01-0.048). The ESC noted there is evidence of an association between stigma and QoL in people living with HIV¹. However, the FLAIR and ATLAS trials did not measure stigma and whether this was reduced with the LAIs. The ESC considered if evidence of a meaningful effect on stigma were available to support the QoL benefit claimed, it expected the magnitude of the observed QoL improvement could have been greater. However, overall, the ESC reiterated its view the claimed utility benefit was uncertain in terms of health benefits and other factors (such as convenience), as discussed in paragraphs 6.20 and 6.21 above. The Pre-PBAC Response considered that the 0.02 utility gain was conservative, and likely to be an underestimate of the true benefit.
- 6.49 As discussed in paragraph 6.20, there were several issues with relying on the SF-6D analysis presented in the resubmission to inform any QoL benefits with CAB LA + RPV LA compared to oral ART.
- 6.50 Additional information regarding patient preferences and utility was provided in the EVA-29155 report. The EVA-29155 report was a vignette-based TTO study of 201 UK people living with HIV performed to examine potential utility differences between treatment modalities. The EVA-29155 report found that the proportion of patients who experienced privacy, emotional wellbeing and adherence anxiety associated with HIV and HIV medications were not statistically significantly different between patients who prefer daily oral tablets (n=76) and patients who prefer two monthly injections (n=125) (Table 13). Instead, the only categories which were statistically significantly different between patients who prefer tablets compared to patients who preferred LAI were convenience of scheduling (those who had problems adhering to daily schedule statistically significantly more likely to prefer two monthly injection) and whether patients had problems with taking HIV medications as prescribed (those who had no problems more likely to prefer tablets). This suggested that the potential QoL benefit associated with LAI may be due to the convenience of dosing schedule rather than any stigma or emotional issue or even adherence benefits. Furthermore, the EVA-29155 report did not support a claim of difference in utility for LAI and oral ART as the mean utility difference between injections every two months and single tablet daily was not statistically significantly different (difference = 0.002, p-value = 0.7884).

¹ Mengting Zhu, Yan Guo, Yiran Li, Chengbo Zeng, Jiaying Qiao, Zhimeng Xu, Yu Zeng, Weiping Cai, Linghua Li & Cong Liu (2020) HIV-related stigma and quality of life in people living with HIV and depressive symptoms: indirect effects of positive coping and perceived stress, *AIDS Care*, 32:8, 1030-1035, DOI: [10.1080/09540121.2020.1752890](https://doi.org/10.1080/09540121.2020.1752890)

Table 13: Summary of responses to demographic questions in EVA-29155 report

Characteristic	Participants who preferred one tablet over injections every two months (N=76)	Participants who preferred injections every two months over one tablet (N=125)	Relative Risk (CI)
Difficulty adhering to a daily schedule for any reason (e.g., bad memory, job, lifestyle, travel)	14 (18.4%)	42 (33.6%)	1.82 (1.07, 3.11)
Difficulty swallowing pills for any reason (e.g., physical, phobia/aversion, medical condition)	2 (2.6%)	9 (7.2%)	2.74 (0.61, 12.33)
Privacy issue: Not always comfortable taking HIV medication to avoid revealing your HIV status	6 (7.9%)	19 (15.2%)	1.93 (0.80, 4.61)
Emotional well-being: Having to take HIV medication every day reminds me that I have HIV and/or of a mistake or bad memory from my past	8 (10.5%)	20 (16.0%)	1.52 (0.70, 3.28)
Adherence anxiety: I worry about missing doses and not being suppressed anymore or transmitting the disease	8 (10.5%)	22 (17.6%)	1.67 (0.78, 3.57)
I must take food at the same time as my HIV treatment	10 (13.2%)	25 (20.0%)	1.52 (0.77, 2.99)
I have no problem taking my HIV medication as prescribed	44 (57.9%)	45 (36.0%)	0.62 (0.46, 0.84)

Source: Table 3-4, p137 of resubmission

- 6.51 The PSCR disagreed with the interpretation of the outcomes of the EVA-29155 report in the commentary and argued there was no evidence to suggest the claim the utility benefit was due to convenience and that there were many reasons why people living with HIV may experience difficulty adhering to a daily regimen or taking their medicine as prescribed. As noted above in paragraph 6.21, the PSCR also argued that the utility gain of 0.02 represents the QoL benefit for the subgroup of patients that have already stated they prefer LAI over oral therapy. As already noted, the ESC considered this approach to application of utilities being based on a subgroup of patients who have already indicated a preference for the LAI was unconventional and considered the utility gain in the general analysis may be a closer representation of the likely utility impact.
- 6.52 The ESC considered it was not appropriate to apply a utility gain (and price advantage) based on preferences alone, as it would be equally true for patients who prefer oral therapy over LAIs. The ESC considered it was reasonable to conclude there was a plurality of reasons why people living with HIV would report difficulties taking their HIV medicines as prescribed or adhering to a daily schedule, including convenience factors for some people. Overall, the ESC considered it would likely not be possible to clearly identify and attribute utility gains to health benefits or other factors for the purposes of informing the cost-utility model.
- 6.53 Given the proposed price of CAB LA + RPV LA plus the assumed administration cost was lower than the weighted basket of ARTs every two months, along with the assumed utility benefit with CAB LA + RPV LA, the resubmission's base case ICER reported that CAB LA + RPV LA was dominant (less expensive and more effective) than the basket ART comparator.

6.54 The results of the stepped economic evaluation are presented in Table 14. The results indicated that the model was sensitive to changing the dosing frequency to two-monthly and the duration of the analysis. It remained uncertain whether all patients would be treated using the two-monthly dosing or if a proportion of patients would have administrations every eight weeks, and as such the ICER may be less optimistic than presented.

Table 14: Stepped derivation of the base-case economic evaluation

Analysis	CAB LA + RPV LA cost (\$)	Comparator cost (\$)	Incremental cost (\$)	Incremental QALY	ICER
Trial based <ul style="list-style-type: none"> Q8W dosing 2-year time horizon 	████████	████████	████████	35.09	████████ ¹
Dose frequency Q2M <ul style="list-style-type: none"> Q2M dosing 2-year time horizon 	████████	████████	████████	35.09	████████ ²
Incorporate mortality <ul style="list-style-type: none"> Q2M dosing 2-year time horizon All-cause mortality 	████████	████████	████████	35.04	████████ ²
Base case: 10-year time horizon <ul style="list-style-type: none"> Q2M dosing 10-year time horizon All-cause mortality 	████████	████████	-████████	125.48	Dominant (████████ ³)

Source: Table 3.9, p146 of the resubmission

ART=basket of antiretrovirals, CAB = cabotegravir, ICER = incremental cost effectiveness ratio, LA = long-acting, RPV = rilpivirine, QALY = quality-adjusted life year, Q8W = 8-weekly, Q2M = 2-monthly

The redacted values correspond to the following ranges:

¹ \$55,000 to < \$75,000

² \$5,000 to < \$15,000

³ Dominant

6.55 The results of the univariate sensitivity analyses conducted by the resubmission and during the evaluation of the economic model are shown in Table 15. Based on these results, the key drivers of the economic model were the assumption of the weighted basket of ARTs as the comparator (rather than the least expensive alternative therapy) and the assumed utility increment, which was highly uncertain and was likely biased, favouring CAB LA + RPV LA.

Table 15: Results of sensitivity analyses of economic model

Analyses	Incremental cost	Incremental QALY	Cost/QALY
Base case	- [REDACTED]	125.48	[REDACTED] ¹
Comparator (base case basket of ART)			
• All less expensive ARTs (<i>DTG/ABC/3TC, DTG/RPV and DTG/3TC</i>)	[REDACTED]	125.48	[REDACTED] ²
• Dual active ART only	[REDACTED]	125.48	[REDACTED] ³
• Least expensive ART only (<i>DTG/3TC</i>)	[REDACTED]	125.48	[REDACTED] ⁴
Utility increment (base case 0.02)			
• 0.002	- [REDACTED]	12.55	[REDACTED] ¹
• 0.035	- [REDACTED]	219.60	[REDACTED] ¹
Injectable administration cost (base case \$12.40)			
• \$17.75, MBS item 3	- [REDACTED]	125.48	[REDACTED] ¹
• \$38.75, MBS item 23	- [REDACTED]	125.48	[REDACTED] ¹
Injection site reaction disutility (base case 0)			
• 0.01 x 1.7%	[REDACTED]	124.41	[REDACTED] ¹

Source: Constructed during evaluation with input from Table 3.13, p149 of the resubmission
 3TC = lamivudine, ART=basket of antiretrovirals, CAB = cabotegravir, DTG = dolutegravir, ICER = incremental cost effectiveness ratio, RPV = rilpivirine, QALY = quality-adjusted life year

Text in italics indicate values calculated during evaluation

The redacted values correspond to the following ranges:

¹ Dominant

² \$35,000 to < \$45,000

³ \$55,000 to < \$75,000

⁴ \$95,000 to < \$115,000

6.56 The ESC considered the CUA was highly uncertain and may not be reliable, given the modelled QoL benefit some patients may experience with the option of a long-acting injectable over daily oral ART was uncertain and very small.

6.57 The Pre-PBAC Response offered a revised lower price for CAB RA + RPV LA with a DPMQ of \$ [REDACTED] (approximately \$ [REDACTED] higher than the cost of an equivalent duration of treatment with DTG/RPV) and reiterated that the claimed utility gain of 0.02 was driven by genuine health benefits, and therefore the revised lower price further improved the cost-effectiveness of CAB LA + RPV LA.

Drug cost/patient/year

6.58 The estimated medicine costs per patient are provided in Table 16, based on the submission’s proposed price, not the revised offer in the Pre-PBAC Response. The costs for CAB LA + RPV LA are shown separately for the first and subsequent years of treatment as these differ due to the CAB + RPV oral lead in and loading dose required in year 1.

Table 16: Annual costs of medicine per patient

Treatment	Cost / year (\$)
CAB LA + RPV LA (Year 1) ^a	██████████
CAB LA + RPV LA (Year 2 onwards) ^b	██████████
ART ^c	██████████

Source: Table 3-8, p146 of the resubmission

^a one month of oral lead in with CAB and RPV tablets, plus six injections

^b six injections each year

^c based on 365 days of weighted oral ART

CAB = cabotegravir, RPV = rilpivirine, LA = long-acting, ART = basket of oral antiretrovirals

Estimated PBS usage & financial implications

- 6.59 This resubmission was not considered by DUSC. As per the previous submission, an epidemiological approach was used to estimate the financial impact associated with listing CAB LA + RPV LA on the PBS for the treatment-experienced HIV population that is virologically suppressed and switching therapy ('treatment switch population'). The methodology used to estimate the utilisation and financial impact of listing CAB LA + RPV LA remained the same as the previous submission, but data used to inform model inputs were updated to the latest available data.
- 6.60 The estimated use and financial implication of CAB LA + RPV LA at the submission's requested effective price are presented in Table 17. The Pre-PBAC Response offered a reduced price for CAB LA + RPV LA (DPMQ \$██████████) but did not provide updated utilisation and financial estimates at this price, although it claimed that the listing at this price would result in an approximate net save to Government over 6 years (due to replacing higher cost ARTs, which have a larger market share).

Table 17: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use and estimated financial implications of CAB LA + RPV LA (PBS and RPBS)						
Prevalent HIV patients	1	1	1	1	1	1
Virologically suppressed (97%)	1	1	1	1	1	1
Patients who will switch (26%)	2	2	2	2	2	2
Eligible switch patients (27%-100%)	2	3	3	3	3	3
Initiating patients (%)	3	3	3	3	3	3
Continuing patients (93%)	4	3	3	3	3	3
Script numbers						
CAB tablets	3	3	3	3	3	3
CAB+RPV injections	5	5	1	1	6	6
Total	5	1	1	1	6	6
PBS/RPBS cost less co-pay						
CAB tablets	7	7	7	7	7	7
CAB+RPV injections (eff)	8	9	10	10	11	11
Total (eff)	12	9	10	11	11	11
Estimated changes in use and financial impact of other medicines (PBS and RPBS)						
Changes in script numbers						
Prescriptions not used by patients initiating and continuing treatment with CAB+RPV^a						
DTG/RPV	4	3	3	3	3	3
DTG/ABC/3TC	3	3	2	2	2	2
BIC/FTC/TAF	2	2	5	5	5	5
ELV/c/FTC/TAF	3	3	3	3	3	3
RPV/FTC/TAF	3	3	3	3	3	3
DTG/3TC	4	4	3	3	3	3
Additional rilpivirine tablet use from patients initiating CAB+RPV						
RPV	3	3	3	3	3	3
Total	2	5	1	1	1	6
Cost offsets from prescriptions not used by patients initiating and continuing treatment with CAB+RPV						
DTG/RPV	7	7	7	7	7	7
DTG/ABC/3TC	7	7	7	8	8	8
BIC/FTC/TAF	8	8	12	12	12	12
ELV/c/FTC/TAF	7	7	7	7	7	7
RPV/FTC/TAF	7	7	7	7	7	7
DTG/3TC	7	7	7	7	7	7
Additional cost from rilpivirine tablet use from patients initiating CAB+RPV						
RPV	7	7	7	7	7	7
Total cost of other PBS medicines	8	9	10	11	11	11
Net financial implications						
Net cost to PBS/RPBS (eff)	7	7	7	7	7	7
Net MBS costs ^b	7	7	7	7	7	7
Net cost to Government health budget	7	7	7	7	7	7

Source: Table 4-2, 4-3, 4-5- 4-7, 4-9 -4-14, pp157, 158, 160-166 of the resubmission.

3TC = lamivudine; BIC = bictegravir; CAB = cabotegravir; DTG = dolutegravir; ELV/c = elvitegravir/cobicistat; FTC = emtricitabine; RPV = rilpivirine; TAF = tenofovir alafenamide; pub = published; eff = effective.

a. Error identified where the population split was incorrect. The population split did not account for DTG/3TC in the denominator, thereby overestimating the number of scripts affected and costs offset. This was corrected during the evaluation.

b. There were errors in the cell referencing for the calculation of MBS decreased cost. Instead of calculating number of urinalysis based on BIC/FTC/TAF, ELV/c/FTC/TAF and RPV/FTC/TAF (continuing and initiation), the submission calculated these based on DTG/RPV,

DTG/ABC/3TC, BIC/FTC/TAF, ELV/c/FTC/TAF and RPV/FTC/TAF initiating and DTG/RPV continuing. This was corrected during evaluation. The same error was made in the previous submission.

The redacted values correspond to the following ranges:

¹ 20,000 to < 30,000

² 5,000 to < 10,000

³ 500 to < 5,000

⁴ < 500

⁵ 10,000 to < 20,000

⁶ 30,000 to < 40,000

⁷ \$0 to < \$10 million

⁸ \$10 million to < \$20 million

⁹ \$30 million to < \$40 million

¹⁰ \$40 million to < \$50 million

¹¹ \$50 million to < \$60 million

¹² \$20 million to < \$30 million

- 6.61 The total cost to the PBS/RPBS of listing CAB LA + RPV LA after correcting for errors (see footnotes for Table 17), and based on the proposed effective price in the resubmission, was \$0 to < \$10 million in Year 1, decreasing to a net cost saving in Year 6, a total of \$0 to < \$10 million over 6 years.
- 6.62 Cost savings were mainly driven by the lower (effective) price of CAB LA + RPV LA in continuing patients compared to the replaced oral ARTs. Despite a cost saving observed during Years 5-6, there was an overall net cost of \$0 to < \$10 million to the Government health budget (with MBS costs taken in account) over the first six years of listing. The estimated net cost to the Government budget of listing CAB LA + RPV LA was more costly in the resubmission than the previous submission, which had estimated \$0 to < \$10 million in Year 1, decreasing to a net cost saving in Year 6 (overall net cost of \$0 to < \$10 million). There were several differences between (re)submissions, with the inclusion of the less costly DTG/3TC FDC in the resubmission leading to lower cost offsets. At the same time, an overall larger market share (+1.26%) of the more costly comparators (BIC/FTC/TAF, ELV/c/FTC/TAF and RPV/FTC/TAF) was a competing factor that increased a proportion of the cost offset estimates. There were also differences in the estimated number of patients treated with CAB LA + RPV LA, with a slight increase in the number of patients estimated to initiate treatment in year 1 to year 3 in the resubmission compared to the previous submission but fewer initiations in year 4 to year 6, though the number who continue treatment with CAB LA + RPV LA over the first six years of listing was consistently higher in the resubmission.
- 6.63 Overall, the resubmission's estimated usage of CAB LA + RPV LA was uncertain. The following points were noted by the evaluation and the ESC regarding the resubmission's financial estimates:
- There was potential that the utilisation may be overestimated as the PBAC had previously considered that the results of the previous willingness to pay study did not indicate a strong preference for LAI therefore the uptake of CAB LA + RPV LA

was likely lower than expected (paragraph 7.11, cabotegravir-rilpivirine PSD, March 2021 PBAC meeting); however

- The ESC noted that MBS items for general practice should not be included in the estimated financial implications as these costs/savings to Government will not be realised in clinical practice;
- It may not be appropriate to assume that patients would only consider treatment with CAB LA + RPV LA once a lifetime, which the resubmission assumed by assigning a diminishing proportion of patients who have not been offered CAB LA + RPV LA previously to the eligible patient pool. This may have led to an underestimate of the number of eligible switch patients in years 2 to 6.

6.64 The resubmission identified the variables used to estimate the uptake of CAB LA + RPV LA and the baseline 'switch population' as the main sources of uncertainty. This remained unchanged from the previous submission. In addition, the resubmission conducted a sensitivity analysis to estimate the use of oral CAB tablets for planned missed doses CAB LA + RPV LA, although this was not part of the requested restriction for oral tablets.

6.65 The PSCR reiterated that the uptake of CAB LA + RPV LA in Australia would be approximately █%. The ESC considered the uptake of CAB LA + RPV LA in practice was uncertain, however considered the methods used to derive the utilisation and financial estimates and structure of the estimates were generally reliable for decision making.

Quality Use of Medicines

6.66 The sponsor advised it was investigating a range of initiatives to improve service delivery and, as a result, optimise delivery of CAB LA + RPV LA, focused on the following (these remained unchanged from the previous submission):

- Supply chain and delivery: Partnering with a third-party provider that in-licenses and distributes prescription medicines for direct to clinic cold-chain delivery and removing patient responsibility for maintaining cold-chain.
- Healthcare professionals support: The sponsor has employed a National Implementation Specialist to support the introduction of Cabenuva into Australia. This will include training all appropriate staff on gluteus medius injections, planning and organising support infrastructure such as direct-to-clinic cold-chain logistics, liaising with other healthcare professionals closer to patients' homes to support direct-to-clinic delivery, if required, and delivering optimal patient support programs and appointment reminder systems.
- Patient support: Welcome handbook for patients who have been prescribed Cabenuva and website support for adherence.
- Partnering with healthcare professionals: Ongoing work is being conducted by the sponsor involving detailed clinic service delivery interviews with established HIV

service providers to determine optimum implementation of Cabenuva across different settings and to work with healthcare professionals to develop the most appropriate service model. Interim results have identified that clinics have differing requirements and the implementation plan must be adapted to cater for these requirements.

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of cabotegravir oral tablets and cabotegravir and rilpivirine long-acting injectable (CAB LA + RPV LA), on the basis that it should be available only under special arrangements under Section 100 (Highly Specialised Drugs Program – Community Access). The PBAC's recommendation for listing was based on, among other matters, its assessment, that the cost-effectiveness would be acceptable if the listings were cost-minimised against the least costly alternative. However, as discussed below, the PBAC recognised there were additional benefits that justified a premium for CAB LA + RPV LA.
- 7.2 The PBAC reiterated that it was satisfied CAB LA + RPV LA is of noninferior comparative effectiveness (in terms of virologic suppression outcomes) and safety to daily oral anti-retroviral therapy (ART) alternatives on the PBS. The PBAC was also satisfied the resubmission adequately supported that it provides additional benefits in terms of quality of life (QoL) and/or adherence advantages for a small number of people living with HIV (PLHIV) in a range of complex individual circumstances, however these health benefits were difficult to reliably quantify. The PBAC appreciated the additional analyses of the trial data in this resubmission exploring utility gains for switching from daily oral therapy to long-acting injections. However, it did not accept the specific utility gain of 0.02 claimed in the cost-utility analysis presented in the submission because it was not possible to differentiate health benefits from other factors, such as convenience (discussed further in paragraph 7.9 below). The PBAC considered the sponsor hearing and consumer comments particularly valuable in highlighting the potential additional health benefits with CAB LA + RPV LA for some PLHIV and how short-term adherence to oral ART would be manageable in the context of becoming eligible for long-acting injections.
- 7.3 The PBAC recalled it considered the comparator nominated in the March 2021 submission, DTG/RPV fixed dose combination (FDC) (Juluca®), reasonable, however noted the resubmission revised the comparator to be a weighted basket of therapies. The PBAC did not consider the nominated weighted basket of comparators appropriate given that there are not identifiable patient populations in which each of the treatments are used. The PBAC considered that, given the established therapeutic relativities across the listed daily oral ART products, that the ART FDCs outlined in Table 3 were all relevant alternative therapies.
- 7.4 The PBAC noted the advice provided in the sponsor hearing, which clarified there were PLHIV in a range of circumstances that impacts their ability to adhere to a daily oral

regimen. The PBAC also noted the clinician advised there was a planned phase IV clinical study of CAB LA + RPV LA and its findings in the screening phase were that patients in such circumstances can receive additional support to remain adherent during the initial daily oral virologic suppression period prior to switching to CAB LA + RPV LA. The PBAC considered the input from the clinician was informative and thanked them for their input.

- 7.5 The PBAC noted the comments from consumers and clinicians strongly supported the listing of a long-acting injectable option for the management of HIV infection and outlined the potential benefits for a small number of PLHIV in terms of improved QoL and/or adherence benefits for some patients in certain populations, such as Aboriginal and/or Torres Strait Islander people, those living in rural or remote settings and individuals with complex living or social circumstances. The Committee noted the comments highlighted the range of complex circumstances many PLHIV face and indicated between 10-20% of the population had issues adhering to a daily oral regimen or would have improved QoL from a long-acting injectable option administered in a clinical setting. The PBAC also noted the input from clinicians that specifically highlighted the issues faced by Aboriginal and/or Torres Strait Islander PLHIV in terms of shame, fear of disclosure and increased mobility for cultural reasons and the additional challenges to both QoL and adherence these can create. The PBAC considered the consumer and clinician input was valuable and thanked the respondents for their contributions.
- 7.6 In noting the comments from consumers and clinicians, the PBAC acknowledged there was a clinical need for alternatives to daily oral ART therapy for a small number of PLHIV under a range of circumstances and agreed there was a clinical place for the listing of a long-acting injectable to address adherence issues and improve QoL from treatment with daily oral ART.
- 7.7 The PBAC noted no new clinical trials were presented, however the submission presented a *post hoc* analysis of QoL using the pooled SF-12 data from FLAIR and ATLAS converted to short-form six-dimension (SF-6D).
- 7.8 The PBAC re-affirmed its view expressed in March 2021 that CAB LA + RPV LA is likely to be of noninferior comparative effectiveness, in terms of virologic suppression of HIV, and overall noninferior comparative safety to daily oral ART.
- 7.9 The PBAC noted the additional *post hoc* analyses of the SF-12 data to derive SF-6D values and agreed with the numerous issues raised by the ESC highlighting the weaknesses of the utility estimate. The PBAC agreed with the ESC that the claimed 0.02 utility gain was highly selective and based on a group of patients who have expressed a preference for a long-acting injectable option, which was an unconventional method for assessing a utility gain. Furthermore, the small utility gain was considered of uncertain clinical significance and almost certainly included elements of patient convenience rather than QoL improvements, as was noted by ESC in considering the patient preferences and utility provided in the EVA-29155 report

(see paragraph 6.51).

- 7.10 While recognising that the availability of a long-acting injectable option for the management of HIV is likely to offer some QoL and adherence benefits for a small number of patients, the PBAC considered the extent of benefit was difficult to quantify and given its view the claimed utility gain was not reliable for decision making, also considered the presented cost utility analysis was similarly uninformative for decision making. However, based on the input from consumers and clinicians and the sponsor hearing in support of the submission, the PBAC considered that on the basis of potential health benefits from likely improved adherence and improved QoL for a small number of PLHIV, a price advantage of no more than █% over the least costly relevant alternative (Dovato®, dolutegravir/lamivudine) would be acceptable. The PBAC also considered the proposal from the sponsor for oral cabotegravir to be priced the same as dolutegravir was reasonable.
- 7.11 The PBAC considered the likely uptake of CAB LA + RPV LA in the virologically suppressed population was uncertain but unlikely to exceed the █% uptake level estimated in the submission. The Committee noted that the Pre-PBAC Response claimed that there would be a net cost saving to Government (at the proposed DPMQ of \$█), and although the extent of any savings were considered uncertain, the PBAC considered it was unlikely the listing of CAB LA + RPV LA would result in a cost to the R/PBS (due to substitution with a range of oral ARTs at different price points).
- 7.12 The PBAC advised that the listing of CAB LA + RPV LA should include notes to indicate that increased quantities and repeats should not be authorised, given that the injections must be given in a clinical setting and patients would need to attend a clinic at regular intervals. These notes would also be appropriate for the CAB tablet listing, given the limited duration of the oral lead-in phase. The PBAC considered that the recommendation that patients treated with CAB LA + RPV LA should have previously received oral CAB and RPV would be more appropriate as Administrative Advice rather than a Treatment criterion, given that, as per the approved TGA PI, the oral lead-in phase was intended to assess the tolerability of CAB and RPV.
- 7.13 The PBAC advised that cabotegravir oral tablets and CAB LA + RPV LA are suitable for prescribing by nurse practitioners, consistent with other HIV ART therapies.
- 7.14 The PBAC advised that cabotegravir oral tablets and CAB LA + RPV LA should not be treated as interchangeable with any other drugs.
- 7.15 The PBAC recommended that the Early Supply Rule should apply.
- 7.16 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2009* for Pricing Pathway A were not met. Specifically, the PBAC found that in the circumstances of its recommendation for CAB LA + RPV LA:
- a) The treatment is not expected to provide a substantial and clinically relevant

improvement in efficacy over daily oral ART (given the uncertainty associated with quantifying the benefits as described in paragraph 7.9);

- b) The treatment is not expected to address a high and urgent unmet clinical need given the overall high level of virologic suppression among current daily oral ART options in the Australian context (a view previously expressed at its March 2021 meeting);
- c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.17 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:

Recommended

8 Recommended listing

8.1 Add new items:

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty packs	Max. qty units	No.of Rpts	Available brands
CABOTEGRAVIR cabotegravir 30 mg tablet, 30	NEW	1	30	0	Vocabria
			Max. qty (packs) multiplier = 1 Additional Number of Repeats: nil		
Restriction Summary [new] / Treatment of Concept: [new]					
Concept ID (for internal Dept. use)	Category / Program: Section 100 – Highly Specialised Drugs Program Community Access (CA)				
	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]				
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
	Condition: HIV infection				
9007	Indication: HIV infection				
23142	Clinical criteria:				
23141	Patient must be virologically suppressed on a stable antiretroviral regimen for at least 6 months				
	AND				
	Clinical criteria:				
New CC1	The treatment must be in combination with rilpivirine tablets				
	AND				
	Clinical criteria:				
New CC2	Patient must intend to proceed to treatment with intramuscular administration of cabotegravir and rilpivirine;				

MEDICINAL PRODUCT medicinal product pack	PBS item code	Max. qty. packs	Max. qty. units	No. of Rpts	Available brands
CABOTEGRAVIR cabotegravir 600 mg/3 mL modified release injection, 3 mL vial	NEW	1	1 (1 combination pack)	5	Cabenuva®
RILPIVIRINE rilpivirine 900 mg/3 mL modified release injection, 3 mL vial					
			Max. qty (packs) multiplier = 1 Additional Number of Repeats: nil		
Restriction Summary [new] / Treatment of Concept: [new]					
Concept ID	Category / Program: Section 100 – Highly Specialised Drugs Program Community Access (CA)				
(for internal Dept. use)	Prescriber type: <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners				
	Restriction type: <input checked="" type="checkbox"/> Authority Required – Streamlined [new code]				
	Condition: HIV infection				
9007	Indication: HIV infection				
	Clinical criteria:				
New CC4	Patient must have previously received PBS-subsidised therapy for this condition.				
	AND				
7890	Clinical criteria:				
7889	The treatment must be the sole PBS-subsidised therapy for this condition.				
	Administrative Advice:				
NEW AA1	It is recommended that patients have previously received 4 weeks of PBS-subsidised initial oral lead-in treatment with cabotegravir and rilpivirine				
7606	Administrative Advice: No increase in the maximum quantity or number of units may be authorised.				
7607	Administrative Advice: No increase in the maximum number of repeats may be authorised.				
7608	Administrative Advice: Special Pricing Arrangements apply.				

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

ViiV Healthcare welcomes the PBAC recommendation to list Cabenuva on the PBS for the treatment of HIV.