

## **5.03 CABOTEGRAVIR/CABOTEGRAVIR and RILPIVIRINE**

**Tablet containing cabotegravir 30 mg,**

**Vocabria<sup>®</sup>,**

**Pack containing 1 injection of cabotegravir 600 mg in 3 mL and 1 injection of rilpivirine 900 mg in 3 mL,**

**Cabenuva<sup>®</sup>,**

**ViiV Healthcare Pty Ltd.**

### **1 Purpose of Application**

- 1.1 The submission 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 HIV in virologically suppressed patients (at initiation). This was the first submission for CAB LA + RPV LA and oral CAB considered by the PBAC.
- 1.2 Listing was requested on the basis of a cost benefit analysis (CBA) against a comparator of a fixed dose combination (FDC) of dolutegravir (DTG) and RPV (DTG/RPV, with the tradename Juluca) based on the submission's claim of "non-inferior antiviral effectiveness and improved patient acceptability for CAB LA + RPV LA".
- 1.3 Table 1 summaries the key components of the clinical issue addressed by the submission.

**Table 1: Key components of the clinical issue addressed by the submission**

Component	Description
Population	Treatment of HIV infection in adults who are virologically suppressed (HIV-1 RNA <50 copies per mL) and switching therapy.
Intervention	<ul style="list-style-type: none"> <li>• Oral lead in: CAB 30mg PO once daily and RPV 25mg PO once daily for ONE month</li> <li>• Initiation injection: CAB 600mg (3mL) IM and RPV 900mg (3mL) IM at separate gluteal sites</li> <li>• Continuation injection: one month following initiation injection: CAB 600mg (3mL) IM and RPV 900mg (3mL) IM at separate gluteal sites then every TWO months</li> </ul>
Comparator	DTG/RPV Juluca (same HIV treatment class to CAB LA + RPV LA; e.g. dual therapy containing the same NNRTI with an INSTI, indicated for treatment experienced PLHIV and restricted for use as the 'sole PBS-subsidised therapy for HIV')
Outcomes	<p>Primary:</p> <ul style="list-style-type: none"> <li>• Proportion of subjects with HIV-1 RNA ≥50 copies/ml at week 48</li> </ul> <p>Secondary:</p> <ul style="list-style-type: none"> <li>• Proportion of participants with Plasma HIV-1 RNA &lt;50 copies/mL</li> <li>• Incidence of treatment emergent genotypic and phenotypic resistance in subjects with confirmed virologic failure (CVF)</li> <li>• Incidence of disease progression (HIV associated conditions, AIDS, death)</li> <li>• Incidence and severity of AE and laboratory abnormalities</li> <li>• Treatment satisfaction using HIVTSQ</li> </ul>
Clinical claim	<ul style="list-style-type: none"> <li>• CAB LA + RPV LA is non-inferior in terms of effectiveness in comparison to DTG/RPV for the treatment of HIV infection in treatment experienced patients.</li> <li>• 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).</li> <li>• CAB LA + RPV LA has an acceptable safety profile for the treatment of HIV infection.</li> </ul>

Source: Table 3 of the submission.

AIDS = acquired immunodeficiency syndrome; CAB = cabotegravir; DTG = dolutegravir; HIV = Human Immunodeficiency Virus; HIVTSQ= HIV treatment satisfaction questionnaire; IM = intramuscular; INSTI = integrase strand transfer inhibitor (INSTI); LA = long acting; NNRTI = non-nucleotide reverse transcriptase inhibitors; PLHIV = people living with HIV; PO = orally; RNA = ribonucleic acid; QoL = quality of life; RPV = rilpivirine

## 2 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	1	0	\$ [REDACTED]	Vocabria®, ViiV Healthcare Pty Ltd
Cabotegravir 600 mg in 3mL single-dose vial and Rilpivirine 900 mg in 3mL single dose vial, long-acting suspension for injection, 1 pack	1 pack	5	\$2,827.74 (pub) \$ [REDACTED] (eff)	Cabenuva®, ViiV Healthcare Pty Ltd

### Requested restriction cabotegravir tablets

<b>Episodicity:</b>	Chronic
<b>Condition:</b>	HIV infection
<b>Treatment phase:</b>	Initial
<b>Restriction:</b> Section 100 Highly Specialised Drugs Program (Community Access)	<input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	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: Table 7, p37 of the submission.

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

<b>Episodicity:</b>	Chronic
<b>Condition:</b>	HIV infection
<b>Treatment phase:</b>	Continuing
<b>Restriction:</b> Section 100 Highly Specialised Drugs Program (Community Access)	<input checked="" type="checkbox"/> Streamlined
<b>Treatment criteria:</b>	Patient must have previously received PBS-subsidised therapy for this condition. AND Patient must 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: Table 8, p37 of the submission.

- 2.1 A special pricing arrangement was proposed. The requested price was based on a CBA versus the DTG/RPV FDC.
- 2.2 The draft product information describes the oral tolerability testing as 'recommended' rather than mandatory, however the requested listing describes this as mandatory prior to commencing LA therapy. The Pre-Sub-Committee Response (PSCR) stated that

oral tolerability testing will not be mandatory and noted the requested restriction should be adjusted accordingly.

- 2.3 The submission noted that oral therapy (oral bridging) with CAB and RPV tablets may be used to replace up to two months of injections. However, the requested restriction for CAB tablets only covers the initial phase, and does not cover use for this oral bridging in the event where a deviation of more than 7 days from a scheduled injection visit cannot be avoided. It may be clinically relevant to list oral CAB to allow for patients to remain on treatment where there may be expected short-term gaps in LA injectable therapy. However, conversely, there is a risk of leakage of oral CAB tablets for ongoing use, beyond the recommended maximum of 2 months in the draft product information. The PSCR noted that the requested listing in the submission did not include provision for short term oral dosing for planned missed LA injectable doses and requested this be included in the listing.
- 2.4 The draft product information contains information on two different dosing regimens – a one monthly dosing regimen and a two monthly dosing regimen. The TGA Advisory Committee on Medicines (ACM) advised that both one monthly and two monthly dosing schedules are approvable, with the recommendation that the decision about which schedule to choose should be left up to the discretion of the treating clinician and that the regimen should be changed if the two monthly dosage schedule does not result in maintenance of viral suppression. PBS listing was only being sought for the CAB LA 600mg + RPV LA 900mg strength, dosed two monthly. The PSCR indicated the sponsor does not intend to bring the 1-monthly regimen vials to the Australian market if the 2-monthly regimen is registered by the TGA and therefore listing was not sought for that regimen.
- 2.5 The proposed ‘two monthly’ dosage frequency was not entirely consistent with the clinical trial, in which patients were treated every eight weeks (Q8W). These were not comparable, with a Q8W dosing frequency suggesting 56 days between injections (as used in ATLAS-2M trial) and the requested ‘two monthly’ dosing frequency suggesting ~61 days between injections. The difference of five days between ‘two monthly’ and Q8W frequency may be clinically relevant, as this was almost equal to the allowed deviation (seven days) of the scheduled injection according to the draft product information and in ATLAS-2M. This means that a patient who has a dose  $\geq 3$  days later than expected at a ‘two monthly’ frequency ( $\geq 64$  days between doses), while still within the allowable deviation according to the draft product information (maximum =  $61 + 7 = 68$  days between doses) would have had a ‘missed dose’ by the definition of ATLAS-2M ( $56 + 7 = 63$  days maximum between doses). Given that the drug levels are likely to be lowest at the end of a dosing interval, this discrepancy in the maintenance frequency could plausibly have an impact on the efficacy of CAB LA + RPV LA as lower drug levels were more likely to lead to virological failure. The PSCR noted the difference in CAB and RPV exposure between every 2 months and Q8W dosing is minimal and the TGA did not query the dosing interval. The ESC noted that even if the impact was considered not to be clinically relevant, this has a tangible

impact on the economics and financial estimates. The ESC further requested that more detail on the implementation in Australian clinical practice be provided in the pre-PBAC response, including administration costs for nurse support and clinical scheduling compared to the current 6-12 monthly clinic visits, how clinics would manage cold supply chain, and other adjustments required for tighter maintenance schedules. The Pre-PBAC Response clarified the sponsor consulted with 27 healthcare professionals across multiple clinics to devise the implementation plan and noted this consultation indicated that most patients will see a doctor every four-to-six months and a nurse in between clinician visits. The Pre-PBAC Response also noted this consultation was used to inform the selection of the MBS item used in the economic model.

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

### **3 Background**

#### **Registration status**

3.1 The submission was made under TGA/PBAC Parallel Process. Cabotegravir/rilpivirine was TGA registered on 23 February 2021.

3.2 The indications are as follows:

Cabotegravir 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.; and

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.

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

### **4 Population and disease**

4.1 HIV infects cells of the immune system, 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 antiretroviral therapy (ART) for the suppression of HIV are administered orally on a daily basis. The submission claimed a LA injectable 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 submission noted HIV-specific and medical challenges imposed by daily oral ART can make it difficult for some PLHIV to achieve and maintain optimal adherence to treatment. The ESC noted there was no evidence presented to support the claim that a LA injectable treatment will improve adherence, or that adherence with oral treatment regimens was an issue in Australian clinical practice. The ESC noted the HIV FUTURES 9, ARCSHS, 2019 publication<sup>1</sup> found that 77% of PLHIV in Australia reported satisfaction with current therapy and 70% reported that current ART was convenient.
- 4.3 As the submission was seeking listing only in HIV patients who are already virologically suppressed (HIV RNA <50 copies per mL), patients who are eligible for CAB LA + RPV LA should not be experiencing any adherence or malabsorption issues, and therefore were unlikely to obtain any benefits from improved adherence.

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

## 5 Comparator

- 5.1 The submission nominated the DTG/RPV oral FDC (with the tradename Juluca) as the main comparator. The main arguments provided in support of this nomination were that this oral therapy is the same drug class as CAB LA + RPV LA, and both CAB LA + RPV LA and Juluca: (i) are two-drug HIV regimens; (ii) contain a potent integrase strand transfer inhibitor (INSTI) with CAB being an analogue of DTG; (iii) contain the non-nucleoside reverse transcriptase inhibitor (NNRTI) drug rilpivirine; (iv) are only indicated as a complete switch treatment option for HIV infection in the treatment experienced setting in patients that are 'virologically suppressed on a stable ART regimen for at least 6 months'; (v) have a (proposed) restriction for use as the 'sole PBS-subsidised therapy for HIV'; and (vi) have demonstrated non-inferiority to oral ART through their relative clinical trial programs.
- 5.2 While the nominated main comparator was reasonable, it was not the only relevant comparator. The submission inappropriately did not nominate any secondary comparators or provide justification for why alternative FDCs were not appropriate comparators. This was inconsistent with financial estimates presented, as the

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<sup>1</sup> [https://www.latrobe.edu.au/\\_\\_data/assets/pdf\\_file/0007/1058614/HIV-Futures-9.pdf](https://www.latrobe.edu.au/__data/assets/pdf_file/0007/1058614/HIV-Futures-9.pdf)

submission assumed that CAB LA + RPV LA would replace a range of other oral ART FDCs (Juluca, Triumeq, Biktarvy, Odefsey and Genvoya – see Table 2 for components of each FDC and a summary of FDCs).

**Table 2: Summary of fixed-dose combinations which may potentially be substituted**

FDC or other combination components	Abbreviations	Tradename	DPMQ (Nov 2020)	Basis of listing
Elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide	ELV/c/FTC/TAF	Genvoya®	\$1963.86	CM to TDF/FTC/ELV/c
Rilpivirine / emtricitabine / tenofovir alafenamide	RPV/FTC/TAF	Odefsey®	\$1963.86	CM to RPV/FTC/TDF
Bictegravir / emtricitabine / tenofovir alafenamide	BIC/FTC/TAF	Biktarvy®	\$1848.42	CM to Triumeq
Dolutegravir / abacavir / lamivudine	DTG/ABC/3TC	Triumeq®	\$1707.80	CM to EFV/FTC/TDF
Dolutegravir / lamivudine	DTG/3TC	Dovato®	\$1443.30	CM to individual components
Dolutegravir / rilpivirine	DTG/RPV	Juluca®	\$1732.60	CM to Eviplera/Stribild and Odefsey/Genvoya <sup>a</sup>

Source: constructed during evaluation using information from Table 1, dolutegravir with lamivudine PSD July 2020 and the therapeutic relativity sheets. DPMQs extracted 16 November 2020

CM = cost minimised; DPMQ = dispensed price for maximum quantity; FDC = fixed dose combination; INSTI = integrase strand transfer inhibitors,

<sup>a</sup> Obtained from therapeutic relativity sheet, however the public summary documents indicated the main comparator was individual components.

5.3 For the requested population, both DTG/3TC (Dovato, DPMQ: \$1,443.30) and DTG/RPV (Juluca [main comparator] DPMQ: \$1,732.60) are PBS-listed medicines which are less costly than CAB LA + RPV LA (requested effective DPMQ: \$ [REDACTED]) and could be replaced in practice. If treatment with CAB LA + RPV LA is substantially more costly than an alternative therapy or alternative therapies, the PBAC could only recommend listing of CAB LA + RPV LA 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)*).

5.4 The ESC noted that in its previous consideration of DTG/3TC (Dovato®) for virologically suppressed, treatment experienced patients at the July 2020 meeting that the PBAC accepted that DTG/RPV and DTG/3TC were of non-inferior comparative efficacy and safety (paragraphs 6.19 – 6.21, Dolutegravir with lamivudine Public Summary Document (PSD), July 2020 PBAC meeting) and therefore considered it may be a relevant alternative and less costly comparator.

*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 presentation outlined the reality of the experience of living with HIV, and the impact the disease has on quality of life, in terms of anxiety, stigma and the fear of unintentional or unwanted disclosure of

HIV status and the impact these issues have on every life, even in people who are virologically suppressed. The PBAC considered the presentation was informative and highlighted that viral suppression is not the only objective of effective management of HIV.

### **Consumer comments**

6.2 The PBAC noted and welcomed the input from the National Association for People Living with HIV (NAPWHA), the National Aboriginal Community Controlled Health Organisation (NACCHO) and Thorne Harbour Health (Vic) via the Consumer Comments facility on the PBS website.

- The PBAC noted the comments from NAPWHA highlighted that anxiety, stigma and fear of unintentional disclosure of HIV status are a real concern for many people living with HIV that has direct impacts on mental health and quality of life and also noted this viewpoint was reflected in the sponsor hearing presentation.
- The Committee also noted the input from NACCHO highlighted the benefits of a long acting injectable option for some Aboriginal and Torres Strait Islander peoples, particularly for a small number of people who may have adherence issues and represent an increased transmission risk. The comments also highlighted that HIV infection and the fear of unintentional disclosure is an additional mental health issue for Aboriginal and Torres Strait Islander peoples, who may face additional discrimination and rejection by their community if their HIV status were disclosed in such a way. The PBAC considered it would need more detail from NACCHO regarding the suggestion that there is a component of the ATSI population that would choose LAIs and two monthly visits, including information on remote access.
- The PBAC noted the input from Thorne Harbour Health (Vic) that highlighted the potential advantages of a supervised long acting injectable option for management of HIV infection for older patients with neurocognitive impairments or drug problems and are likely to be less adherent to daily oral therapy.

### **Clinical trials**

6.3 No head-to-head trials comparing CAB LA + RPV LA Q8W and DTG/RPV FDC were identified. Instead, a claim of non-inferiority in terms of effectiveness was made via a two-step indirect comparison of CAB LA + RPV LA Q8W and DTG + RPV (which was assumed to be the same as the DTG/RPV FDC) using Bucher's method with the following steps (refer to Table 3):

- CAB LA + RPV LA Q4W vs DTG + RPV: These were anchored on oral ART as a common comparator; then
- CAB LA + RPV LA Q8W vs DTG + RPV: Comparison was made using CAB LA + RPV LA

Q4W as a common comparator (outcome of step 1).

6.4 The two-step indirect treatment comparison was based on five randomised controlled trials:

- Study 201584 (hereafter referred to as “FLAIR”, n=566): following oral induction with oral DTG/abacavir (ABC)/lamivudine (3TC) in ART naïve individuals, patients were randomised to either continue treatment with oral DTG/ABC/3TC (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 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 every eight week (Q8W) regimen (n=524) in virologically suppressed individuals.
- Two trials (SWORD 1 and 2) for DTG + RPV taken concomitantly were identified, with their results pooled (n=1,028). It was assumed that DTG + RPV would be equivalent to the DTG/RPV FDC. The PBAC has previously noted that the TGA has accepted that DTG + RPV taken concomitantly was bioequivalent to the DTG/RPV FDC (Paragraph 6.18, dolutegravir with rilpivirine PSD, July 2018). Both SWORD 1 and 2 compared DTG + RPV taken concomitantly (n= 516) with continued treatment with ART (n=512) in virologically suppressed individuals. These trials have previously been considered by the PBAC.

**Table 3: Trials used in each step of two step indirect comparison between CAB LA + RPV LA two monthly and DTG/RPV FDC**

	<b>CAB LA + RPV LA Q8W</b>	<b>CAB LA + RPV LA Q4W</b>	<b>DTG/RPV FDC</b>
Step 1 (Oral ART as common comparator)	-	FLAIR pooled with ATLAS	SWORD 1 and 2
Step 2 (CAB LA + RPV LA Q4W as common comparator, from step 1)	ATLAS-2M	-	Results from Step 1

CAB = cabotegravir; LA = long acting; RPV = rilpivirine; ART = antiretroviral therapy; DTG = dolutegravir; FDC = fixed dose combination; Q8W = every eight weeks, Q4W = every four weeks

Source: Adapted from Figure 21, p112 of the submission.

6.5 Details of the trials presented in the submission are provided in Table 4.

**Table 4: Trials and associated reports presented in the submission**

Trial ID	Protocol title/ Publication title	Publication citation
<b>CAB LA + RPV LA trials</b>		
FLAIR	Orkin, C. et al. Long-acting Cabotegravir and Rilpivirine after oral induction for HIV-1 infection.	New England Journal of Medicine 2020; 382(12): 1124-1135.
	Orkin, C. et al. 2020. 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
	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.	New England Journal of Medicine 2020; 382(12): 1112-1123.
	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.	Journal of Acquired Immune Deficiency Syndromes 2020; 85(4): 498-506 Publish ahead of print.
ATLAS-2M	Overton, E. et al. Cabotegravir + Rilpivirine every 2 months is noninferior to monthly dosing: Week 48 results from the ATLAS-2M study Conference on Retroviruses and Opportunistic infections; March 8-11, Boston, MA	March 2020
	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
<b>DTG/RPV trials</b>		
SWORD 1 SWORD 2	Libre, J. M., Hung, C. C., Brinson, C. & et al. Efficacy, safety, and tolerability of dolutegravir-rilpivirine for the maintenance of virological suppression in adults with HIV-1: phase 3 randomised, non-inferiority SWORD-1 and SWORD-2 studies.	Lancet 2018; 391: 839-849
	Aboud, M., Orkin, C., Podzamczar, D et al. Efficacy and safety of dolutegravir-rilpivirine for maintenance of virological suppression in adults with HIV-1: 100-week data from the randomised, open-label, phase 3 SWORD-1 and SWORD-2 studies.	Lancet 2019; 6: e576-87.
	A Phase III, randomized, multicentre, parallel group, non-inferiority study evaluating the efficacy, safety and tolerability of switching to dolutegravir plus rilpivirine from current INI-, NNRT- or PI-based antiretroviral regimen in HIV-1-infected adults who are virologically suppressed. 48-week results. 3 May 2017. 2016N287382_00.	SWORD 1 CSR 2017
	A Phase III, randomized, multicentre, parallel group, non-inferiority study evaluating the efficacy, safety and tolerability of switching to dolutegravir plus rilpivirine from current INI-, NNRT- or PI-based antiretroviral regimen in HIV-1-infected adults who are virologically suppressed. 48-week results. 3 May 2017. 2016N287539_00.	SWORD 2 CSR 2017

Source: Table 11, p41 of the submission.

## 6.6 The key features of the randomised trials are summarised in the

6.7 Table 5. Overall, all trials had a low risk of bias (although open-label, the primary outcome of HIV RNA copies per mL were objective).

**Table 5: Key features of the included evidence**

Trial , N	Trial Design	Interventions	Population	Main Outcomes								
FLAIR N=566 <sup>a</sup>	Phase III, OL, RCT, non-inferiority	<p><b>Induction Phase (20 weeks)</b> Oral DTG/ABC/3TC FDC (NRTI substitution allowed)</p> <p><b>Maintenance phase (100 weeks)</b> CAB LA + RPV LA group:  <ul style="list-style-type: none"> <li>• Oral CAB 30mg + RPV 25mg OD for 4 weeks, then</li> <li>• IM CAB LA 600mg + RPV LA 900mg (loading dose), then</li> <li>• IM CAB LA 400mg + RPV LA 600mg every 4 weeks</li> </ul>                     Control group: Oral DTG/ABC/3TC FDC daily (or alternative DTG + 2NRTIs)</p>	<p>HIV-1 infected, ≥18 years of age, ART-naive</p> <p>Subjects who had an HIV 1 RNA &lt;50 c/mL at the Week -4 Visit (i.e. 16 weeks after induction phase starts) were eligible to enter the maintenance Phase.</p>	Proportion of participants with HIV-RNA ≥50 copies/mL as per FDA Snapshot algorithm at Week 48								
ALTAS N=616	Phase III, OL, RCT non-inferiority	<p><b>Maintenance phase (52 weeks)</b> CAB LA + RPV LA group:  <ul style="list-style-type: none"> <li>• Oral CAB 30mg + RPV 25mg OD for 4 weeks, then</li> <li>• IM CAB LA 600mg + RPV LA 900mg (loading dose), then</li> <li>• IM CAB LA 400mg + RPV LA 600mg every 4 weeks</li> </ul>                     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 HIV-RNA ≥50 copies/mL as per FDA Snapshot algorithm at Week 48								
ATLAS-2M N=1,045	Phase IIIb, OL, RCT, non-inferiority trial	<p><b>Maintenance phase (52 weeks)</b></p> <p>Patients receiving ART prior to trial:</p> <table border="1"> <tr> <td>Q4W</td> <td>Oral CAB 30mg + RPV 25mg OD for 4 weeks, then IM CAB LA 600mg + RPV LA 900mg (loading dose), then IM CAB LA 400mg + RPV LA 600mg every 4 weeks</td> </tr> <tr> <td>Q8W</td> <td>Oral CAB 30mg + RPV 25mg OD for 4 weeks, then IM CAB LA 600mg + RPV LA 900mg (loading dose) at week 4 and 8, then IM CAB LA 400mg + RPV LA 600mg every 8 weeks</td> </tr> </table> <p>Patients receiving CAB LA + RPV LA Q4W prior to trial:</p> <table border="1"> <tr> <td>Q4W</td> <td>IM CAB LA 400mg + RPV LA 600mg every 4 weeks</td> </tr> <tr> <td>Q8W</td> <td>IM CAB LA 400mg + RP LA 600mg every 8 weeks</td> </tr> </table>	Q4W	Oral CAB 30mg + RPV 25mg OD for 4 weeks, then IM CAB LA 600mg + RPV LA 900mg (loading dose), then IM CAB LA 400mg + RPV LA 600mg every 4 weeks	Q8W	Oral CAB 30mg + RPV 25mg OD for 4 weeks, then IM CAB LA 600mg + RPV LA 900mg (loading dose) at week 4 and 8, then IM CAB LA 400mg + RPV LA 600mg every 8 weeks	Q4W	IM CAB LA 400mg + RPV LA 600mg every 4 weeks	Q8W	IM CAB LA 400mg + RP LA 600mg every 8 weeks	HIV-1 infected, ≥18 years of age, ART-experienced, virologically suppressed (HIV-1 RNA<50 copies/mL) on a stable ART regimen	Proportion of participants with HIV-RNA ≥50 copies/mL as per FDA Snapshot algorithm at Week 48
Q4W	Oral CAB 30mg + RPV 25mg OD for 4 weeks, then IM CAB LA 600mg + RPV LA 900mg (loading dose), then IM CAB LA 400mg + RPV LA 600mg every 4 weeks											
Q8W	Oral CAB 30mg + RPV 25mg OD for 4 weeks, then IM CAB LA 600mg + RPV LA 900mg (loading dose) at week 4 and 8, then IM CAB LA 400mg + RPV LA 600mg every 8 weeks											
Q4W	IM CAB LA 400mg + RPV LA 600mg every 4 weeks											
Q8W	IM CAB LA 400mg + RP LA 600mg every 8 weeks											
SWORD 1 & 2 N=1,024	Phase III, OL, RCT, non-inferiority	<p><b>Maintenance phase (148 weeks)</b> 50mg tablet DTG + 25mg tablet RPV taken with a meal; daily OR Current anti-retroviral. 2 NRTIs + INI, 2 NRTIs + NNRTI, or 2 NRTIs and a PI, administered according to respective product labelling</p>	Virologically suppressed on a stable ART regimen for at least 6 months with no history of treatment failure	Proportion of patients with HIV-1 RNA <50 c/mL at 48 weeks								

Source: Table 12-14, p43-45 of the submission, Libre 2018

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

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

6.8 Additionally, patient satisfaction with treatment was reported using the HIV Treatment Satisfaction Questionnaire (HIVTSQ) in all trials. Patient related quality of life data was also reported using the 12 item Short Form (SF-12) health survey, a shorter alternative to the SF-36 in FLAIR and ATLAS.

6.9 The ESC noted there were differences in the trial population and the Australian HIV population, such as median time on treatment (longer in the Australian HIV population), patient age (the Australian population tends to be older) and further noted that in general, Australian rates of diagnosis and treatment are high, with an estimated 90% of estimated HIV cases diagnosed and 89% of those receiving anti-retroviral therapy<sup>2</sup>.

### ***Comparative effectiveness***

#### **Primary outcomes – virological failure and virological success**

6.10 The results for the primary outcome of the CAB LA + RPV LA trials of virological failure (confirmed viral load  $\geq 50$  copies/mL or discontinued due to lack of efficacy or other reason while not below threshold) are presented in Table 6.

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<sup>2</sup> National update on HIV, viral hepatitis and sexually transmissible infections in Australia: 2009–2018. Sydney: Kirby Institute, UNSW Sydney (published 2020).

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

Trial ID	DTG + RPV	ART	CAB LA + RPV LA Q4W	CAB LA + RPV LA Q8W	RD (95% CI)	Adjusted RD <sup>a</sup> (95% CI)
<b>DTG+RPV vs ART</b>						
SWORD 1&2	3/513 (<1)	6/511 (1)	-	-	-0.6 (-1.7 to 0.6)	-0.5 (-1.4 to 0.5)
<b>CAB+RPV Q4W vs ART</b>						
FLAIR	-	7/283 (2.5)	6/283 (2.1)	-	-0.4 (-2.8 to 2.1)	-0.4 (-2.8 to 2.1)
ATLAS	-	3/308 (1.0)	5/308 (1.6)	-	0.6 (-1.1 to 2.4)	0.6 (-1.2 to 2.5)
Pooled FLAIR & ATLAS	-	10/591 (1.7)	11/591 (1.9)	-	0.2 (-1.3 to 1.7)	0.2 (-1.4 to 1.7)
Step 1: Indirect analysis (DTG+RPV vs CAB+RPV Q4W)					-0.8% (-2.6%, 1.1%)	na
<b>CAB+RPV Q8W vs Q4W</b>						
ATLAS-2M ITT-E	-	-	5/523 (1.0)	9/522 (1.7)	0.8 (-0.6 to 2.2)	0.8 (-0.6 to 2.2)
ATLAS-2M w/exposure	-	-	0/196 (0)	4/195 (2.1)	2.1 (0.1 to 5.2)	na
ATLAS-2M w/o exposure	-	-	5/327 (1.5)	5/327 (1.5)	0.0 (-2.2 to 2.2) <sup>b</sup>	na
Step 2: Indirect analysis (CAB+RPV Q8W ITT-E vs DTG+RPV)					1.6% (-0.7%, 3.9%)	na
Step 2: Indirect analysis (CAB+RPV Q8W w/exposure vs DTG+RPV)					2.9% (-0.3%, 6.1%)	na
Step 2: Indirect analysis (CAB+RPV Q8W w/o exposure vs DTG+RPV)					0.8% (-2.1%, 3.7%) <sup>b</sup>	na

Source: Table 35, 41&57, p85, 90&114 of the submission.

Text in italics indicate values calculated or extracted during evaluation

RD = risk difference; CI = confidence interval; CAB = cabotegravir, RPV = rilpivirine; DTG = dolutegravir; Q8W = eight weekly dosing of CAB + RPV, Q4W = four weekly dosing of CAB + RPV; w/exposure = previous exposure to CAB + RPV; w/o exposure = without previous exposure to CAB + RPV, na = not applicable; ITT-E = intention-to-treat exposed

<sup>a</sup> 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. Based on Cochran-Mantel Haenszel stratified analysis adjusting for age (<50,  $\geq$  50 years old) and baseline third agent class (PI, NNRTI, INI) for SWORD trials.

<sup>b</sup> Updated during the evaluation to RD of 0 (-2.2, 2.2) (from ATLAS-2M CSR, p 97). The submission presented a RD of 0 (-1.9, 1.9) and the resultant RD for the indirect comparison of 0.8% (-1.9%, 3.4%).

- 6.11 The results of the indirect comparison between CAB LA + RPV LA Q8W and DTG + RPV supported the clinical claim of non-inferiority for the proportion of patients meeting the nominated non-inferiority margin of 4% (RD = 0.8%, 95% CI: -2.1%, 3.7%).
- 6.12 It was noted that the submission excluded patients with prior CAB LA + RPV LA exposure in step 2 of their indirect comparison for the primary and secondary outcome. No justification for this was provided by the submission. Patients with prior exposure to the intervention and overall patients in ATLAS-2M were added to the analyses (compared to DTG + RPV in step 2) during evaluation for completeness and consideration. Results indicated that patients with prior exposure to CAB LA + RPV LA in ATLAS-2M did not meet the non-inferiority margin (RD = 2.9%, 95% CI: -0.3%, 6.1%). When considering the ITT-E population from ATLAS-2M, the non-inferiority margin was only just met (RD = 1.6%, 95% CI: -0.7%, 3.9%).
- 6.13 A more conservative approach of treating patients with missing data, or who switched or discontinued treatment as virological failures (Missing, Switch, Discontinue = Failure) in the analyses was performed during the evaluation and are presented in Table 7. These results are the complement to the proportion of patients who experienced virological success (see Table 8).

Table 7: Results for the proportion of subjects with plasma HIV-1 RNA  $\geq 50$  copies/mL or no virological data at Week 48

Trial ID	DTG + RPV	ART	CAB LA + RPV LA Q4W	CAB LA + RPV LA Q8W	RD fixed effects (95% CI)	RD random effects (95% CI)
<b>DTG+RPV vs ART</b>						
SWORD 1&2	27/513 (5.3)	26/511 (5.1)	-	-	0.2 (-2.5, 2.9)	0.2 (-2.5, 2.9)
<b>CAB+RPV Q4W vs ART</b>						
FLAIR	-	19/283 (6.7)	18/283 (6.4)	-	-0.4 (-4.6, 3.9)	-0.4 (-4.6, 3.9)
ATLAS	-	14/308 (4.5)	23/308 (7.5)	-	2.9 (-0.9, 6.9)	2.9 (-0.9, 6.9)
Pooled FLAIR & ATLAS	-	33/591 (5.6)	41/591 (6.9)	-	1.4 (-1.4, 4.1)	1.4 (-1.8, 4.6)
Step 1: Indirect analysis (DTG+RPV vs CAB+RPV Q4W)					-1.2% (-5.1%, 2.7%)	-1.2% (-5.4%, 3.0%)
<b>CAB+RPV Q8W vs Q4W</b>						
ATLAS-2M ITT-E	-	-	34/523 (6.5)	30/522 (5.8)	-0.8 (-3.7, 2.2)	-0.8 (-3.7, 2.2)
ATLAS-2M w/exposure	-	-	7/196 (3.6)	9/195 (4.6)	0 (-0.03, 0.1)	0 (-0.03, 0.1)
ATLAS-2M w/o exposure	-	-	27/327 (8.3)	21/327 (6.4)	0 (-0.1, 0.02)	0 (-0.1, 0.02)
Step 2: Indirect analysis (CAB+RPV Q8W ITT-E vs DTG+RPV)					0.4% (-4.5%, 5.3%)	0.4% (-4.5%, 5.3%)
Step 2: Indirect analysis (CAB+RPV Q8W w/exposure vs DTG+RPV)					1.2% (-2.7%, 5.1%)	1.2% (-2.7%, 5.1%)
Step 2: Indirect analysis (CAB+RPV Q8W w/o exposure vs DTG+RPV)					1.2% (-2.7%, 5.1%)	1.2% (-2.7%, 5.1%)

RD = risk difference; CI = confidence interval; CAB = cabotegravir, RPV = rilpivirine; DTG = dolutegravir; Q8W = eight weekly dosing of CAB + RPV, Q4W = four weekly dosing of CAB + RPV; w/exposure = previous exposure to CAB + RPV; w/o exposure = without previous exposure to CAB + RPV; ITT-E = intention-to-treat exposed

Source: constructed during evaluation using StatsDirect

- 6.14 Non-inferiority between CAB LA + RPV LA Q4W and DTG + RPV was met in step 1 (RD = -1.2%, 95% CI: -5.1%, 2.7%) assuming a 4% non-inferiority margin. However, non-inferiority could not be concluded between CAB LA + RPV LA Q8W (using ATLAS-2M ITT-E data) and DTG + RPV (RD = 0.4%, 95% CI: -4.5%, 5.3%) in step 2, nor when analysed via CAB LA + RPV LA subgroups of previous exposure/non-exposure to CAB LA + RPV LA (RD = 1.2%, 95% CI: -2.7%, 5.1%).
- 6.15 For the outcome of virological success (Table 8), the results of the indirect comparison between CAB LA + RPV LA and DTG + RPV met the specified margin (RD = 0.7%, 95% CI: -4.9%, 6.2%). The submission did not explicitly state the non-inferiority margin for virological success, though its analysis of indirect comparison indicated that a non-inferiority margin at 10% was used. When analysed via patients with prior exposure to the intervention and overall patients in ATLAS-2M, the results of the indirect comparisons also met the specified margin for both groups.

**Table 8: Results for the proportion of subjects with plasma HIV-1 RNA <50 copies/mL at Week 48**

Trial ID	DTG + RPV	ART	CAB LA + RPV LA Q4W	CAB LA + RPV LA Q8W	RD (95% CI)	Adjusted RD <sup>a</sup> (95% CI)
<b>DTG+RPV vs ART</b>						
SWORD 1&2	486/513 (95)	485/511 (95)	-	-	-0.2 (-2.9 to 2.5)	-0.2 (-3.0 to 2.5)
<b>CAB+RPV Q4W vs ART</b>						
FLAIR	-	264/283 (93.3)	265/283 (93.6)	-	0.4 (-3.7 to 4.4)	0.4 (-3.7 to 4.5)
ATLAS	-	294/308 (95.5)	285/308 (92.5)	-	-2.9 (-6.7 to 0.8)	-3.0 (-6.7 to 0.7)
Pooled FLAIR & ATLAS	-	558/591 (94.4)	550/591 (93.1)	-	-1.4 (-4.1 to 1.4)	-1.4 (-4.1 to 1.4)
Step 1: Indirect analysis (DTG+RPV vs CAB+RPV Q4W)					1.2% (-2.7%, 5.0%)	na
<b>CAB+RPV Q8W vs Q4W</b>						
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) <sup>b</sup>	na
Step 2: Indirect analysis (CAB+RPV Q8W ITT-E vs DTG+RPV)					-0.4% (-5.3%, 4.5%)	na
Step 2: Indirect analysis (CAB+RPV Q8W w/exposure vs DTG+RPV)					-2.3% (-8.1%, 3.7%)	na
Step 2: Indirect analysis (CAB+RPV Q8W w/o exposure vs DTG+RPV)					0.6% (-5.1%, 6.3%) <sup>b</sup>	na

Source: Table 36, 38&58, p86, 88&114 of the submission.

RD = risk difference; CI = confidence interval; CAB = cabotegravir, RPV = rilpivirine; DTG = dolutegravir; Q8W = eight weekly dosing of CAB + RPV, Q4W = four weekly dosing of CAB + RPV; w/exposure = previous exposure to CAB + RPV; w/o exposure = without previous exposure to CAB + RPV, ITT-E = intention-to-treat exposed

RD = risk difference; CI = confidence interval

<sup>a</sup> 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. Based on Cochran-Mantel Haenszel stratified analysis adjusting for the following baseline stratification factors: age group (< or >=50 years old) and baseline third agent (PI, NNRTI, INI) for SWORD trials.

<sup>b</sup> Value presented in the submission, based on RD of 1.9 (-2.1, 5.8) could not be verified. When updated to RD of 1.8 (-2.3, 6.0) (from ATLAS-2M CSR, p 101), the resultant RD for the indirect comparison was 0.6% (-5.1%, 6.3%), which remains within the non-inferiority threshold.

6.16 Overall, while the indirect comparison appeared to support the claim that CAB LA + RPV LA Q8W was non-inferior to the DTG/RPV FDC with regards to virological failure, there were some potential concerns as:

- Using the Missing, Switch, Discontinue = Failure algorithm, non-inferiority for the outcome of patients who experienced virological failure could not be concluded for CAB LA + RPV LA Q8W versus DTG + RPV; and
- While the nominated non-inferiority margins have been previously accepted by the PBAC, the two-step indirect comparison used to generate the results may have introduced additional material uncertainty not captured by the confidence interval, which only captures random variation and not uncertainty due to transitivity. For a two-step indirect comparison there is more uncertainty due to transitivity than in a standard indirect comparison, such that the confidence interval is too narrow (as a measure of uncertainty) and extremely difficult to interpret in the context of a pre-specified non-inferiority margin. It was noted that the for the proportion of patients who experienced virological failure, the risk difference for CAB LA + RPV LA Q8W compared to DTG + RPV was +1.6%, 95%CI (-0.7%, 3.9%), and the upper 95% confidence interval was just below the 4% non-inferiority margin.

6.17 There may also be differences in the virological failure rate between the Q8W maintenance frequency used in ATLAS-2M and the proposed 'two monthly'

maintenance frequency, as the time between doses in a ‘two monthly’ frequency would be longer. The PSCR argued the results of the POLAR study, a 12-month open label rollover study from the LATTE study used 2-monthly dosing (with a maximum dose interval of 67 days) maintained high levels of virologic suppression and found no events of confirmed virologic failure. The ESC noted the TGA had not raised any issues regarding any issues relating to 8-weekly or 2-monthly doses.

**Secondary outcomes – patient reported outcomes**

- 6.18 Patient reported outcomes (PROs) were a key focus of the CAB LA + RPV LA trials given they were designed to evaluate the first LA injectable treatment for HIV.
- 6.19 The SF-12 health survey, a shorter alternative to the SF-36 and including only one or two items from each of the eight health concepts of the SF-36, was used to measure quality of life in FLAIR and ATLAS. No statistically significant differences between treatment arms were reported at any time point for either physical or mental components.
- 6.20 The HIVTSQ was identified by the submission as an important measure, designed to assess satisfaction with patients’ current antiretroviral therapy.
- 6.21 The submission used a distribution-based approach to determine the minimal clinically important difference (MCID) for HIVTSQ. This used the standard deviation and the within treatment group mean change in score such that the MCID threshold corresponded to half the SD of the within-group mean. Therefore, if the change in mean from baseline was greater than half the SD of the mean, the criteria for demonstrating a MCID was met. The submission stated that the MCID threshold was derived through the methodology proposed by Rai et al., 2015, in their methods to estimate an MCID for PROs in systemic lupus erythematosus clinical trials. It was unclear whether the arbitrary designation of ‘half the standard deviation of the within group mean’, based on a study from an unrelated clinical area (systemic lupus erythematosus) was an acceptable MCID as it did not account for the relative magnitude of change from baseline. The estimated MCID for HIVTSQ, expressed as a percentage change from baseline, represented an improvement of only 5-7%.
- 6.22 Analyses of HIVSTQ results were performed across all trials during the evaluation using the submission’s method of calculation and nominated MCID and are presented in Table 9. It should be noted that while SWORD 1&2 measured HIVTSQ, the version used was different to those used in FLAIR, ATLAS and ATLAS-2M, which included additional items and were scored differently therefore, a comparison across SWORD 1 and 2 with FLAIR, ATLAS and ATLAS-2M was likely not meaningful.

**Table 9: Results for the HIVSTQ, change from baseline in total treatment satisfaction by visit**

Outcome	FLAIR		ATLAS		ATLAS-2M <sup>a</sup>		SWORD 1&2 <sup>b</sup>	
	CAB+RPV (283)	ART (283)	CAB+RPV (308)	ART (308)	Q8W (522)	Q4W (523)	DTG+RPV (513)	ART (511)
<b>Baseline</b>								
• n	259	266	302	298	319	323	513	507
• Mean total (%)	59.3 (90)	59.1 (90)	55.3 (84)	55.4 (84)	57.7 (87)	56.7 (86)	54.4 (91)	53.9 (90)
<b>Week 24</b>								
• n	257	257	300	288	319	323	509	506
• Mean change <sup>c</sup>	1.6	-0.5	6.4	1.1	5.1	4.0	1.8	0.2
• 95% CI	(0.8, 2.5)	(-1.4, 0.3)	(5.6, 7.3)	(0.2, 1.9)	(4.4, 5.8)	(3.3, 4.7)	nr	nr
• SD <sup>d</sup>	6.9	6.9	7.4	7.5	6.5	6.4	6.4	6.0
• MCID <sup>e</sup>	3.5	3.5	3.7	3.7	3.3	3.2	3.2	3.0
• MCID met	no	no	yes	no	yes	yes	no	no
<b>Week 44/48</b>								
• n	253	256	300	294	319	323	509	505
• Mean change <sup>c</sup>	1.3	0.5	6.1	0.4	4.9	3.1	1.5	0.4
• 95%CI	(0.5, 2.1)	(-0.3, 1.4)	(5.2, 7.0)	(-0.5, 1.4)	(4.0, 5.7)	(2.3, 4.0)	nr	nr
• SD <sup>d</sup>	6.5	6.9	8.0	8.1	7.6	7.6	7.0	6.0
• MCID <sup>e</sup>	3.3	3.5	4	4	3.8	3.8	3.5	3.0
• MCID met	no	no	yes	no	yes	no	no	no
• MCID as % of baseline	5.6%	5.9%	7.2%	7.2%	6.6%	6.7%	6.4%	5.6%

Source: Table 36, 38&58, p86, 88&114 of the submission, Table 66, p159 of SWORD 1 CSR, Table 65, p154 of SWORD 2 CSR.

HIV = Human Immunodeficiency Virus; HIVSTQ = HIV treatment satisfaction questionnaire; MCID = minimal clinically important difference; CAB = cabotegravir; DTG = dolutegravir; RPV = rilpivirine; Q8W = every eight weeks, Q4W = every four weeks

<sup>a</sup> Only participants without prior exposure to CAB + RPV included

<sup>b</sup> Max score 60 for SWORD 1&2 trials, 66 for all others

<sup>c</sup> Adjusted means. FLAIR: Based on ANCOVA: change from baseline score = baseline score + Induction Baseline (Week -20) HIV-1 RNA (<100,000, 100,000 c/mL) + sex at birth (female, male) + age (<50, 150 Years) + race (white, non-white) + Treatment (CAB +RPV, CAR). ATLAS: adjusting for Baseline score, sex at birth, age, race (white, non-white), and third agent class (INI, PI, NNRTI). ATLAS-2M: adjusting for Baseline score, sex at birth, age, race (white, non-white), and third agent class (INI, PI, NNRTI)

<sup>d</sup> Calculated SD for CAB + RPV trials:  $SD = \sqrt{(n) \cdot (Upper\ CI - Lower\ CI) / (\alpha, df^2)}$ , as used in the submission

<sup>e</sup> MCID= half SD. If mean change>MCID, MCID is met, as used in the submission

CI= confidence interval; SD=standard deviation; MCID= minimal clinically important difference

6.23 Using the submission’s methodology, the MCID threshold 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 significant uncertainty with the results.

6.24 The submission stated that 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 and unlikely to be of clinical significance.

6.25 The PSCR disagreed with the evaluation and argued there were substantial differences between the injectable and oral study arms and that the results of the HIVTSQ analyses are clinically meaningful. Further, the PSCR disagreed with the evaluation and

argued that a subsequent post-hoc analysis to derive preference-based utility values from available trial data found that treatment with CAB LA + RPV LA was associated with a statistically significant improvement in SF-6D scores at weeks 24 and 48 vs. current oral anti-retroviral therapy. This post-hoc analysis was not evaluated.

- 6.26 The ESC considered that the claim of improved treatment satisfaction with CAB LA + RPV LA over current oral ART was likely overstated and not supported by the available evidence. Further, the ESC considered that there did not appear to be a significant unmet clinical need in the HIV treatment space for a long acting injectable as effective virologic suppression appears to be the primary driver behind patient satisfaction and there was limited evidence of adherence issues in the majority of the population. The ESC agreed, however, that a long acting injectable option for effective management of HIV infection would provide additional convenience for some patients and may also provide a level of additional adherence benefit in small sub-populations with known adherence issues.
- 6.27 The Pre-PBAC Response argued the views expressed by the ESC that there did not appear to be a significant unmet clinical need for a long acting injectable did not account for real issues faced by people living with HIV and further argued these issues were complex and combined a range of emotional challenges, medical needs, patient preferences and the need to improve treatment adherence in some sub-populations. The Pre-PBAC Response further noted the input from organisations (discussed in paragraph 6.2) highlighted the reality and complexity of these issues and reinforced there was a genuine clinical need for alternatives to daily oral ART.
- 6.28 The Pre-PBAC Response further argued that the HIVTSQ is a validated questionnaire and disputed the view expressed by the ESC that the difference between treatment arms was numerically small and unlikely to be of clinical significance. The Response noted the result from the ATLAS study, which resulted in a treatment difference of 5.68 on the HIVTSQ, met the nominated MCID.
- 6.29 Overall, the PBAC considered the claim of improved patient satisfaction was not adequately supported as there was no evidence of improvement in quality of life measured by SF-12, and the nominated minimal clinically important difference (MCID) for HIVTSQ appeared to be an arbitrary measure and was likely inappropriate. It was also unclear if the trials were powered to detect meaningful differences in HIVTSQ given they were not primary outcomes, and patients enrolled in the CAB LA + RPV LA trials would likely be more biased towards favouring a LA injection as the route of administration.

### ***Comparative harms***

- 6.30 Table 10 presents a summary of adverse events (AEs) across the randomised trials.

Table 10: Summary of key adverse events in the randomised trials at Week 48

Outcome, n (%)	FLAIR		ATLAS		ATLAS-2M		SWORD 1&2	
	CAB+ RPV Q4W (283)	ART (283)	CAB+ RPV Q4W (308)	ART (308)	CAB+ RPV Q8W (522)	CAB+ RPV Q4W (523)	DTG+ RPV (513)	ART (511)
Any AE	267 (94)	225 (80)	294 (95)	220 (71)	473 (91)	482 (92)	395 (77)	364 (71)
Any AE, excluding ISRs	246 (87)	225 (80)	264 (86)	220 (71)	403 (77)	441 (84)	395 (77)	364 (71)
ISR, n (%)	239 (86)	na	250 (83)	na	392 (76)	390 (75)	na	na
Any Grade 3 to 5 AEs	31 (11)	11 (4)	35 (11)	24 (8)	41 (8)	49 (9)	148 (28)	120 (24)
Any Grade 3 to 5 AEs, excluding ISRs <sup>a</sup>	22 (8)	11 (4)	25 (8)	24 (8)	29 (6)	30 (6)	33 (6)	21 (4)
Any drug-related AE	236 (83)	28 (10)	255 (83)	8 (3)	400 (77)	399 (76)	97 (19)	9 (2)
Any drug-related AE, excluding ISRs	79 (28)	28 (10)	88 (29)	8 (3)	109 (21)	125 (24)	97 (19)	9 (2)
AEs leading to withdrawal	9 (3)	4 (1)	10 (3)	1 (<1)	12 (2)	13 (2)	21 (4)	3 (<1)
Any SAE	18 (6)	12 (4)	13 (4)	14 (5)	27 (5)	19 (4)	27 (5)	21 (4)
SAEs related to study treatment	1 (<1)	0	0	1 (<1)	3 (<1)	1 (<1)	4 (1)	1 (<1)
Fatal SAEs	0	0	0	1 (<1)	1 (<1)	0	1 (<1)	1 (<1)
Drug related fatal SAEs	0	0	0	0	0	0	0	0

Source: Table 46 & 47, p99 & 100 of the submission; Llibre 2018.

AE = adverse event; ISR = injection site reaction; SAE = serious adverse event

- 6.31 The most commonly reported AE for CAB LA + RPV LA was injection site reaction (ISR). As noted in the TGA clinical evaluation report, the ISRs varied from pruritus and erythema to pain and abscess formation and were generally mild or moderate with no serious (Grade 4 or 5) ISRs. Most ISRs resolved within 7 days although 16% lasted for 8 to 14 days and 17% lasted for >14 days.
- 6.32 An indirect comparison was performed during the evaluation that indicated no significant differences between the CAB LA + RPV LA and DTG + RPV at week 48 when ISRs were excluded. The TGA evaluator noted that non-ISR AEs that occurred more frequently with CAB LA + RPV LA were haemorrhoids, pyrexia, dizziness, fatigue, and headache. The most common reason for withdrawal was the development of acute viral hepatitis, of which there were eight cases in the CAB LA + RPV LA group and zero cases in the ART group. This particular observation requires additional monitoring.
- 6.33 The TGA clinical evaluator considered that “overall, CAB LA + RPV LA suspension for IM injection appeared to be well-tolerated with an acceptable safety profile that is similar to other ART regimens. Although ISRs occurred frequently, few were treatment limiting. Other important risks of hepatotoxicity (including acute viral hepatitis) should be weighed against the convenience of once monthly dosing” (TGA clinical evaluation report round 2, p 36).

### Benefits/harms

- 6.34 A comparison of benefits and harms for CAB LA + RPV LA versus DTG + RPV has not been presented, given the submission’s claim of non-inferior effectiveness and acceptable safety.

- 6.35 The claim of additional benefits to patients who have an unmet need for an alternative to daily oral ART was not adequately supported by the patient reported outcomes presented in the clinical evidence.

### **Clinical claim**

- 6.36 The submission described CAB LA + RPV LA as non-inferior in terms of effectiveness compared with DTG/RPV in the treatment of HIV infection in treatment experienced patients. Although the results of the submission's indirect comparison indicated non-inferiority was met, this claim requires consideration given that:
- Using the Missing, Switch, Discontinue = Failure algorithm, non-inferiority for the outcome of patients who experienced virological failure could not be concluded for CAB LA + RPV LA Q8W versus DTG + RPV; and
  - While the nominated non-inferiority margins have been previously accepted by the PBAC, the two-step indirect comparison used to generate the results may have introduced additional material uncertainty not captured by the confidence interval. The confidence interval of a two-step indirect comparison may be too narrow (as a measure of uncertainty) and extremely difficult to interpret in the context of a pre-specified non-inferiority margin.
- 6.37 Comparatively, the results of one-step indirect comparison results (for DTG + RPV vs CAB + RPV Q4W) consistently produced more favourable results (when considering the point estimate for the risk difference) for the Q4W option compared to Q8W (in 2-step analyses) with regard to virological failure and virological success. However, it was noted that ACM advised that, overall, the efficacy and safety of Q8W dosing appears to be similar to that of Q4W, and that both the one monthly and two monthly dosing scheduled are approvable.
- 6.38 On balance, the ESC considered the claim of non-inferior comparative effectiveness of CAB LA + RPV LA Q8W and DTG/RPV, with regards to HIV virological suppression, was probably reasonable but noted the non-inferiority margin bordered on CAB LA + RPV LA Q8W not meeting the non-inferiority margin.
- 6.39 The submission claimed that the CAB LA + RPV LA Q8W “has an acceptable safety profile for the treatment of HIV infection”. This was reasonable. While 75-86% of all patients treated with CAB LA + RPV LA in FLAIR, ATLAS and ATLAS-2M experienced ISRs, few were treatment limiting. Despite there being potential safety signals with hepatotoxicity, the TGA also considered that overall, CAB LA + RPV LA suspension for IM injection appeared to be well-tolerated with an acceptable safety profile that is similar to other ART regimens. An indirect comparison was performed during the evaluation that indicated no significant differences between the CAB LA + RPV LA and DTG + RPV at week 48 when ISRs were excluded. The ESC considered this claim was reasonable.

- 6.40 The submission also stated 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). Overall, the ESC considered the claim of improved patient quality of life was not adequately supported as:
- Patients with adherence problems were unlikely to be the target population as only patients who are virologically suppressed are eligible for CAB LA + RPV LA treatment.
  - SF-12 results in FLAIR and ATLAS did not report any statistically significant differences between patients treated with CAB LA + RPV LA Q4W and oral ART at any time point.
  - The HIVTSQ results presented had substantial issues that limited its applicability. The patient population enrolled in the open label FLAIR, ATLAS and ATLAS-2M trials were also likely to be biased in favour of the CAB LA + RPV LA injection therefore, any PROs were likely to be unreliable.
  - the claims were not supported by Australian data.
- 6.41 The PBAC considered that the claim of non-inferior comparative effectiveness in terms of virological response was reasonable.
- 6.42 The PBAC considered that the claim of superior comparative effectiveness for QoL impacts was not adequately supported by the data.
- 6.43 The PBAC considered that the claim of non-inferior safety was reasonable.

### ***Economic analysis***

- 6.44 The submission conducted a CBA against the primary comparator DTG/RPV. The submission inappropriately presented a cost benefit analysis (CBA) based on a willingness to pay (WTP) study (from a discrete choice experiment (DCE)) as the primary, and only, analysis. However, the PBAC guidelines v5.0 state (p64) that a CBA should not be presented as the primary analysis, as the PBAC “is unlikely to be convinced of a cost-effectiveness claim if a CBA is presented without a cost-utility analysis (CUA)”, and (p203) that a CBA should only be presented as a supplementary analysis. The Pre-PBAC Response acknowledged that a CBA is preferably provided as a supplementary analysis, however a DCE was considered as a method to support benefits such as anxiety, stigma, fear of unintentional disclosure, medical conditions which may affect oral dosing and patient preferences and these factors will be considered by patients when choosing a long acting injectable option over oral therapy. The PBAC did not consider the requested price advantage based on consumer surplus from a DCE based WTP study was appropriate.

6.45 A supplementary cost utility analysis (CUA) was presented in the PSCR, based on SF-6D utility scores derived from SF-12 results from the ATLAS and FLAIR trials. This supplementary CUA was not evaluated.

**Cost-minimisation analysis (CMA)**

6.46 The PBAC agreed with the ESC that the most reasonable basis for listing CAB LA + RPV LA, based on the available information, would be on a cost minimisation basis with the least costly alternative. The ESC reiterated its view that based on the relativities established in the DTG/3TC submission in July 2020 that it was also a relevant, and less costly alternative (paragraph 5.4 refers). CMAs against DTG/RPV and DTG/3TC with equi-effective doses based on Q8W and 2-monthly regimens were conducted based on this advice.

6.47 The cost minimisation was based on the price of DTG/RPV and DTG/3TC, conducted over a two year period (consistent with the time horizon chosen for other drugs considered by the PBAC which include loading doses in year one, such as bDMARDs). A cost-minimisation analysis considering the CAB LA + RPV LA (400mg/600mg) Q4W dosing regimen was also included for completeness. The key components of the CMA are summarised in Table 11.

**Table 11: Key components and assumptions of the cost-minimisation analysis**

Component	Claim or assumption
Therapeutic claim: effectiveness	CAB LA + RPV LA IM maintenance Q8W (or every two months) after oral and injection initiation is non-inferior in proportion of patients experiencing virological failure at 48 weeks compared to DTG/RPV. The PBAC may wish to consider whether this claim is reasonable.
Therapeutic claim: safety	CAB LA + RPV LA Q8W has an acceptable safety profile for the treatment of HIV infection compared to DTG/RPV. This claim is reasonable. CAB LA + RPV LA is associated with injection site reactions.
Evidence base	Two-step indirect comparison of CAB LA + RPV LA Q8W and DTG + RPV. Cost minimisation versus DTG/3TC was also considered on the basis of established therapeutic relativities.
Equi-effective doses	CAB LA 600mg + RPV LA 900mg injection Q8W (or every two months) after 1-month oral lead in (and 2 loading injections 1 month apart) is equivalent to one DTG/RPV FDC 50/25mg or one DTG/3TC FDC 50/300mg tablet taken once daily.
Direct medicine costs	Medicine cost of one dose of CAB LA + RPV LA Q8W was lower than the cost of 60 tablets of the DTG/RPV FDC (two month's supply).
Other costs or cost offsets	Yes; administration costs for injections. Adverse events cost not included, therefore resultant cost of CAB LA + RPV LA likely to be underestimated.

CAB = cabotegravir, LA = long acting, RPV = rilpivirine, Q8W = every 8 weeks, DTG = dolutegravir, FDC = fixed dose combination  
Source: Table 60, p122 of the submission.

6.48 The results of the CMA are presented in the tables below. The price of CAB LA + RPV LA (both oral lead in and LA injection) based on price parity to the DTG/RPV FDC may be overestimated due to the following:

- Cost of CAB tablets may not be accurate. Consistent with the submission's cost benefit analysis, the cost-minimisation analysis assumed the cost of one-month treatment with oral CAB (30mg) matches with that of DTG + RPV taken as individual medicines at the agreed ex-manufacturer price for that period. This is the price

proposed by the sponsor. This may not be accurate if DTG + RPV is not the least costly comparator.

- The ESC considered the use of MBS item 10997 was unlikely to be a reasonable reflection of the cost of MBS services for the administration of CAB LA + RPV LA. MBS item 10997 is used for administration cost of CAB LA + RPV LA. MBS item 10997 refers to “Service provided to a person with a chronic disease by a practice nurse or an Aboriginal and Torres Strait Islander health practitioner if: a) the service is provided on behalf of and under the supervision of a medical practitioner; and b) the person is not an admitted patient of a hospital; and c) the person has a GP Management Plan, Team Care Arrangements or Multidisciplinary Care Plan in place; and d) the service is consistent with the GP Management Plan, Team Care Arrangements or Multidisciplinary Care Plan” (Fee: \$12.40, benefit: 100% = \$12.40). The description for use around this item states “a maximum of 5 services per patient in a calendar year”, however, particularly in the first year of treatment, the required number of additional visits were above the specified threshold. The ESC considered that use of a standard Level B consultation of less than 20 minutes (MBS item 23, 100% benefit = \$38.75) was a more appropriate base case assumption. The Pre-PBAC Response argued that MBS item 23 (professional attendance by a GP) was inappropriate for any economic analysis and argued that their clinician survey had identified that most consultations for administration would be with nurses and that item 10997 was the most appropriate MBS item to use.
- The cost of adverse events were not included, despite increased adverse events associated with CAB LA + RPV LA (namely ISRs due to the administration route). It was possible that ISRs may require further treatment and the costs for CAB LA + RPV LA treatment may be underestimated.
- The two tables below present three cost minimisation scenarios (all including oral lead-in dosing), including CAB LA + RPV LA Q8W and Q2M vs. DTG/RPV oral tablet once daily (Table 12), CAB LA + RPV LA Q8W and Q2M vs. DTG/3TC oral tablet once daily (Table 13). The updated CMAs undertaken for the ESC advice were based on ex-manufacturer prices (AEMP).

**Table 12: Results of the cost-minimisation analysis to DTG/RPV using AEMP (over 2 years)**

Component	CAB + RPV Q8W	CAB + RPV Q2M	DTG/RPV
Cost CAB 25mg tablets, oral lead-in <sup>a</sup>	\$ [REDACTED]	\$ [REDACTED]	\$0
Cost RPV 25mg tablets, oral lead-in	\$ [REDACTED] <sup>b</sup>	\$ [REDACTED] <sup>b</sup>	\$0
Administration cost, year 1 (MBS23) <sup>c</sup>	\$232.50 (6 visits) <sup>d</sup>	\$213.13 (5.5 visits) <sup>f</sup>	\$0 (NA)
Administration cost, year 2 (MBS23) <sup>c</sup>	\$174.38 (4.5 visits) <sup>e</sup>	\$155.00 (4 visits) <sup>g</sup>	\$0 (NA)
Number of doses/scripts, year 1	7	6.5	6
Number of doses/scripts, year 2	6.5	6	6
Ex-manufacturer Price (per script)	\$ [REDACTED]	\$ [REDACTED]	\$1,684.86 <sup>b</sup>
Total cost for 2 years (undiscounted)	\$ [REDACTED]	\$ [REDACTED]	\$20,218.32
Total cost for 2 years (discounted)	\$ [REDACTED]	\$ [REDACTED]	\$19,736.93

Source: Constructed during evaluation.

- <sup>a</sup> Approved ex-manufacturer price based on DPMQ of \$ [REDACTED] for CAB tablets proposed in the submission.
- <sup>b</sup> PBS-listed approved ex-manufacturer price
- <sup>c</sup> Assume MBS item 23 (Professional attendance by a general practitioner) 100% benefit \$38.75 instead of submission's assumption of MBS 10997 (Service provided to a person with a chronic disease by a practice nurse), 100% benefit \$12.40
- <sup>d</sup> Assume 7 injections + 1 visit for oral tablets = 8 total visits in year 1. Assume patient would attend doctor twice a year with oral ART, therefore an incremental 6 visits/injections incurred
- <sup>e</sup> Assume 6.5 injections/total visits in year 2. Assume patient would attend doctor twice a year with oral ART, therefore an incremental 4.5 visits/injections incurred
- <sup>f</sup> Assume 6.5 injections + 1 visit for oral tablets = 7.5 total visits in year 1. Assume patient would attend doctor twice a year with oral ART, therefore an incremental 5.5 visits/injections incurred
- <sup>g</sup> Assume 6 injections/total visits in year 2. Assume patient would attend doctor twice a year with oral ART, therefore an incremental 4 visits/injections incurred

**Table 13: Results of the cost-minimisation analysis to DTG/3TC using AEMP (over 2 years)**

Component	CAB + RPV Q8W	CAB + RPV Q2M	DTG/3TC
Cost CAB 25mg tablets, oral lead-in <sup>a</sup>	\$ [REDACTED]	\$ [REDACTED]	\$0
Cost RPV 25mg tablets, oral lead-in	\$ [REDACTED] <sup>b</sup>	\$ [REDACTED] <sup>b</sup>	\$0
Administration cost, year 1 (MBS23) <sup>c</sup>	\$232.50 (6 visits) <sup>d</sup>	\$213.13 (5.5 visits) <sup>f</sup>	\$0 (NA)
Administration cost, year 2 (MBS23) <sup>c</sup>	\$174.38 (4.5 visits) <sup>e</sup>	\$155.00 (4 visits) <sup>g</sup>	\$0 (NA)
Number of doses/scripts, year 1	7	6.5	6
Number of doses/scripts, year 2	6.5	6	6
Ex-manufacturer Price (per script)	\$ [REDACTED]	\$ [REDACTED]	\$1,395.56 <sup>b</sup>
Total cost for 2 years (undiscounted)	\$ [REDACTED]	\$ [REDACTED]	\$16,746.72
Total cost for 2 years (discounted)	\$ [REDACTED]	\$ [REDACTED]	\$16,347.99

Source: Constructed during evaluation.

- <sup>a</sup> Approved ex-manufacturer price based on DPMQ of \$ [REDACTED] for CAB tablets proposed in the submission.
- <sup>b</sup> PBS-listed approved ex-manufacturer price
- <sup>c</sup> Assume MBS item 23 (Professional attendance by a general practitioner) 100% benefit \$38.75 instead of submission's assumption of MBS 10997 (Service provided to a person with a chronic disease by a practice nurse), 100% benefit \$12.40
- <sup>d</sup> Assume 7 injections + 1 visit for oral tablets = 8 total visits in year 1. Assume patient would attend doctor twice a year with oral ART, therefore an incremental 6 visits/injections incurred
- <sup>e</sup> Assume 6.5 injections/total visits in year 2. Assume patient would attend doctor twice a year with oral ART, therefore an incremental 4.5 visits/injections incurred
- <sup>f</sup> Assume 6.5 injections + 1 visit for oral tablets = 7.5 total visits in year 1. Assume patient would attend doctor twice a year with oral ART, therefore an incremental 5.5 visits/injections incurred
- <sup>g</sup> Assume 6 injections/total visits in year 2. Assume patient would attend doctor twice a year with oral ART, therefore an incremental 4 visits/injections incurred

Cost-benefit analysis (CBA)

- 6.49 The ESC advised it did not consider the CBA sufficiently reliable to inform decision-making, as there were significant issues with the estimation of WTP using the DCE, including:
- the lack of oral ART as an option for alternative treatment, or consideration of current oral treatment preferences in the modelling (to ensure any surplus was attributable only to LA injection dose form), meaning the WTP and consumer surplus for LA injections were overestimated
  - the fact that claimed benefits around quality of life, anxiety and stigma were not included in the DCE
  - the lack of face validity with magnitude of the calculated consumer surplus compared to co-payments that patients faced,
  - incorrect representation of LA injection with regards to safety and oral bridging availability.

Further evaluation on the CBA is provided below.

- 6.50 The CBA presented by the submission incorporated a consumer surplus from patient benefits of a LA ART valued through a willingness to pay (WTP) study and included the incremental cost due to administration of CAB LA + RPV LA. The total cost benefit of CAB LA + RPV LA was compared to the cost of treatment with DTG/RPV based on the submission's claim of "non-inferior antiviral effectiveness and improved patient acceptability for CAB LA + RPV LA", such that the total cost benefit for each alternative are equal over a period of 10 years.
- 6.51 The sponsor commissioned a WTP study to examine the treatment preferences for HIV and to elicit preferences for the attributes associated with treatment. A discrete choice experiment (DCE) was used to determine WTP and to estimate the benefit (consumer surplus) to patients receiving CAB LA + RPV LA. See Table 4 for a summary of the WTP/DCE study and Figure 1 for an example of a choice scenario where participants were asked to choose their preferred treatment.

**Table 14: Summary of the willingness to pay study**

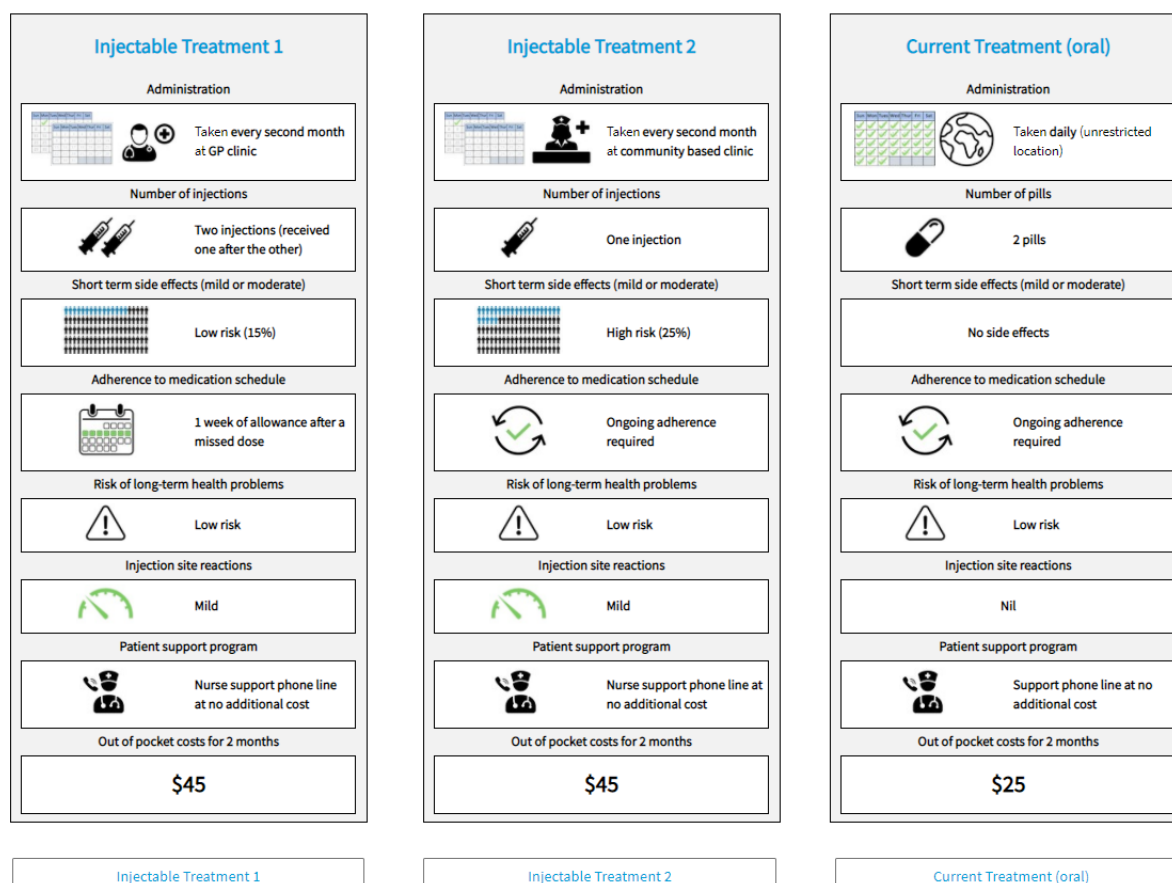
Component	Summary
Design	<p>Discrete choice experiment (DCE) that asked participants to select their preferred treatment out of two hypothetical injectable treatment alternatives, 'injection 1' and 'injection 2', and their current treatment, which was a fixed oral ART defined by the participant.</p> <p>The treatment alternatives were described by differing levels of attributes (frequency of administration, location of administration, number of pills/injections, short term side effects, adherence to medication dosing regimen, long term health problems, injection site reactions, patient support program and out of pocket costs). Based on patient-reported eligibility for concessional healthcare costs (i.e., reduced patient co-payments), patients were either shown general or concessional out-of-pocket medication costs.</p> <p>Each participant was presented with 12 scenarios.</p>
Population	<p>Eligibility criteria: 18 years and over; have been diagnosed with HIV; currently using antiretroviral therapy for HIV; and Australian citizen or permanent resident.</p> <p>99 participants completed the DCE. 89% male, half were aged 51 years or older and approximately three quarters listed their sexual orientation as lesbian, gay or homosexual (78%), reside in a metro/city area (77%) and/or reported their ethnicity as Australian or European (76%). The sample included participants representing all states, with the majority from NSW (38%) and VIC (18%).</p>
Analysis methods	Latent class model
Segmentation	Participants were classed based on their preferences for HIV treatments. Participants in segment 1 (64%) were reluctant to give up their current treatment whereas those in segment 2 (36%) showed strong preference for the injection treatment. It was noted that participants who currently pay for their medication, are currently employed and those with a lower quality of life score were likely to be in segment 2.
Relative attribute importance	In both classes, risk of side effects, location of administration and out of pocket costs were the greatest contributors to preference.
Consumer surplus	<p>Calculated under 2 scenarios, where patient co-payment for the two-monthly cost of HIV treatment is at its maximum (\$41 for general and \$6.60 for concession) in scenario 1, and where patient co-payment is at its minimum (\$0) in scenario 2.</p> <p>Results: The total willingness to pay for the two monthly LA injection was found to be between \$33.50 and \$43.27 for the aggregate market and between \$52 to \$158 in segment 2.</p>

Source: Compiled during evaluation using information from Attachment F to the submission.

**Figure 1: Example of a discrete choice experiment scenario**

Scenario 1 of 12: Please review the following treatment options and choose the option you would prefer as your long-term treatment for HIV.  
Use your mouse to hover over the images to see more information about the features.

- Please assume that the injectable treatment is based on clinical trials informed by robust scientific data and are recommended by current HIV treatment guidelines.
- Please assume that all the treatment options are comparable in keeping your viral load undetectable (i.e. all treatment options are equally effective).
- Once you start the two monthly injection treatment, oral bridging is available in situations where you can't make it back in for your next scheduled injection.
- If you switch to the injection treatment and do not like it, you can discontinue the injection and transition into any fully active oral regimen that you will need to continue for at least 52 weeks from your last injection.



Source: Figure 1, p13 of Attachment F in the submission

6.52 As discussed in paragraph 6.40, the submission stated that CAB LA + RPV LA provides additional benefits to patients who have an unmet need for an alternative to daily oral ART. These include 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.

6.53 Inappropriately, the WTP study did not assess the value or impact of these proposed factors which may impact on QoL except for preference and convenience. Instead, the WTP choice sets (Figure 1) reported on variations in:

- Out of pocket costs (which should be the same for oral ART and LA injections under the PBS, but understandably used as a measure of patient willingness to pay);
  - Patient convenience (e.g. in what setting the injections may be delivered); and
  - Other attributes included number of injections, frequency of side effects, whether a 7 day administration window was allowed (somewhat confusingly labelled as ‘adherence’ within the choice sets) and risk of long term problems. The availability of a support phone program (which was not part of the treatment for which listing was being sought) was also considered.
- 6.54 Therefore, it was considered that the WTP study was not designed to, and did not, provide reliable information on whether LA ART injections would improve health related QoL in areas that were proposed (e.g. the emotional challenges or adherence) among PL HIV compared to oral daily ART.
- 6.55 It was also unclear why a DCE was necessary in this case. The WTP by patients who prefer a two monthly injection instead of a daily oral ART would be simple to elicit with a direct contingent valuation method. The outcome is neither unobservable nor difficult to measure and the difference between LA injection and oral ART do not appear to be particularly difficult for the patient to contextualise or internalise. There is some evidence<sup>3</sup> that DCEs will report higher WTP estimates compared to contingent valuation studies, which would favour CAB LA + RPV LA.
- 6.56 The DCE is based on the assumption that all treatment options/alternatives have similar efficacy in keeping viral load undetectable. It was unclear if this was adequately supported, particularly as Q8W dosing was associated with more CVF compared to Q4W.
- 6.57 The results of the DCE could not be independently verified based on the information provided. Moreover, beyond the applicability of the WTP study described in paragraphs 6.53 to 6.54, there were a number of issues with the DCE methodology which further limited the reliability of the results and its relevance to the current submission:
- The DCE did not allow for a switch to another oral ART as a viable alternative. By not allowing another oral ART as a viable alternative (patients were only asked to compare two injection scenarios with their current ART for each choice set), the DCE inappropriately assigned all the consumer surplus which would have been observed from any treatment switch to the LA injection dose form. Additionally, the latent class model results indicated that preferences for the status quo (current

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<sup>3</sup> DANYLIV, A., PAVLOVA, M., GRYGA, I., & GROOT, W. (2012). WILLINGNESS TO PAY FOR PHYSICIAN SERVICES: COMPARING ESTIMATES FROM A DISCRETE CHOICE EXPERIMENT AND CONTINGENT VALUATION. *Society and Economy*, 34(2), 339-357. Retrieved December 19, 2020, from <http://www.jstor.org/stable/90002260>

oral treatment) have not been estimated in the modelling and only the preferences for injections have been modelled. The ESC considered both of these factors have significantly overestimated the consumer surplus specifically attributable to the LA injection dose form.

- The magnitude of the calculated consumer surplus lacked face validity when compared to the magnitude of patient co-payments.
- Patients reported a statistically significantly negative preference for treatments with ‘high risk’ of low grade, manageable side effects, which was defined as a 25% risk. In FLAIR, ATLAS and ATLAS-2M, at least 75% of patients experienced at least one ISR, and at least 77% of patients experienced an AE (excluding ISR). Therefore it was possible the DCE underrepresented the risk of adverse events associated with LA injections.
- Claimed benefits in terms of quality of life, stigma, anxiety and worry were not included in the DCE as attributes and therefore it does not directly value these claimed health benefits.
- There was a lack of information known to patients that could bias the results. The study assumed missed injections could be covered by tablets but the submission was not seeking this listing, therefore any missed doses would have to be funded by another source.
- Confidence intervals for consumer surplus estimates were not reported, therefore the accuracy of the estimates was unknown. In the case of exenatide in July 2015, the ESC previously “did not consider it was appropriate to expect the PBAC to make decisions without some information about the bounds of the WTP estimates” (Exenatide PSD, July 2015, paragraph 6.17).

6.58 Based on the DCE, the submission estimated an additional consumer surplus of \$109.74 per dose of CAB LA + RP LA which was applied as a cost offset in the CBA. Overall, the consumer surplus for treatment with CAB LA + RPV LA derived from the WTP study, even in patients who were in favour of LA injections, was likely to be overestimated.

6.59 The submission proposed that at a DPMQ per two monthly dose of \$ [REDACTED], CAB LA + RPV LA would have price parity compared to the DTG/RPV FDC (DPMQ \$1,732.60). Overall, the results of the submission’s CBA may not be accurate, given that:

- Assumed ‘two monthly’ dosing, rather than Q8W dosing as per the ATLAS-2M trial. This would have resulted in lower number of injections required.
- Consumer surplus benefit (applied as a cost offset) derived from the DCE in the analysis was likely overestimated. Additionally, it was inappropriate to attribute 100% of the consumer surplus in the CBA, as the PBAC has previously stated that any consumer surplus should be shared between the sponsor, the consumer and the Government (Exenatide PSD, July 2015, paragraph 6.33).

- Five additional administration visits were included in Year 1 for CAB LA + RPV LA, when six visits should have been included. There was also uncertainty around the MBS item used and whether this was appropriate for the patient population.
  - The cost of adverse events were not included, despite increased adverse events associated with CAB + RPV (namely ISRs due to the administration route).
- 6.60 It is relevant to note that the requested premium was based on cost offsets (consumer surplus) for patient preferences rather than actual health gains. Without corresponding clinical evidence to show that the injectable treatment of CAB LA + RPV LA leads to improved adherence and improved health outcomes, funding a price advantage for patient preferences does not provide a sufficient basis for quantifying the potential benefit and improved health outcomes, and therefore is not a basis for a higher price. It was noted that in its consideration for exenatide once weekly, the PBAC did not accept the price advantage based on the WTP results presented but instead ‘was more persuaded that there would be significant impacts on quality of life for patients that were likely to lead to health benefits’ (Paragraphs 7.5, exenatide PSD July 2015).
- 6.61 Overall, the CBA presented on the basis of the submission’s claim of improved patient acceptability was likely unreasonable, given that:
- There were significant issues with the estimation of WTP using the DCE, including the lack of oral ART as an option for alternative treatment (to ensure any surplus was attributable only to LA injection dose form), lack of face validity with magnitude of benefit compared to co-payments that patients faced, and incorrect representation of LA injection with regards to safety and oral bridging availability.
  - The WTP study did not identify which attributes contributed to the perceived gain in consumer surplus. The PBAC has previously stated (Exenatide PSD, July 2015, paragraph 7.5) that in the instance where a price advantage was accepted for tobramycin, they were more persuaded by the provision of significant impacts on quality of life for patients that were likely to lead to health benefits.
  - No confidence interval for consumer surplus estimates were provided. The ESC previously “did not consider it was appropriate to expect the PBAC to make decisions without some information about the bounds of the WTP estimates” (Exenatide PSD, July 2015, paragraph 6.17).
- 6.62 The PSCR argued that the DCE did not include parameters such as reduced stigma, reduced risk of unwanted disclosure and the daily reminder of living with HIV as there was a necessary limitation on the number of parameters to maintain validity of the DCE. The PSCR further argued that these benefits are likely to have been considered when respondents considered their responses in the DCE and therefore these were incorporated into the consumer surplus. The ESC considered that such an assumption was unjustified and advised the DCE-informed CBA approach was not appropriate.

**Drug cost/patient/year**

- 6.63 The drug cost per patient per year is \$ [redacted] based on the submission’s requested DPMQ of \$ [redacted] for CAB tablets and \$ [redacted] for CAB LA + RPV LA injections. This calculation is based on 1 script for CAB + RPV tablets (oral lead-in), followed by 7 scripts for CAB LA + RPV LA injections (based on Q8W dosing) in Year 1. It is anticipated that there will be 6.5 scripts for CAB LA + RPV LA required from Year 2 onwards at a cost of \$ [redacted] per year. This compares with a cost of \$10,540 for the DTG/RPV, assuming 6.08 scripts (365/60) per year.
- 6.64 If the price for CAB LA + RPV LA Q8W from the CMA were used, the drug cost per patient per year is \$ [redacted] in Year 1 and \$ [redacted] in subsequent years, based on the DPMQ of \$ [redacted] for CAB tablets and \$ [redacted] for CAB LA + RPV LA injections.

**Estimated PBS usage & financial implications**

- 6.65 This submission was not considered by DUSC. The submission took an epidemiological approach to estimating use and financial impact.
- 6.66 The estimated net cost to the government budget of listing CAB LA + RPV LA on the PBS/RPBS was \$0 to \$10 million in Year 1, decreasing to a net saving in Year 6. Cost savings were mainly driven by the lower (effective) price of the proposed medicine compared to therapies being replaced. Despite a cost saving observed during Years 3-6, 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.
- 6.67 The estimated use and financial implications of CAB LA + RPV LA are presented in Table 15.

**Table 15: Estimated net financial implications of the proposed CAB + RPV listing**

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>4.2 Estimation of use and financial impact of the proposed medicine (PBS and RPBS)</b>						
Prevalent HIV patients	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>
Virologically suppressed	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>
Patients who will switch	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>	[redacted] <sup>2</sup>
Eligible switch patients	[redacted] <sup>2</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>
Initiating patients	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>
Continuing patients	[redacted] <sup>4</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>
Script numbers						
CAB tablets	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>	[redacted] <sup>3</sup>
CAB+RPV injections	[redacted] <sup>5</sup>	[redacted] <sup>5</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>6</sup>	[redacted] <sup>6</sup>
Total	[redacted] <sup>5</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>1</sup>	[redacted] <sup>6</sup>	[redacted] <sup>6</sup>
PBS/RPBS cost less co-pay						
CAB tablets	\$ [redacted] <sup>7</sup>	\$ [redacted] <sup>7</sup>	\$ [redacted] <sup>7</sup>	\$ [redacted] <sup>7</sup>	\$ [redacted] <sup>7</sup>	\$ [redacted] <sup>7</sup>
CAB+RPV injections (pub)	\$ [redacted] <sup>8</sup>	\$ [redacted] <sup>9</sup>	\$ [redacted] <sup>10</sup>	\$ [redacted] <sup>11</sup>	\$ [redacted] <sup>12</sup>	\$ [redacted] <sup>12</sup>
CAB+RPV injections (eff)	\$ [redacted] <sup>13</sup>	\$ [redacted] <sup>8</sup>	\$ [redacted] <sup>14</sup>	\$ [redacted] <sup>9</sup>	\$ [redacted] <sup>9</sup>	\$ [redacted] <sup>9</sup>
Total (pub)	\$ [redacted] <sup>8</sup>	\$ [redacted] <sup>9</sup>	\$ [redacted] <sup>11</sup>	\$ [redacted] <sup>12</sup>	\$ [redacted] <sup>12</sup>	\$ [redacted] <sup>12</sup>
Total (eff)	\$ [redacted] <sup>13</sup>	\$ [redacted] <sup>8</sup>	\$ [redacted] <sup>14</sup>	\$ [redacted] <sup>9</sup>	\$ [redacted] <sup>9</sup>	\$ [redacted] <sup>9</sup>
<b>4.3 Estimation of changes in use and financial impact of other medicines (PBS and RPBS)</b>						
Changes in script numbers						

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	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
<b>Prescriptions not used by patients who initiated treatment with CAB+RPV</b>						
Juluca	4	4	4	4	4	4
Triumeq	3	3	3	3	3	3
Biktarvy	3	3	3	3	3	3
Genvoya	3	3	3	3	3	3
Odefsey	3	3	3	3	4	4
<b>Prescriptions not used by patients who are continuing treatment with CAB+RPV from previous year</b>						
Juluca	4	4	4	3	3	3
Triumeq	4	3	3	2	2	2
Biktarvy	4	3	2	2	5	5
Genvoya	4	3	3	3	3	2
Odefsey	4	3	3	3	3	3
<b>Additional rilpivirine tablet use from patients initiating CAB+RPV</b>						
Rilpivirine	3	3	3	3	3	3
<b>Total</b>	<b>2</b>	<b>5</b>	<b>1</b>	<b>1</b>	<b>1</b>	<b>6</b>
<b>Cost offsets from prescriptions not used by patients who initiated treatment with CAB+RPV</b>						
Juluca	-\$7	-\$7	-\$7	-\$7	-\$7	-\$7
Triumeq	-\$7	-\$7	-\$7	-\$7	-\$7	-\$7
Biktarvy	-\$7	-\$7	-\$7	-\$7	-\$7	-\$7
Genvoya	-\$7	-\$7	-\$7	-\$7	-\$7	-\$7
Odefsey	-\$7	-\$7	-\$7	-\$7	-\$7	-\$7
<b>Cost offsets from prescriptions not used by patients who are continuing treatment with CAB+RPV from previous year</b>						
Juluca	\$7	-\$7	-\$7	-\$7	-\$7	-\$7
Triumeq	-\$7	-\$7	-\$7	15	15	15
Biktarvy	-\$7	-\$7	15	15	13	13
Genvoya	-\$7	-\$7	-\$7	7	7	15
Odefsey	-\$7	-\$7	-\$7	7	7	7
<b>Additional cost from rilpivirine tablet use from patients initiating CAB+RPV</b>						
Rilpivirine – initiating (first yr)	\$7	\$7	\$7	\$7	\$7	\$7
<b>Total cost of other PBS medicines</b>	<b>13</b>	<b>8</b>	<b>14</b>	<b>9</b>	<b>9</b>	<b>9</b>
<b>4.4 Estimated financial implications for the PBS/RPBS</b>						
Net cost to PBS/RPBS (pub)	\$15	\$13	\$13	\$13	\$8	\$8
Net cost to PBS/RPBS (eff)	\$7	\$7	-\$7	-\$7	-\$7	-\$7
<b>4.5 Estimated financial implications for the health budget</b>						
Net change in PBS/RPBS scripts	3	3	3	3	3	3
MBS additional costs	\$7	\$7	\$7	\$7	\$7	\$7
MBS decreased costs <sup>a</sup>	-\$7	-\$7	-\$7	-\$7	-\$7	-\$7
Net MBS costs	\$7	\$7	\$7	\$7	\$7	\$7
<b>Net cost to Government health budget</b>	<b>\$7</b>	<b>\$7</b>	<b>\$7</b>	<b>-\$7</b>	<b>-\$7</b>	<b>-\$7</b>

<sup>a</sup> there were errors in the cell referencing for the calculation of MBS decreased cost. Instead of calculating number of urinalysis based on Biktarvy, Genvoya and Odefsey (continuing and initiation), the submission calculated these based on Juluca, Triumeq, Biktarvy, Genvoya, Odefsey initiating and Juluca continuing. Corrected during evaluation.

Text in italics indicate values calculated during evaluation

Source: Table 75 – 77, 79 - 84, p138 – 144 of the submission.

CAB = cabotegravir; RPV = rilpivirine; pub = published; eff = effective.

The redacted values correspond to the following ranges:

<sup>1</sup> 20,000 to < 30,000

<sup>2</sup> 5,000 to < 10,000

<sup>3</sup> 500 to < 5,000

<sup>4</sup> < 500

<sup>5</sup> 10,000 to < 20,000

<sup>6</sup> 30,000 to < 40,000

<sup>7</sup> \$0 to < \$10 million

<sup>8</sup> \$30 million to < \$40 million

<sup>9</sup> \$50 million to < \$60 million

<sup>10</sup> \$60 million to < \$70 million

<sup>11</sup> \$70 million to < \$80 million

<sup>12</sup> \$80 million to < \$90 million

<sup>13</sup> \$20 million to < \$30 million

<sup>14</sup> \$40 million to < \$50 million

<sup>15</sup> \$10 million to < \$20 million

6.68 Overall, the ESC considered the submission's estimated usage of CAB LA + RPV LA was uncertain and may be underestimated. The following points were noted regarding the submission's financial model:

- An error was identified in the calculation of the cost of urinalysis required for Biktarvy, Genvoya and Odefsey which resulted in an underestimation of decreased MBS costs and was corrected during the evaluation;
- The financial model was based on one initiation dose during the first year. This was inappropriate and inconsistent with the draft product information. Moreover, if a Q8W frequency for CAB LA + RPV LA was used, then the number of doses per year when continuation should be 6.5, not 6.08;
- Costs of adverse events management were not included;
- There was uncertainty around the MBS item used for treatment administration and whether this was appropriate for the patient population. The cost of additional visits may be underestimated; and
- It may not be appropriate to assume that patients would only consider treatment with CAB LA + RPV LA once in a lifetime, which the submission assumed by assigning a diminishing proportion of patients who have not been offered CAB LA + RPV LA previously to the eligible patient pool.

6.69 A sensitivity analysis around the financial estimates assuming a Q8W dose frequency (56 day between doses, translating to 7 CAB LA + RPV LA doses per year in initiation patients and 6.52 doses per year in continuing patients) instead of two monthly (6 CAB LA + RPV LA doses per year in initiation patients and 6.08 doses per year in continuing patients) was conducted during the evaluation. This had a significant effect on the financial impact, increasing the net cost to around \$0 to \$10 million per year (from \$0 to \$10 million or less), for a total of \$20 million to < \$30 million over the first six years of listing.

6.70 The PSCR also agreed it was reasonable to list CAB tablets for short-term continuing use for patients who will miss planned dosing of CAB LA + RPV LA, however did not provide any utilisation or financial estimates for use for this population. The Pre-PBAC Response provided estimates for the utilisation of oral CAB for periods of planned missed doses based on the number of oral CAB packs provided in the ATLAS2M trial and noted only 1 pack was provided for this purpose in the study. The utilisation estimates of oral CAB for missed doses are presented in the table below.

**Table16: Utilisation and financial estimates of oral cabotegravir for planned missed doses**

Total	2021	2022	2023	2024	2025	2026
CAB 30 mg oral tablet packs dispensed	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>	█ <sup>1</sup>
Cost	\$█ <sup>2</sup>	\$█ <sup>2</sup>	\$█ <sup>2</sup>	\$█ <sup>2</sup>	\$█ <sup>2</sup>	\$█ <sup>2</sup>

Source: Table 2, Pre-PBAC Response.

The redacted values correspond to the following ranges:

<sup>1</sup> < 500

<sup>2</sup> \$0 to < \$10 million

## Quality Use of Medicines

6.71 The sponsor has advised they are investigating a range of initiatives to improve service delivery and, as a result, optimise delivery of CAB LA + RPV LA, focused on the following:

- 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 is employing 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 patient’s home 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.

## Financial Management – Risk Sharing Arrangements

6.72 No special pricing arrangement was requested for CAB tablets. However, the sponsor requested a special pricing arrangement for CAB LA + RPV LA injections with an effective price of \$█ per two monthly injection compared to a published price of \$2,827.74.

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

## **7 PBAC Outcome**

- 7.1 The PBAC did not recommend the listing of cabotegravir (CAB) tablets or cabotegravir and rilpivirine long acting injections (CAB LA + RPV LA). In deciding not to recommend the listing, the PBAC considered the presented evidence did not support a conclusion that CAB and CAB LA + RPV LA offered advantages in terms of quality of life, reduced anxiety or worry associated with daily oral therapy or fear of unintentional disclosure of HIV status. Furthermore, the PBAC considered the economic analysis, which relied on a cost benefit analysis (CBA) 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 anti-retroviral therapy (ART) were claimed.
- 7.2 The PBAC welcomed the input from the National Association of People Living with HIV (NAPWHA) and the views expressed in the Sponsor Hearing, which highlighted that anxiety, worry and fear of unintentional disclosure are concerns for many people with HIV. The Committee acknowledged that some people living with HIV may feel anxiety and worry with regards to the daily reminder of daily oral therapy and the risk of unwanted disclosure of HIV status, and these issues impact their lives. However, the PBAC considered it was unclear if the availability of a long acting injectable alternative to oral ART would provide tangible improvements in patients' quality of life and further considered the clinical data and economic analyses presented did not allow an exploration of these issues. Therefore the PBAC considered it was not possible to assess the magnitude of any potential health benefits and how value could be attributed to them (in economic terms).
- 7.3 The PBAC noted the submission argued there was an unmet need for an alternative to daily oral ART therapy, however considered this claim was not adequately supported. 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. However, the PBAC noted the additional input from the National Aboriginal Community Controlled Health Organisation (NACCHO) which highlighted that under-diagnosis of HIV and adherence to daily oral therapy remains a concern in some Aboriginal and Torres Strait Islander communities. On that basis, the PBAC accepted that a long acting injectable option such as CAB LA + RPV LA may offer advantages in communities where HIV transmission and treatment adherence are of concern. However, no evidence was presented to show that the availability of the long acting injections would alleviate adherence issues in this population.
- 7.4 The Committee considered the nominated primary comparator of combination dolutegravir with rilpivirine was reasonable, however considered that other relevant alternatives may include other single tablet fixed-dose combinations such as those containing tenofovir alafenamide, dolutegravir + abacavir + lamivudine (Triumeq<sup>®</sup>) and dolutegravir with lamivudine (Dovato<sup>®</sup>) (see Comparator section).

- 7.5 The PBAC noted the key CAB LA + RPV LA clinical trials were good quality, open label randomised controlled trials comparing the long acting injectable at four-weekly or eight-weekly intervals to current oral ART regimens. The PBAC also noted the populations recruited in the trials had substantially higher reported preference for long acting injectable treatment (>90%) than was reported for individuals in the willingness-to-pay (WTP) study conducted in Australia for the submission (36%). The PBAC considered this difference may limit the generalisability of the secondary patient reported outcomes reported in the study to the Australian population. The Committee considered that the results of the patient reported outcomes in the studies may also be an unreliable basis to assess potential health benefits in terms of quality of life, anxiety, stigma or fear of unintentional disclosure in the Australian population (see paragraph 6.28). The PBAC considered further exploration of the impact of these issues in the Australian HIV population would be informative.
- 7.6 The PBAC noted that the submission relied on a multi-step indirect comparison to compare CAB LA + RPV LA Q8W and DTG/RPV FDC. Whilst there were uncertainties with the indirect comparisons, the PBAC considered that the evidence presented supported a conclusion that CAB LA + RPV LA, either given once every four weeks or once every eight weeks, is of non-inferior comparative effectiveness to daily oral ART regimens, in terms of virological control of HIV.
- 7.7 The PBAC noted that secondary patient reported outcomes formed the basis of the submission's claim of advantages over daily oral ART therapy. Based on the evidence presented, the PBAC considered 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. The PBAC noted the results of the HIVTSQ in the FLAIR and ATLAS trials were associated with a statistically significant improvement in treatment satisfaction, however also noted the numerical differences between the LA injectable and oral ART arms was small and the lower bound of the 95% CI would not have met any of the proposed within-group minimally important clinical differences. The PBAC was therefore uncertain if the differences in results of the HIVTSQ were clinically significant. Furthermore, the PBAC noted the results of the SF-12 health surveys in FLAIR and ATLAS did not report any statistically significant differences in either the mental or physical domains between long acting injectable therapy and daily oral ART. Therefore, the PBAC considered that although for some patients the option of a long acting injectable 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 quality of life.
- 7.8 The PBAC considered that the evidence presented supported a conclusion that overall, CAB LA + RPV LA is likely to be of non-inferior comparative safety to daily oral ART therapy. The PBAC also noted the Advisory Committee for Medicines (ACM) noted a number of cases of hepatitis disease flare in trial patients with HIV and hepatitis B/C co-infection and advised that these occurrences in the clinical trials should be noted in the Product Information.

- 7.9 The PBAC considered the CBA presented to support the requested price premium was inappropriate and uninformative for decision making. The PBAC considered the discrete choice experiment (DCE) based WTP study used to inform the CBA was flawed for the reasons outlined by the ESC in paragraph 6.48. Furthermore, the PBAC noted it did not include any variables to assess benefits around quality of life, anxiety or stigma and given these were the primary claimed advantages of CAB LA + RPV LA, considered the economic analysis did not provide a basis upon which to consider the potential value of any claimed advantages over daily oral therapy.
- 7.10 Given the clinical evidence did not substantively establish that a CAB LA + RPV LA provides the claimed benefits in terms of quality of life improvements, reduced anxiety or stigma, the PBAC considered that based on its assessment that CAB LA + RPV LA is of non-inferior comparative efficacy for the treatment of HIV infection and also of non-inferior comparative safety to daily oral ART regimens, that the most appropriate basis for a listing would be if it were cost minimised to the least costly alternative.
- 7.11 The PBAC considered that the utilisation of CAB LA + RPV LA was likely overestimated, and considered the results of the WTP study did not indicate a strong preference for the long acting injectable over current oral ART and therefore agreed uptake of CAB LA + RPV LA was likely to be lower than expected. The Committee agreed with the Pre-PBAC Response and considered that use of oral CAB for periods of planned missed doses was likely to be very low.
- 7.12 The PBAC considered an early re-entry pathway would be acceptable if the resubmission accepted listing on a cost minimisation basis to the least costly comparator, with appropriate MBS administration costs (see paragraph 6.47) and presented an economic analysis to that effect. The resubmission must be lodged by week 7 of the current PBAC cycle or the next cycle. If these terms are not acceptable to the sponsor, a standard re-entry pathway is available. The PBAC considered that any such re-submission where listing on a cost minimisation basis is not accepted should be supported by a full cost utility analysis.
- 7.13 The PBAC noted that this submission is eligible for an Independent Review.

**Outcome:**

Rejected

## **8 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.

## **9 Sponsor's Comment**

ViiV Healthcare maintains there is strong evidence to support the claim that CAB LA + RPV LA (Cabenuva) provides additional benefit compared with daily oral therapy for many people living with HIV (PLHIV) in terms of quality of life, reducing the burden of the daily reminder of HIV, reduced anxiety or worry associated with adherence to daily oral therapy or fear of unintentional disclosure of HIV status. It was important to see consumer comments reinforcing the requirement to support PLHIV and these unmet needs through access to longer acting therapy. ViiV will continue to work with the PBAC to ensure this innovative treatment option becomes available to Australians living with HIV.

ViiV Healthcare are disappointed the committee felt the DCE was flawed. ViiV disagrees with the PBAC statement that 'benefits such as stigma and associated reminder of disease, fear of unintentional disclosure, patient preference were not assessed appropriately within the experiment and the model'. On the contrary, these benefits were assessed in the experiment because they are benefits associated with the change in mode / frequency to an injection and are therefore captured in the preference for this mode and shown in the mode constant in the model. It is the point of the experiment to determine patient preferences and quantify them.