PRESS RELEASE

For media and investors only

ViiV Healthcare presents data for long-acting cabotegravir and rilpivirine for the treatment of HIV showing continued virologic suppression to 96 weeks

Long-term efficacy and safety data from the phase IIIb ATLAS-2M study reinforce the therapeutic potential of long-acting cabotegravir and rilpivirine

---

London, 6 March 2020 – ViiV Healthcare, the global specialist HIV company majority owned by GlaxoSmithKline plc ("GSK"), with Pfizer Inc. and Shionogi Limited as shareholders, today presented positive long-term data from its global phase IIIb ATLAS-2M study of the first complete, long-acting regimen of cabotegravir and rilpivirine for the treatment of HIV. Week 96 findings reinforce the primary (proportion of participants with plasma HIV-1 RNA ≥50 c/mL at Week 48 (Snapshot, ITT-E)), and secondary endpoints (proportion of participants with plasma HIV-1 RNA ≥50 or <50 c/mL at Week 96 (Snapshot, ITT-E)), initially assessed at Week 48, and now showing efficacy of both monthly dosing and every 2-month dosing over the long-term in virologically suppressed adults with HIV-1.[1] These data were presented at the virtual Conference on Retroviruses and Opportunistic Infections (CROI 2021). The every 2-month dosing regimen of cabotegravir and rilpivirine is under investigation and not approved in the US or Canada.

Hans Jäeger, MD, former Medical Director of MVZ Karlsplatz, HIV Research and Clinical Care Centre, Munich, and investigator for the ATLAS-2M study, said, "The ATLAS-2M 96-week data reinforces the therapeutic potential of this long-acting regimen for the treatment of HIV. It provides an option that could change the treatment experience for some people living with HIV by removing the need for daily pills for the treatment of HIV. Taking a pill every day can come as an unwelcome daily reminder of their HIV status or it may add to their fears that their HIV status might be disclosed by someone seeing their HIV medication. This regimen can enable people living with HIV to reduce the days they receive treatment from 365 to 12 or 6 per year, representing a paradigm shift in their experience of HIV treatment."

Kimberly Smith, M.D., Head of Research & Development at ViiV Healthcare, said, "At ViiV Healthcare, our research and development is underpinned by a commitment to innovation and a desire to make a difference to the lives of people living with HIV. Long-acting cabotegravir and rilpivirine is a first-of-its-kind regimen that removes the need for daily therapies after the initiation phase. These long-term data confirm that every 2-month dosing is non-inferior to monthly dosing, which means people living with HIV who are virologically suppressed can reduce the number of days they take treatment to 6 times per year, allowing more time between doses with this regimen."

ATLAS-2M met its primary endpoint at Week 48, demonstrating that the efficacy of long-acting cabotegravir and rilpivirine dosed every 2-months (every eight weeks) was non-inferior to monthly dosing (every four weeks). Week 48 primary endpoint (proportion of participants with plasma HIV-1 RNA ≥50 c/mL) results showed every 2-month dosing (9/522 [1.7%]) and monthly dosing (5/523 [1.0%]) were similarly effective (adjusted difference: 0.8%, 95% confidence interval [CI]: -0.6, 2.2).[2] Week 96 findings reinforced the primary endpoint: the efficacy of every 2-month dosing was non-inferior to monthly dosing of long-acting cabotegravir and rilpivirine, with 2.1% (11/522) and 1.1% (6/523) of participants, respectively, having HIV-1 RNA ≥50 c/mL (adjusted difference: 1.0%, 95% CI: -0.6-2.5).[1] The 96-week ATLAS-2M study secondary endpoint, showed that rates of virologic suppression were similar between the two arms, with 91.0% (475/522) of participants in the every 2-month dosing arm and 90.2% (472/523) in the monthly dosing arm achieving HIV-1 RNA <50 c/mL (adjusted difference: 0.8%, 95% CI: -2.8-4.3).[1]

Week 96 findings reported confirmed virologic failures (CVFs), defined as two consecutive viral loads ≥200 c/mL, in 1.7% (9/522) of participants in the every 2-month dosing arm and 0.4% (2/523) in the monthly dosing arm.[1] The rate of CVF was low overall [1% (11/1,045], with only one participant in the every 2-month dosing arm meeting the criterion in the second year of therapy. This patient developed a rilpivirine resistance-associated mutation (RAM) Y181C, and no integrase inhibitor (INSTI) RAMS.[1]

Safety profiles were comparable between the two treatment arms, with no new safety signals identified since the 48-week analysis.[1,2] Injection site reactions (ISRs) were the most common adverse events (AE) (16% [74/473] in the every 2-month dosing arm and 12% [54/468] in the monthly dosing arm), with one leading to withdrawal between weeks 48 and 96.[1] Most ISRs (99%)

were mild or moderate and self-resolving, with a median duration of three days. Over the entire 96 weeks, in the every 2-month dosing arm, 1% (7/522) of participants discontinued due to ISRs, vs 2% (11/523) in the monthly dosing arm.[1]

The most common non-injection site reactions drug-related AEs were pyrexia and fatigue. Grade ≥ 3 adverse events were seen in 11% (57/522) of participants in the every 2-month arm and 12% (65/523) in the once monthly arm. Adverse events leading to withdrawal were seen in 3% (18/522) of participants in the every 2-month arm and 4% (19/523) in the monthly arm. [1]

ViiV Healthcare's cabotegravir in combination with Janssen's rilpivirine was co-developed as part of a collaboration with Janssen and builds on ViiV Healthcare's industry-leading portfolio that is centered on delivering innovative medicines for the HIV community.

The long-acting regimen of cabotegravir and rilpivirine is licensed as a once-monthly treatment in Canada and USA under the brand name Cabenuva.[3] A supplemental New Drug Application has been submitted to the US Food and Drug Administration for expanding the use of Cabenuva as an HIV treatment to include use of every 2-month dosing in the US. Cabenuva is listed in Australia for both monthly and every 2-month dosing. The long-acting regimen has also received Marketing Authorisation under the brand names Vocabria (cabotegravir) and Rekambys (rilpivirine) in Europe for both monthly dosing and every 2-month dosing. Further regulatory applications have been submitted and are being reviewed by other regulatory bodies worldwide.

-END-

Notes to editor

About cabotegravir

Cabotegravir is an integrase strand transfer inhibitor (INSTI) developed by ViiV Healthcare for the treatment of HIV-1 in virologically suppressed adults. It is being evaluated in combination with injectable rilpivirine as a long-acting formulation.

INSTIs inhibit HIV replication by preventing the viral DNA from integrating into the genetic material of human immune cells (T-cells). This step is essential in the HIV replication cycle and is also responsible for establishing chronic infection.

About rilpivirine

The oral formulation of rilpivirine is also authorised for the treatment of HIV-1 infection in combination with other antiretroviral agents in antiretroviral treatment-naïve patients 12 years of age and older and weighing at least 35 kg with a viral load ≤ 100,000 HIV RNA copies/mL.

Rilpivirine long-acting is a prolonged-release suspension for IM injection being developed by Janssen Sciences Ireland UC, one of the Janssen Pharmaceutical Companies of Johnson & Johnson.

Rilpivirine is a non-nucleoside reverse transciptase inhibitor (NNRTI) that works by interfering with an enzyme called reverse transcriptase, which in turn stops the virus from multiplying.

Administration and dosing of cabotegravir and rilpivirine

Cabotegravir injection used in combination with rilpivirine injection will be the first complete long-acting regimen dosed monthly or every 2-months, for virologically suppressed people living with HIV-1. Cabotegravir and rilpivirine injections are administered as two gluteal intramuscular (IM) injections by a healthcare professional at the same appointment. Prior to the initiation of the injections, cabotegravir and rilpivirine oral tablets are taken for approximately one month (at least 28 days) to assess tolerability to the medicines.

Important Safety Information for Cabenuva (cabotegravir 200mg/mL; rilpivirine 300 mg/mL) extended-release injectable suspensions

Cabenuva is indicated as a complete regimen for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.

CONTRAINDICATIONS

- Do not use Cabenuva in patients with previous hypersensitivity reaction to cabotegravir or rilpivirine.
- Do not use Cabenuva in patients receiving carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifabutin, rifampin, rifapentine, systemic dexamethasone (>1 dose), and St John's wort.

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions:

- Hypersensitivity reactions, including cases of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), have been reported during postmarketing experience with rilpivirine-containing regimens. While some skin reactions were accompanied by constitutional symptoms such as fever, other skin reactions were associated with organ dysfunctions, including elevations in hepatic serum biochemistries.
- Serious or severe hypersensitivity reactions have been reported in association with other integrase inhibitors and could occur with Cabenuva.
- Discontinue Cabenuva immediately if signs or symptoms of hypersensitivity reactions develop. Clinical status, including liver transaminases, should be monitored and appropriate therapy initiated. Prescribe the oral lead-in prior to administration of Cabenuva to help identify patients who may be at risk of a hypersensitivity reaction.

Post-Injection Reactions:

- Serious post-injection reactions (reported in less than 1% of subjects) were reported within minutes after the injection of rilpivirine, including dyspnea, agitation, abdominal cramping, flushing, sweating, oral numbness, and changes in blood pressure. These events may have been associated with inadvertent (partial) intravenous administration and began to resolve within a few minutes after the injection.
- Carefully follow the Instructions for Use when preparing and administering Cabenuva to avoid accidental intravenous administration. Observe patients briefly (approximately 10 minutes) after the injection. If a post-injection reaction occurs, monitor and treat as clinically indicated.

Hepatotoxicity:

- Hepatotoxicity has been reported in patients receiving cabotegravir or rilpivirine with or without known pre-existing hepatic disease or identifiable risk factors.
- Patients with underlying liver disease or marked elevations in transaminases prior to treatment may be at increased risk for worsening or development of transaminase elevations.
- Monitoring of liver chemistries is recommended and treatment with Cabenuva should be discontinued if hepatotoxicity is suspected.

Depressive Disorders:

- Depressive disorders (including depressed mood, depression, major depression, mood altered, mood swings, dysphoria, negative thoughts, suicidal ideation or attempt) have been reported with Cabenuva or the individual products.
- Promptly evaluate patients with depressive symptoms.

Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions:

- The concomitant use of Cabenuva and other drugs may result in known or potentially significant drug interactions (see Contraindications and Drug Interactions).
- Rilpivirine doses 3 and 12 times higher than the recommended oral dosage can prolong the QTc interval. Cabenuva should be used with caution in combination with drugs with a known risk of Torsade de Pointes.

Long-Acting Properties and Potential Associated Risks with Cabenuva:

- Residual concentrations of cabotegravir and rilpivirine may remain in the systemic circulation of patients for prolonged periods (up to 12 months or longer). Select appropriate patients who agree to the required monthly injection dosing schedule because non-adherence to monthly injections or missed doses could lead to loss of virologic response and development of resistance.
- To minimize the potential risk of developing viral resistance, it is essential to initiate an alternative, fully suppressive antiretroviral regimen no later than 1 month after the final injection doses of Cabenuva. If virologic failure is suspected, switch the patient to an alternative regimen as soon as possible.

ADVERSE REACTIONS

The most common adverse reactions (incidence ≥2%, all grades) with Cabenuva were injection site reactions, pyrexia, fatigue, headache, musculoskeletal pain, nausea, sleep disorders, dizziness, and rash.

DRUG INTERACTIONS

- Refer to the applicable full Prescribing Information for important drug interactions with Cabenuva, Vocabria, or rilpivirine.

- Because Cabenuva is a complete regimen, coadministration with other antiretroviral medications for the treatment of HIV-1 infection is not recommended.
- Drugs that are strong inducers of UGT1A1 or 1A9 are expected to decrease the plasma concentrations of cabotegravir. Drugs that induce or inhibit CYP3A may affect the plasma concentrations of rilpivirine.
- Cabenuva should be used with caution in combination with drugs with a known risk of Torsade de Pointes.

USE IN SPECIFIC POPULATIONS

- **Pregnancy:** There are insufficient human data on the use of Cabenuva during pregnancy to adequately assess a drug-associated risk for birth defects and miscarriage. Discuss the benefit-risk of using Cabenuva during pregnancy and conception and consider that cabotegravir and rilpivirine are detected in systemic circulation for up to 12 months or longer after discontinuing injections of Cabenuva. An Antiretroviral Pregnancy Registry has been established.
- **Lactation:** The CDC recommends that HIV-1–infected mothers in the United States not breastfeed their infants to avoid risking postnatal transmission of HIV-1 infection. Breastfeeding is also not recommended due to the potential for developing viral resistance in HIV-positive infants, adverse reactions in a breastfed infant, and detectable cabotegravir and rilpivirine concentrations in systemic circulation for up to 12 months or longer after discontinuing injections of Cabenuva.

Please see full Prescribing Information.

European Important Safety Information (ISI)

Vocabria ISI

The following Important Safety Information is based on the Summary of Product Characteristics for Vocabria. Please consult the full Summary of Product Characteristics for all the safety information. Vocabria (cabotegravir) injection is indicated, in combination with rilpivirine injection, for the treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class

Vocabria injection is indicated for the treatment of HIV-1 in combination with rilpivirine injection, therefore, the prescribing information for rilpivirine injection should be consulted for recommended dosing.

Vocabria tablets are indicated in combination with rilpivirine tablets for the short-term treatment of Human Immunodeficiency Virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA <50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the NNRTI and INI class for:

- oral lead in to assess tolerability of Vocabria and rilpivirine prior to administration of long acting Vocabria injection plus long acting rilpivirine injection.
- oral therapy for adults who will miss planned dosing with Vocabria injection plus rilpivirine injection.

Vocabria tablets are only indicated for treatment of HIV-1 in combination with rilpivirine tablets, therefore, the prescribing information for Edurant tablets should also be consulted for recommended dosing.

Prior to starting Vocabria injection, healthcare professionals should have carefully selected patients who agree to the required injection schedule and counsel patients about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance with missed doses.

Following discontinuation of Vocabria and rilpivirine injection, it is essential to adopt an alternative, fully suppressive antiretroviral regimen no later than one month after the final injection of Vocabria when dosed monthly and no later than two months after the final injection of Vocabria when dosed every 2 months.

Elderly (≥65 years of age): No dose adjustment is required in elderly patients. There are limited data available on the use of cabotegravir in patients aged 65 years and over.

Paediatrics (<18 years of age): The safety and efficacy of Vocabria in children and adolescents aged under 18 years have not been established. No data are available.

Contraindications

Hypersensitivity to cabotegravir or rilpivirine or to any of the excipients.

Concomitant use with: rifampicin, rifapentine, carbamazepine, oxcarbazepine, phenytoin or phenobarbital.

Special Warnings and Precautions for Use

Vocabria injection

Risk of resistance following treatment discontinuation

To minimise the risk of developing viral resistance it is essential to adopt an alternative, fully suppressive antiretroviral regimen no later than one month after the final injection of Vocabria when dosed monthly and no later than two months after the final injection of Vocabria when dosed every 2 months.

Residual concentrations of cabotegravir may remain in the systemic circulation of patients for prolonged periods (up to 12 months or longer), therefore, physicians should take the prolonged release characteristics of Vocabria injection into consideration when the medicinal product is discontinued.

If virologic failure is suspected, an alternative regimen should be adopted as soon as possible.

Baseline factors associated with virological failure

Before starting the regimen, it should be taken into account that multivariable analyses indicate that a combination of at least 2 of the following baseline factors may be associated with an increased risk of virological failure: archived rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI ≥30 kg/m^2. In patients with an incomplete or uncertain treatment history without pre-treatment resistance analyses, caution is warranted in the presence of either BMI ≥30 kg/m^2 or HIV-1 A6/A1 subtype.

Hypersensitivity reactions

Hypersensitivity reactions have been reported in association with other integrase inhibitors. These reactions were characterised by rash, constitutional findings and sometimes organ dysfunction, including liver injury. While no such reactions have been observed to date in association with Vocabria, physicians should remain vigilant and should discontinue Vocabria and other suspected medicinal products immediately, should signs or symptoms of hypersensitivity develop (including, but not limited to, severe rash, or rash accompanied by fever, general malaise, fatigue, muscle or joint aches, blisters, oral lesions, conjunctivitis, facial oedema, hepatitis, eosinophilia or angioedema). Clinical status, including liver aminotransferases should be monitored and appropriate

therapy initiated. Administration of oral lead-in is recommended to help identify patients who may be at risk of a hypersensitivity reaction.

Hepatotoxicity

Hepatotoxicity has been reported in a limited number of patients receiving Vocabria with or without known pre-existing hepatic disease.

Monitoring of liver chemistries is recommended and treatment with Vocabria should be discontinued if hepatotoxicity is suspected.

HBV/HCV co-infection

Patients with hepatitis B co-infection were excluded from studies with Vocabria. It is not recommended to initiate Vocabria in patients with hepatitis B co-infection. Physicians should refer to current treatment guidelines for the management of HIV infection in patients co-infected with hepatitis B virus.

Limited data is available in patients with hepatitis C co-infection. Monitoring of liver function is recommended in patients with hepatitis C co-infection.

Interactions with medicinal products

Caution should be given to prescribing Vocabria injection and tablets with medicinal products that may reduce its exposure.

Concomitant use of Vocabria injection with rifabutin is not recommended.

Polyvalent cation containing antacids are recommended to be taken at least 2 hours before and 4 hours after taking Vocabria tablets.

Effect of other medicinal products on the pharmacokinetics of cabotegravir

Cabotegravir is primarily metabolised by uridine diphosphate glucuronosyl transferase (UGT) 1A1 and to a lesser extent by UGT1A9. Medicinal products which are strong inducers of UGT1A1 or UGT1A9 are expected to decrease cabotegravir plasma concentrations leading to lack of efficacy.

Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions (ARs) from monthly dosing studies were injection site reactions (up to 84%), headache (up to 12%) and pyrexia* (10%).

The most frequently reported ARs from ATLAS-2M every 2-month dosing were injection site reactions (76%), headache (7%) and pyrexia* (7%).

*Pyrexia includes the following: feeling hot, body temperature increased.

Description of selected adverse reactions

Local injection site reactions (ISRs)

Up to 1% of subjects discontinued treatment with Vocabria plus rilpivirine because of ISRs. When dosing monthly, up to 84% of subjects reported injection site reactions; out of 30393 injections, 6815 ISRs were reported. When dosing every 2 months, 76% of patients reported injection site reactions; out of 8470 injections, 2507 ISRs were reported.

The severity of reactions was generally mild (Grade 1, 70%-75% of subjects) or moderate (Grade 2, 27%-36% of subjects). 3-4% of subjects experienced severe (Grade 3) ISRs. The median duration of overall ISR events was 3 days. The percentage of subjects reporting ISRs decreased over time.

Weight increased

At the Week 48 time point, subjects in studies FLAIR and ATLAS, who received Vocabria plus rilpivirine gained a median of 1.5 kg in weight subjects continuing on their current antiretroviral therapy (CAR) gained a median of 1.0 kg (pooled analysis). In the individual studies FLAIR and ATLAS, the median weight gains in the Vocabria plus rilpivirine arms were 1.3 kg and 1.8 kg respectively, compared to 1.5 kg and 0.3 kg in the CAR arms.

At the 48 week timepoint, in ATLAS-2M the median weight gain in both the monthly and 2-monthly CAB+RPV dosing arms was 1.0 kg.

Pregnancy

There are a limited amount of data from the use of cabotegravir in pregnant women. The effect of Vocabria on human pregnancy is unknown.

Cabotegravir was not teratogenic when studied in pregnant rats and rabbits but, exposures higher than the therapeutic dose showed reproductive toxicity in animals. The relevance to human pregnancy is unknown.

Vocabria injection is not recommended during pregnancy unless the expected benefit justifies the potential risk to the foetus.

Cabotegravir has been detected in systemic circulation for up to 12 months or longer after an injection

Breast-feeding

It is expected that cabotegravir will be secreted into human milk based on animal data, although this has not been confirmed in humans. Cabotegravir may be present in human milk for up to 12 months or longer after the last cabotegravir injection.

It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Rekambys (rilpivirine injection) ISI

The following Important Safety Information is based on the Summary of Product Characteristics for Rekambys (rilpivirine injection). Please consult the full Summary of Product Characteristics for all the safety information.

Rekambys is indicated, in combination with cabotegravir injection, for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with, agents of the NNRTI and INI class

Rekambys should always be co-administered with a cabotegravir injection. The prescribing information for cabotegravir injection should be consulted for recommended dosing.

Prior to the initiation of Rekambys, rilpivirine oral tablets, together with cabotegravir oral tablets, should be taken for approximately 1 month (at least 28 days) to assess tolerability to rilpivirine and cabotegravir. One rilpivirine 25-mg tablet should be taken with a meal with one cabotegravir 30-mg tablet once daily.

Prior to starting Rekambys, the healthcare professional should carefully select patients who agree to the required injection schedule and counsel patients about the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance associated with missed doses.

Following discontinuation of Rekambys in combination with cabotegravir injection, it is essential to adopt an alternative, fully suppressive antiretroviral regimen no later than one month after the last every 1 month injection of Rekambys or two months after the last every 2 months injection of Rekambys.

Elderly: There is limited information regarding the use of Rekambys in patients > 65 years of age. No dose adjustment of Rekambys is required in older patients.

Paediatric Patients: The safety and efficacy of Rekambys in children and adolescents aged < 18 years have not been established. No data are available.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Rekambys must not be co-administered with the following medicinal products, which may result in loss of therapeutic effect of Rekambys:

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifabutin, rifampicin, rifapentine
- the systemic glucocorticoid dexamethasone, except as a single dose treatment
- St John's wort (Hypericum perforatum).

Special Warnings and Precautions for Use

Risk of resistance following treatment discontinuation

To minimise the risk of developing viral resistance it is essential to adopt an alternative, fully suppressive antiretroviral regimen no later than one month after the last every 1 month injection of Rekambys or two months after the last every 2 months injection of Rekambys.

Long-acting properties of rilpivirine injection

Residual concentrations of rilpivirine may remain in the systemic circulation of patients for prolonged periods (up to 4 years in some patients) and should be considered upon discontinuation of Rekambys.

Baseline factors associated with virological failure

Before starting the regimen, it should be taken into account that multivariable analyses indicate that a combination of at least 2 of the following baseline factors may be associated with an increased risk of virological failure: archived rilpivirine resistance mutations, HIV-1 subtype A6/A1, or BMI ≥30 kg/m^2. In patients with an incomplete or uncertain treatment history without pre-treatment resistance analyses, caution is warranted in the presence of BMI ≥30 kg/m^2 and/or HIV-1 subtype A6/A1.

Post-injection reactions

Partial intravenous administration may result in AEs due to temporarily high plasma concentrations. In clinical studies, serious post-injection reactions were reported within minutes after the injection of rilpivirine, including dyspnoea, agitation, abdominal cramping, flushing, sweating, oral numbness, and changes in blood pressure. These events were very rare and began to resolve within a few minutes after the injection.

Carefully follow the Instructions for Use when preparing and administering Rekambys to avoid accidental intravenous administration. Observe patients briefly (approximately 10 minutes) after the injection. If a patient experiences a post-injection reaction, monitor and treat as clinically indicated.

Cardiovascular

Rekambys should be used with caution when co-administered with a medicinal product with a known risk of Torsade de Pointes. At supra-therapeutic doses (75 and 300 mg once daily), oral rilpivirine has been associated with prolongation of the QTc interval of the electrocardiogram (ECG). Oral rilpivirine at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc. Plasma rilpivirine concentrations after Rekambys injections are comparable to those during such oral rilpivirine therapy.

HBV/HCV co-infection

Patients with hepatitis B co-infection were excluded from studies with Rekambys. It is not recommended to initiate Rekambys in patients with hepatitis B co-infection. In patients co-infected with hepatitis B receiving oral rilpivirine, the incidence of hepatic enzyme elevation was higher than in patients receiving oral rilpivirine who were not hepatitis B co-infected. Physicians should refer to current treatment guidelines for the management of HIV infection in patients co-infected with hepatitis B virus.

Limited data is available in patients with hepatitis C co-infection. In patients co-infected with hepatitis C receiving oral rilpivirine, the incidence of hepatic enzyme elevation was higher than in patients receiving oral rilpivirine who were not hepatitis C co-infected. The pharmacokinetic exposure of oral and injectable rilpivirine in co-infected patients was comparable to that in patients without hepatitis C co-infection. Monitoring of liver function is recommended in patients with hepatitis C co-infection.

Interactions with other medicinal products

Rekambys should not be administered with other antiretroviral medicinal products, except for cabotegravir injection for the treatment of HIV-1 infection.

Pregnancy

There are limited data of Rekambys in pregnant women. Rekambys is not recommended during pregnancy unless the expected benefit justifies the potential risk. Lower exposures of oral rilpivirine were observed when rilpivirine 25 mg once daily was taken during pregnancy. In the Phase 3 studies with oral rilpivirine, lower rilpivirine exposure, similar to that seen during pregnancy, has been associated with an increased risk of virological failure, therefore viral load should be monitored closely. Alternatively, switching to another ART regimen could be considered.

Undesirable effects

The most frequently reported ARs from every 1 month dosing studies were injection site reactions (up to 84%), headache (up to 12%) and pyrexia (10%).

The most frequently reported ARs from every 2 months dosing were injection site reactions (76%), headache (7%) and pyrexia (7%).

Tabulated list of adverse reactions is available in the full information leaflet.

Description of selected adverse reactions

Local Injection Site Reactions (ISRs)

Up to 1% of subjects discontinued treatment with rilpivirine and cabotegravir injections because of ISRs. When dosing every 1 month in ATLAS, FLAIR, and ATLAS-2M (Q4W arm), up to 84% of subjects reported injections site reactions; out of 30393 injections, 6815 ISRs were reported. When dosing every 2 months in ATLAS-2M (Q8W arm), 76% of subjects reported injection site reactions; out of 8470 injections, 2507 ISRs were reported.

Injection site reactions were generally mild (Grade 1, 70%-75% of subjects) or moderate (Grade 2, 27%-36% of subjects). 3-4% of subjects experienced severe (Grade 3) ISRs. The median duration of ISR events was 3 days. The percentage of subjects reporting ISRs decreased over time.

Weight increased

At the Week 48 time point, subjects in Phase 3 Studies FLAIR and ATLAS, who received rilpivirine plus cabotegravir gained a median of 1.5 kg in weight; subjects continuing on their current antiretroviral regimen (CAR) group gained a median of 1.0 kg (pooled analysis). In the individual studies FLAIR and

ATLAS, the median weight gains in the rilpivirine plus cabotegravir arms were 1.3 kg and 1.8 kg respectively, compared to 1.5 kg and 0.3 kg in the CAR arms.

At the 48 week timepoint, in ATLAS-2M the median weight gain in both the monthly and every 2 months rilpivirine + cabotegravir dosing arms was 1.0 kg.

Pregnancy

The effect of Rekambys on human pregnancy is unknown. A moderate amount of data with oral rilpivirine in pregnant women (between 300-1000 pregnancy outcomes) indicate no malformative or foetal/neonatal toxicity of rilpivirine. A study of 19 pregnant women treated with oral rilpivirine in combination with a background regimen during the second and third trimesters, and postpartum, showed lower exposures of oral rilpivirine during pregnancy, therefore viral load should be monitored closely if Rekambys is used during pregnancy.

Animal studies do not indicate reproductive toxicity. Rekambys is not recommended during pregnancy unless the expected benefit justifies the potential risk.

An alternative oral regimen should be considered in line with current treatment guidelines. After discontinuation of Rekambys, rilpivirine may remain in systemic circulation for up to 4 years in some patients.

Breast-feeding

It is expected that rilpivirine will be secreted into human milk based on animal data, although this has not been confirmed in humans. Rilpivirine may be present in human milk for up to 4 years in some patients after discontinuation of Rekambys.

It is recommended that HIV infected women do not breast-feed their infants under any circumstances in order to avoid transmission of HIV.

Edurant (rilpivirine tablet) ISI

Please refer to the full Summary of Product Characteristics for full prescribing information for Edurant ® (rilpivirine): https://www.medicines.org.uk/emc/product/4968/smpc

Important Safety Information (ISI)

The following Important Safety Information is based on the Summary of Product Characteristics for Edurant ® Please consult the full Summary of Product Characteristics for all the safety information.

Edurant, in combination with other antiretroviral medicinal products, is indicated for the treatment of human immunodeficiency virus type 1 (HIV-1) infection in antiretroviral treatment-naïve patients 12 years of age and older with a viral load ≤ 100,000 HIV-1 RNA copies/ml. Genotypic resistance testing should guide the use of Edurant.

The recommended dose of Edurant is one 25 mg tablet taken once daily. EDURANT must be taken with a meal.

Elderly: There is limited information regarding the use of Edurant in patients > 65 years of age. No dose adjustment of Edurant is required in older patients. Edurant should be used with caution in this population.

Paediatric population: The safety and efficacy of Edurant in children aged < 12 years have not yet been established. No data are available.

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Edurant should not be co-administered with the following medicinal products, as significant decreases in rilpivirine plasma concentrations may occur (due to CYP3A enzyme induction or gastric pH increase), which may result in loss of therapeutic effect of Edurant:

- the anticonvulsants carbamazepine, oxcarbazepine, phenobarbital, phenytoin
- the antimycobacterials rifampicin, rifapentine
- proton pump inhibitors, such as omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole
- the systemic glucocorticoid dexamethasone, except as a single dose treatment
- St John's wort (*Hypericum perforatum*).

Special Warnings and Precautions for Use

While effective viral suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.

<u>Virologic failure and development of resistance</u>

Edurant has not been evaluated in patients with previous virologic failure to any other antiretroviral therapy.

In the pooled efficacy analysis from the Phase III trials in adults through 96 weeks, patients treated with rilpivirine with a baseline viral load > 100,000 HIV-1 RNA copies/ml had a greater risk of virologic failure (18.2% with rilpivirine versus 7.9% with efavirenz) compared to patients with a baseline viral load ≤ 100,000 HIV-1 RNA copies/ml (5.7% with rilpivirine versus 3.6% with efavirenz). The greater risk of virologic failure for patients in the rilpivirine arm was observed in the first 48 weeks of these trials. Patients with a baseline viral load > 100,000 HIV-1 RNA copies/ml who experienced virologic failure exhibited a higher rate of treatment-emergent resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class. More patients who failed virologically on rilpivirine than who failed virologically on efavirenz developed lamivudine/emtricitabine associated resistance.
As with other antiretroviral medicinal products, resistance testing should guide the use of rilpivirine.

Cardiovascular

At supra-therapeutic doses (75 and 300 mg once daily), rilpivirine has been associated with prolongation of the QTc interval of the electrocardiogram (ECG). Edurant at the recommended dose of 25 mg once daily is not associated with a clinically relevant effect on QTc. Edurant should be used with caution when co-administered with medicinal products with a known risk of Torsade de Pointes.

Immune reactivation syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of CART, an inflammatory reaction to asymptomatic or residual opportunistic pathogens may arise and cause serious clinical conditions or aggravation of symptoms. Typically, such reactions have been observed within the first weeks or months of initiation of CART. Relevant examples are cytomegalovirus retinitis, generalised and/or focal mycobacterial infections and *Pneumocystis jiroveci* pneumonia. Any inflammatory symptoms should be evaluated and treatment instituted when necessary.
Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported to occur in the setting of immune reactivation; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Pregnancy

Edurant should be used during pregnancy only if the potential benefit justifies the potential risk. Lower exposures of rilpivirine were observed when rilpivirine 25 mg once daily was taken during pregnancy. In the Phase III studies, lower rilpivirine exposure, similar to that seen during pregnancy, has been

associated with an increased risk of virological failure, therefore viral load should be monitored closely. Alternatively, switching to another ART regimen could be considered.

Important information about some of the ingredients of Edurant

Edurant contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Undesirable effects

During the clinical development program (1,368 patients in the Phase III controlled trials TMC278-C209 (ECHO) and TMC278-C215 (THRIVE)), 55.7% of subjects experienced at least one adverse drug reaction. The most frequently reported adverse drug reactions (ADRs) (≥ 2%) that were at least of moderate intensity were depression (4.1%), headache (3.5%), insomnia (3.5%), rash (2.3%), and abdominal pain (2.0%). The most frequent serious treatment-related ADRs were reported in 7 (1.0%) patients receiving rilpivirine. The median duration of exposure for patients in the rilpivirine arm and efavirenz arm was 104.3 and 104.1 weeks, respectively. Most ADRs occurred in the first 48 weeks of treatment.

Selected treatment emergent clinical laboratory abnormalities (grade 3 or grade 4), considered as ADRs, reported in Edurant treated patients were increased pancreatic amylase (3.8%), increased AST (2.3%), increased ALT (1.6%), increased LDL cholesterol (fasted, 1.5%), decreased white blood cell count (1.2%), increased lipase (0.9%), increased bilirubin (0.7%), increased triglycerides (fasted, 0.6%), decreased haemoglobin (0.1%), decreased platelet count (0.1%), and increased total cholesterol (fasted, 0.1%).

Tabulated list of adverse reactions is available in the full information leaflet.

Description of selected adverse reactions

Immune reactivation syndrome

In HIV infected patients with severe immune deficiency at the time of initiation of combination antiretroviral therapy (CART), an inflammatory reaction to asymptomatic or residual opportunistic infections may arise. Autoimmune disorders (such as Graves' disease and autoimmune hepatitis) have also been reported; however, the reported time to onset is more variable and these events can occur many months after initiation of treatment.

Breast-feeding

It is not known whether rilpivirine is excreted in human milk. Rilpivirine is excreted in the milk of rats. Because of both the potential for HIV transmission and the potential for adverse reactions in breastfed infants, mothers should be instructed not to breast-feed if they are receiving rilpivirine.

About ViiV Healthcare

ViiV Healthcare is a global specialist HIV company established in November 2009 by GlaxoSmithKline (LSE: GSK) and Pfizer (NYSE: PFE) dedicated to delivering advances in treatment and care for people living with HIV and for people who are at risk of becoming infected with HIV. Shionogi joined in October 2012. The company's aim is to take a deeper and broader interest in HIV/AIDS than any company has done before and take a new approach to deliver effective and innovative medicines for HIV treatment and prevention, as well as support communities affected by HIV. For more information on the company, its management, portfolio, pipeline and commitment, please visit www.viivhealthcare.com.

About GSK

GSK is a science-led global healthcare company with a special purpose: to help people do more, feel better, live longer. For further information please visit www.gsk.com/about-us.

ViiV Healthcare media enquires:	Sofia Kalish (Global)	+44 (0)7341 079531	(London)
	Audrey Abernathy	+1 919 605 4521	(US)
GSK enquiries:			
Media enquiries:	Simon Steel	+44 (0) 20 8047 5502	(London)
	Tim Foley	+44 (0) 20 8047 5502	(London)
	Kristen Neese	+1 804 217 8147	(Philadelphia)
	Kathleen Quinn	+1 202 603 5003	(Washington DC)
Analyst/Investor enquiries:	James Dodwell	+44 (0) 20 8047 2406	(London)
	Sonya Ghobrial	+44 (0) 7392 784784	(Consumer)
	Jeff McLaughlin	+1 215 751 7002	(Philadelphia)
	Frannie DeFranco	+1 215 751 4855	(Philadelphia)

Cautionary statement regarding forward-looking statements

GSK cautions investors that any forward-looking statements or projections made by GSK, including those made in this announcement, are subject to risks and uncertainties that may cause actual results to differ materially from those projected. Such factors include, but are not limited to, those described under Item 3.D "Risk Factors" in the company's Annual Report on Form 20-F for 2019 and any impacts of the COVID-19 pandemic.

Registered in England & Wales:
No. 3888792

Registered Office:
980 Great West Road
Brentford, Middlesex
TW8 9GS

References

[1] Jaeger H et al. Week 96 efficacy and safety of cabotegravir + rilpivirine every 2 months: ATLAS-2M. Presented at the Conference on Retroviruses and Opportunistic Infections (CROI) Virtual; March 6-10 2021

[2] Overton E et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. The Lancet. 2020;396(10267):1994-2005.

[3] CABENUVA (cabotegravir, rilpivirine) Prescribing Information. US Approval January 2021.