Dolutegravir-Based Regimens Viral Load Decay at Week 4 Could Predict Sustained Viral Suppression at Week 96

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Introduction

The medium and long-term implications of rapid viral load early-phase decay, during integrase inhibitor–based therapy, are not fully understood.

The integrase inhibitor dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors has been evaluated in 3 phase III studies in treatment-naive subjects.

DTG-based regimens (DBRs) achieved non-inferiority in SPRING-2 vs raltegravir (RAL)-based regimens, while superiority was achieved in SINGLE and FLAMINGO vs Atripla® and boosted darunavir (DRV/r)-based regimens, respectively.1-3

This analysis was conducted to assess the predictive value of rapid virological response (RVR) at Week 4 on sustained virological response (SVR) at Week 96 in naive subjects treated with DBRs.

Methods

Post hoc cross-sectional analysis of subjects enrolled in the naive DTG phase III clinical trials, SPRING-2, SINGLE, and FLAMINGO.

RVR and SVR were assessed at Weeks 4 and 96, respectively, based on HIV-1 RNA <50 as determined by FDA Snapshot.

Positive (PPV) and negative (NPV) predictive values were calculated; PPV as the proportion of subjects suppressed at Week 4 who were also suppressed at Week 96, and NPV as the proportion of subjects not suppressed at Week 4 who were also not suppressed at Week 96.

Results

Table 1. PPV and NPV of SVR at Week 96

<table>
<thead>
<tr>
<th>DBR Regimen</th>
<th>Wk 96 SVR</th>
<th>PPV (%)</th>
<th>95% CI</th>
<th>NPV (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTG (N=441)</td>
<td>86 (81-89)</td>
<td>73 (68-77)</td>
<td>31 (24-39)</td>
<td>24 (18-32)</td>
<td></td>
</tr>
<tr>
<td>EFV (N=411)</td>
<td>85 (82-88)</td>
<td>70 (65-75)</td>
<td>35 (29-42)</td>
<td>28 (23-34)</td>
<td></td>
</tr>
<tr>
<td>SPRING-2 (N=412)</td>
<td>84 (81-88)</td>
<td>73 (68-77)</td>
<td>35 (29-41)</td>
<td>28 (23-33)</td>
<td></td>
</tr>
<tr>
<td>RAL (N=242)</td>
<td>85 (82-88)</td>
<td>72 (67-77)</td>
<td>36 (30-43)</td>
<td>29 (24-35)</td>
<td></td>
</tr>
<tr>
<td>DRV/r (N=242)</td>
<td>84 (81-88)</td>
<td>70 (65-75)</td>
<td>35 (29-41)</td>
<td>28 (23-34)</td>
<td></td>
</tr>
</tbody>
</table>

A total of 2139 subjects were analysed, including those receiving DBRs and comparator arms; 1067 subjects received DTG across the 3 studies.

The analysis revealed that 70% of subjects receiving DBRs achieved RVR at Week 4, and 80% attained SVR at Week 96. PPV and NPV of SVR in the DBR study population were 85% (95% CI: 82%-87%) and 29% (95% CI: 24%-34%), respectively (Figure 1).

The PPV of the DBRs was numerically higher than with RAL. The PPVs for DBRs were consistent with or numerically higher than the comparators, correlating with study outcomes at Week 96, which supports the predictive value of undetectability at Week 4.

The analysis suggests that RVR at Week 4 with DBRs is a potential predictor of SVR at Week 96.

In addition, the NPV of the DBRs was also consistently lower and/or comparable with other regimens. RAL in SPRING-2 showed the numerically highest NPV. The implication of NPV in this context needs further investigation.

Overall, DBRs, in the context of the population analyzed, showed the highest level of undetectability at Week 4 that defined the PPV and NPV.

Conclusions

This analysis suggests that RVR at Week 4 with DBRs is a potential predictor of SVR at Week 96.

The NPV of RVR with DTG is numerically lower than with RAL.

Characterization of patients who do not achieve RVR and subsequent undetectability deserves further investigation.

These data may support clinicians to further individualise therapy and monitoring.

Acknowledgements

The study subjects and their caregivers; the study investigators and research staff; colleagues from ViiV Healthcare and GlaxoSmithKline. This study was sponsored by ViiV Healthcare.

References


Tivicay®  dolutegravir 50mg tablets

Prescribing Information

See Summary of Product Characteristics before prescribing

Indication: HIV in >12 years and >40kg as part of combination therapy. Dosing: 50mg once daily with or without food if no proven/ suspected integrase resistance. 50mg twice daily with efavirenz, nevirapine, tipranavir/ritonavir, etravirine (without boosted PI), carbamazepine, oxcarbazepine, phenytoin, phenobarbital, St John’s Wort or rifampicin. Adults with proven/ suspected integrase resistance: 50mg twice daily preferably with food. Elderly: Limited data in 65+ yrs. Caution in severe hepatic impairment.

Contraindications: Hypersensitivity to any ingredient. Co-administration with dofetilide.

Warnings/precautions: Risk of hypersensitivity reactions. Discontinue dolutegravir and other suspect agents immediately if suspected. Risks of osteonecrosis, immune reactivation syndrome. Monitor LFTs in Hepatitis B/C co-infection and ensure effective Hepatitis B therapy. Caution with metformin: monitor renal function and consider metformin dose adjustment. Use with etravirine requires boosted PI or increased dose of dolutegravir. Use with Mg/Al-containing antacids, calcium, multivitamins or iron requires dosage separation. Pregnancy/lactation: Not recommended. Avoid breastfeeding. Side effects: See SPC for full details. Headache, GI disturbance, insomnia, abnormal dreams, depression, dizziness, rash, pruritus, fatigue, elevations of ALT, AST and CPK, arthralgia, myalgia, hypersensitivity, suicidal ideation or suicide attempt. Basic NHS costs: 30 tablets £498.75

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Date of approval: January 2017

Zinc code: UK/DLG/0055/13(9)
Prescribing Information
Triumeq® ▼ dolutegravir 50mg/abacavir 600mg/lamivudine 300mg tablets

See Summary of Product Characteristics before prescribing.

Indication: HIV in over 12 years and > 40kg. Screen for HLA-B*5701 prior to use. Do not use if HLA-B*5701 positive. Dose: one tablet once daily with or without food. Elderly: Limited data in 65+ yrs. Creatinine clearance <50ml/min or moderate/severe hepatic impairment: Not recommended. Monitor closely in mild hepatic impairment.

Contraindications: Hypersensitivity to any ingredient. Co-administration with dofetilide.

Warnings/precautions: Both abacavir and dolutegravir are associated with risk of hypersensitivity reactions (HSR). Do not initiate in HLA-B*5701+ or previous suspected abacavir HSR. Stop Triumeq without delay if HSR suspected. Never reintroduce any dolutegravir- or abacavir-containing product after suspected HSR. Risks of immune reactivation syndrome, osteonecrosis, increased weight, lipids, glucose. Monitor LFTs in Hepatitis B/C co-infection. Inconclusive data on relationship between abacavir and MI; minimise all modifiable CV risk factors (e.g. smoking, hypertension, hyperlipidaemia). Not recommended if dolutegravir required b.d. (with etravirine [without boosted PI], efavirenz, nevirapine, rifampicin, boosted tipranavir, carbamazepine, oxicarbazeptine, phenytin, phenobarbital and St John’s Wort). Use with cladribine not recommended. Use with Mg/Al-containing antacids, calcium, multivitamins or iron requires dosage separation. Caution with metformin: monitor renal function and consider metformin dose adjustment.

Pregnancy/lactation: Not recommended. Avoid breast-feeding. Side effects: See SPC for details. Headache, insomnia, sleep/dream disorders, GI disturbance, fatigue, hypersensitivity, anorexia, depression, dizziness, somnolence, lethargy, malaise, cough, nasal symptoms, rash, pruritus, alopecia, arthralgia, myalgia, asthma, fever, elevations of ALT, AST and CPK, blood dyscrasias, suicidal ideation or suicide attempt, rhabdomyolysis, lactic acidosis, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis. Basic NHS costs: 30 tablets: £798.16 EU/1/14/940/001. MA holder: ViiV Healthcare UK Ltd, 980 Great West Road, Brentford, Middlesex TW8 9GS. Further information is available from Customer Contact Centre, GlaxoSmithKline UK Ltd, Stockley Park West, Uxbridge, Middlesex UB11 1BT.

POM S1A

Triumeq is a registered trademark of the ViiV Healthcare Group of Companies

Date of approval: January 2017

Zinc code: UK/TRIM/0037/14(7)

Adverse events should be reported. For the UK, reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to GlaxoSmithKline on 0800 221 441.

Adverse events should be reported. For Ireland, adverse events should be reported directly to the HPRA; Freepost, Pharmacovigilance Section, Health Products Regulatory Authority, Earlsfort Terrace, Dublin 2, Tel: +353 1 676 4971, medsafety@hpra.ie. Adverse events should also be reported to GlaxoSmithKline on 1800 244 255.
Kivexa® abacavir 600mg/lamivudine 300mg tablets

Prescribing Information

See Summary of Product Characteristics before prescribing


Warnings/precautions: Risk of hypersensitivity reactions (HSR). Do not initiate in HLA-B*5701+ or previous suspected abacavir HSR. Stop Kivexa without delay if HSR suspected. Never re-introduce any abacavir-containing product after suspected HSR. Risks of virological failure, immune reactivation syndrome, osteonecrosis, increased weight, lipids, glucose. Monitor LFTs in Hepatitis B/C co-infection. Inconclusive data on relationship between abacavir and MI; minimise modifiable CV risk factors (e.g. smoking, hypertension, hyperlipidaemia). Use with cladribine, emtricitabine or high doses of co-trimoxazole not recommended.


Basic NHS costs: 30 tablets: £299.41  EU/1/04/298/002. MA holder: ViiV Healthcare UK Ltd, 980 Great West Road, Brentford, Middlesex TW8 9GS. Further information is available from Customer Contact Centre, GlaxoSmithKline UK Ltd, Stockley Park West, Uxbridge, Middlesex UB11 1BT.

POM  S1A

Kivexa is a registered trademark of the ViiV Healthcare Group of Companies

Date of approval:  October  2016        UK/ABC3TC/0008/13(9)

Adverse events should be reported. For the UK, reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to GlaxoSmithKline on 0800 221 441.

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