



WHO position statement on the use of delamanid for multidrug-resistant tuberculosis

Expedited review of the phase III clinical trial data of delamanid added to an optimised
background MDR-TB regimen

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WHO position statement on the use of delamanid for multidrug-resistant tuberculosis

This Position Statement by the World Health Organization (WHO) on the use of delamanid in the treatment of multidrug-resistant tuberculosis (MDR-TB) has been developed in response to the final data from the phase III, multicentre, randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of delamanid (Trial #242-09-213, hereafter referred to as '*Trial 213*'). The final *Trial 213* data were released in late November by the manufacturer (Otsuka Pharmaceutical, Japan) to WHO and to the European Medicines Authority (EMA) in compliance with EMA regulatory requirements. The original trial protocol and subsequent amendments are registered (#NCT0142670) in the US/NIH clinical trials register (<https://clinicaltrials.gov/ct2/show/NCT01424670>).

Background

- In 2014, WHO issued interim policy guidance on the use of delamanid, a novel medicine developed by Otsuka Pharmaceutical for the treatment of MDR-TB. The interim policy guidance stated that 'delamanid may be added to a MDR-TB regimen in adult patients with pulmonary TB' conditional upon: i) careful selection of patients likely to benefit; ii) patient informed consent; iii) adherence to WHO recommendations in designing a longer MDR-TB regimen; iv) close monitoring of clinical treatment response; and v) active TB drug-safety monitoring and management (aDSM).¹
- The WHO interim policy guidance was based on evidence available at the time from a phase IIb trial and an observational study conducted by the manufacturer. This evidence was considered to be of very low certainty based on GRADE evidence assessment,² and the interim policy was subject to review once phase III trial data became available.¹
- In 2016, the delamanid interim policy was extended to children aged 6-17 years following a review of data from a 6-month safety, efficacy, and pharmacokinetic trial of paediatric patients.³ These data were also considered to be of very low certainty based on GRADE evidence assessment.²
- In mid-October 2017, Otsuka Pharmaceutical communicated the final results of *Trial 213* to the public during the annual UNION World Conference on Lung Health in Mexico. Detailed aggregated data were subsequently submitted to WHO as an Electronic Common Technical Document (eCTD) in late November 2017.⁴

¹ The use of delamanid in the treatment of multidrug-resistant tuberculosis. Interim policy guidance [WHO/HTM/TB/2014.23]. Available from: http://apps.who.int/iris/bitstream/10665/137334/1/WHO_HTM_TB_2014.23_eng.pdf. Geneva: World Health Organization; 2014.

² WHO Handbook for Guideline Development – 2nd ed. Available from:

http://www.who.int/publications/guidelines/handbook_2nd_ed.pdf. Geneva: World Health Organization; 2014.

³ The use of delamanid in the treatment of multidrug-resistant tuberculosis in children and adolescents: interim policy guidance [WHO/HTM/TB/2016.14]. Available from: <http://apps.who.int/iris/bitstream/10665/250614/1/9789241549899-eng.pdf>. Geneva: World Health Organization; 2016.

⁴ Otsuka Pharmaceutical Development & Commercialization, Inc. Unpublished clinical study report on a Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled, Parallel Group Trial to Evaluate the Safety and Efficacy of Delamanid (OPC-

- WHO conducted an expedited external expert review of the data on *Trial 213* data in early December 2017 in order to assess the implications of the results on the 2014 and 2016 interim policy guidance. As data from ongoing observational studies using delamanid are not yet available for review, this document is focused on the results of *Trial 213* and its immediate policy implications.

Expedited review process

- In agreement with the WHO Guidelines Review Committee (GRC), a group of external experts conversant in clinical trials, pharmacology, microbiology, therapeutics and clinical management of MDR-TB was convened to: i) assess the *Trial 213* eCDT data; and ii) advise WHO on the implications of the delamanid *Trial 213* results for both the interim policy guidance and the anticipated update of WHO MDR-TB treatment guidelines scheduled for mid-2018.
- The review comprised a detailed GRADE evidence assessment in full compliance with established WHO/GRC procedures. To ensure procedural and methodological consistency, outcomes of *Trial 213* were assessed according to the same PICO⁵ question that had informed the interim WHO policy guidance, i.e. whether the addition of delamanid to a background regimen based on WHO recommendations can safely improve MDR-TB patient outcomes.
- The primary efficacy endpoint defined in the *Trial 213* protocol was *time to sputum culture conversion over six months*. Secondary trial endpoints were the *proportion of sputum culture conversion at two months and six months*, as well as *treatment outcomes at 24 months*. The *amplification of drug resistance* was included as an exploratory outcome.
- *Trial 213* was not primarily powered to detect differences in long-term patient treatment outcomes. Nevertheless, the expedited review also assessed these outcomes, which included treatment success, cure and survival based on WHO outcome definitions for MDR-TB treatment, all of which were considered to be critical and of greater clinical relevance than time to culture conversion.
- The full findings of this review will be used - together with a GRADE evidence assessment of data from ongoing delamanid observational studies - as part of the evidence for the comprehensive MDR-TB treatment policy update planned by WHO for mid-2018.

Main findings

- *Trial 213* was designed as a phase III, multicentre, randomized, double-blind, placebo-controlled clinical trial comparing two regimens for treatment of MDR-TB in adult pulmonary TB patients. The test regimen consisted of an optimised background regimen (OBR) consistent with WHO and national guidelines, plus delamanid given as 100mg twice a day for two months, followed by 200mg once a day for four months; after six months, participants in the test arm continued to receive OBR for a total treatment duration of 18-24 months. The control regimen consisted of OBR plus an identical appearing placebo for six months, followed by OBR for the remaining duration of therapy.

67683) Administered Orally as 200 mg Total Daily Dose for Six Months in Patients With Pulmonary Sputum Culture-positive, Multidrug-resistant Tuberculosis (Protocol No. 242-09-213). 2017.

⁵ An acronym for **P**opulation, **I**ntervention, **C**omparator and **O**utcomes, referring to the method used to formulate a clinical question in a systematic manner to guide the collection and summarization of relevant evidence through the GRADE system.

All patients were followed for 30 months after randomization.

- Annex 1 provides the details for the assessment of efficacy and safety of delamanid versus placebo added for six months to an optimised background MDR-TB regimen, as obtained from *Trial 213* data.
- The expedited review acknowledged the overall conduct of *Trial 213* to high scientific standards, guided by an extensive and detailed study protocol, and with broad geographical distribution of study sites.⁶
- The GRADE assessment rated the overall certainty of the evidence as moderate. The certainty in the estimates of effect were downgraded one level from high, largely because of imprecision inferred from the relatively wide confidence intervals around most of the outcomes (see column on Effects in Annex 1).
- *Trial 213* screened 714 trial participants for possible inclusion, including participants who were on therapy and exposed to multiple second-line drugs prior to randomization. Of the 714 participants screened, 511 (72%) were eligible for randomization ('intent-to-treat' or ITT population'), and were allocated to the delamanid and placebo arms at a ratio of 2:1 respectively. A total of 341 (67%) participants subsequently received delamanid and 170 (33%) received placebo for six months, in addition to an OBR.
- Of the 511 participants in the ITT population, 327 (64%) were culture-positive at the time of randomization. Consistent with the pre-specified trial protocol, time-to-culture-conversion was evaluated in these 327 participants ('modified intent-to-treat', MITT population). Of note was the exclusion of 36% of ITT participants because their culture results from sputa collected at the time of randomization were negative, contaminated or missing.
- Randomization was stratified by HIV status and bilateral cavitation on chest radiography. Overall, 83/327 participants (25.4%) were either HIV-positive or had bilateral cavitation. Of these, 58/226 (25.7%) received delamanid and 25/101 (24.8%) received placebo. Of 244 patients who were HIV-negative or had unilateral or no cavitation, 74.3% (168/226) received delamanid and 75.2% (76/101) received placebo.
- Baseline comparisons in the ITT population showed that the two treatment arms were balanced demographically. Imbalances occurred in the MITT population as more participants with bilateral cavitation were assigned to the delamanid group, including five participants who were also HIV positive (vs two in the placebo group).
- Randomization was not stratified by baseline drug resistance (in addition to MDR). An imbalance in quinolone resistance at baseline occurred between the two arms in the MITT population – in this group, 16/226 participants (7.1%) receiving delamanid had strains with fluoroquinolone resistance and 10/226 (4.4%) had strains with extensively drug-resistance (XDR, i.e. resistance to both fluoroquinolone and injectable medicines). In comparison, 4/101 participants (4.0%) receiving placebo had strains with fluoroquinolone resistance and 2/101 participants (2.0%) had XDR-TB strains.

⁶ Trial sites in Estonia, Latvia, Lithuania, Republic of Moldova, Peru, the Philippines, and South Africa.

- The delamanid arm in the MITT population included 12 participants with both bilateral cavitation and fluoroquinolone resistance. There were no participants included in the MITT placebo arm (which also did not include any participants with bilateral cavitation only, without fluoroquinolone resistance). Co-factors or confounders that would explain these imbalances could not be found.
- Delamanid dosage was changed to *200 mg once a day* (rather than *100mg twice a day*) after two months, a dosing schedule that had previously been studied only in a few patients, but reported to have achieved the defined pharmacokinetic (PK) and pharmacodynamic (PD) targets defined in the earlier Otsuka phase IIa trial.

Efficacy

- There was **no clinically relevant or statistically significant difference** between the delamanid and placebo study arms in **treatment success**: At 30 months' follow-up, 77.1% of participants receiving delamanid achieved sustained cure versus 77.6% of participants receiving placebo (RR 0.993; 95%CI 0.899 - 1.097).
- There was **no clinically-relevant or statistically significant difference in all-cause mortality** between the two study arms: at 30 months' follow-up mortality was 5.3% in the delamanid group and 4.7% in the placebo group (RR 1.122; 95%CI 0.498 - 2.527);
- There was **no clinically-relevant or statistically significant difference** in two- or six-month **culture conversion**: conversion at six months was documented for 87.6% of participants in the delamanid arm and in 86.1% of those in the placebo arm (RR 1.017; 95%CI 0.927 - 1.115).
- Participants in the **delamanid arm** achieved **culture conversion on average six to 13 days earlier**, depending on the analytic method used to define missing culture results. Using the conservative analytic method required for regulatory purposes, culture conversion was estimated to occur six days earlier in the delamanid group (not statistically significant, $p=0.0562$, see Annex 1); other methods estimated culture conversion to occur up to 13 days earlier in the delamanid group (statistically significant; $p=0.0281$ and $p=0.0052$; see Annex 1).
- Drug susceptibility testing (DST) was reported for baseline isolates from 502/511 participants. Follow-up DST was reported at 26 weeks, but not on the last available positive culture to systematically assess the emergence of resistance. Not all drugs were tested in all patients. Findings were based on low numbers and were not statistically significant, making it difficult to infer clinical significance. Results should therefore be interpreted with caution:
 - Acquired resistance to delamanid was documented in 4/341 ITT participants (1.17%) in the delamanid arm and in none of the 170 ITT participants in the placebo arm.
 - 5/285 (1.8%) participants who received delamanid developed additional resistance to the fluoroquinolones, compared to 5/139 participants (3.6%) in the placebo arms.
 - In a subset of the ITT population for whom DST was conducted, 6/320 (1.9%) in the delamanid arm developed resistance to first-line drugs, compared to 9/139 (6.5%) in the placebo arm.
- *Trial 213* included 48 participants with HIV co-infection from South Africa. In the ITT population, 32 were randomized to the delamanid arm and 16 to the placebo arm. In the MITT population, 12

participants received delamanid and six received placebo. 9/12 participants (75.0%) on delamanid and 5/6 participants (83.3%) on placebo achieved a long-term favourable outcome (differences not statistically significant).

- Overall, the longer MDR-TB regimen used as the optimised background regimen in *Trial 213* had a treatment success rate of 81%, much higher than the overall global value of 54% reported to WHO from the latest national patient cohorts treated under programmatic conditions.⁷ Patient retention was high on *Trial 213*, with 36/339 patients (10.6%) reported to have been lost to follow-up in the delamanid arm and 20/170 (11.8%) in the control arm (differences not statistically significant).
- In the MITT population with fluoroquinolone-resistant or XDR-TB strains, treatment success was lower in the delamanid arm (28/49; 57.1%) than in the control arm (18/22; 81.8%) (RR 0.692; 95%CI 0.502 - 0.954).

Safety

- There was **no significant difference in treatment-emergent adverse events** (TEAEs) between participants receiving delamanid and those receiving placebo. **No previously unknown TEAEs** were recorded. Serious TEAEs were recorded in 89/341 (26.1%) of participants in the delamanid arm and in 47/170 (27.6%) of those in the placebo arm (RR 0.944; 95%CI 0.698 - 1.276). Contrary to earlier trial results, increased delamanid toxicity in patients with lower albumin levels was not confirmed in *Trial 213*. Hepatotoxicity was recorded in 6.5% (22/341) of participants on delamanid and 7.1% (12/170) of those on placebo (RR 0.914; 95%CI 0.464 - 1.802).
- No new or significant drug-drug interactions between delamanid and antiretroviral (ARV) drugs were observed, although the number of participants receiving dual treatment was low and results should be interpreted with caution. Overall, 12/32 participants with HIV co-infection (37.5%) in the delamanid group experienced one or more serious TEAEs compared to 5/16 (31.3%) in the placebo group (RR 1.2; 95%CI 0.51-2.82).
- There was **no significant difference in the prolongation of the Fridericia-corrected QT interval (QTcF)** between participants receiving delamanid and those receiving placebo. New-onset QTcF >500msec was recorded in 7/341 (2.1%) of the participants who received delamanid and in 2/170 (1.2%) of those who received placebo (RR 1.761, 95% CI 0.362 - 8.568). QT prolongation (>60ms from baseline) was observed in 10.3% (35/341) of participants receiving delamanid and 7.1% (12/170) of those on placebo (RR 1.454; 95%CI 0.775 - 2.728).

Conclusions

- *Trial 213* is the first-ever phase III randomized controlled clinical trial for MDR-TB treatment to be completed and reported, and thus represents a much-needed scientific breakthrough to guide treatment. WHO commends the efforts of everyone involved, including those MDR-TB patients who consented to participate.
- Translating the results of *Trial 213* into definitive policy guidance on the use of delamanid in MDR-TB

⁷ World Health Organization. Global Tuberculosis Report 2017. [WHO/HTM/TB/2017.23]. Available from: <http://apps.who.int/iris/bitstream/10665/259366/1/9789241565516-eng.pdf>. Geneva: World Health Organization; 2017.

treatment is, however, challenging for a number of reasons:

- *Trial 213* did not confirm the efficacy findings from the Otsuka phase IIb trials, which suggested statistically significant reductions in mortality and increased culture conversion at two months; in contrast, the safety conclusions were the same as those in the phase IIb trials, and provided reassurance of delamanid as a relatively safe drug compared to many second-line medicines;
 - The demonstrated benefit of delamanid *when added to an optimised background regimen* was small and limited to a modest reduction in time to culture conversion. The clinical and public health relevance of this surrogate outcome remains unclear;
 - The exposure of many trial participants to multiple second-line medicines prior to randomization as well as the inclusion (probably by chance) of a disproportionate number of patients with both fluoroquinolone-resistant strains and bilateral cavitation in the delamanid arm of the MITT population may have masked a potentially stronger efficacy signal for delamanid.
 - *Trial 213* was not designed to indicate which MDR-TB patients would most likely benefit from delamanid, or whether delamanid can effectively replace or protect other medicines in composing MDR-TB regimens.
- The treatment success achieved in the placebo arm in *Trial 213* was much higher than that reported from earlier programmatic MDR-TB treatment cohorts. This was likely due to careful design and strong implementation of the clinical trial (e.g. careful selection of trial investigators, sites, and participants, excluding highest-risk individuals and assuring high standards of care) and probably also to improved MDR-TB management at country level over time (facilitated by earlier detection with rapid molecular diagnostics and improved treatment regimen composition);
 - The favourable outcomes and high patient retention on *Trial 213* were achieved through greatly enhanced efforts to ensure that participants were engaged in their care and not lost to follow-up – an essential message for routine clinical and programmatic care of MDR-TB patients.
 - Further to the expedited expert review of *Trial 213*, WHO will conduct an extensive review of its MDR-TB policy guidelines in mid-2018, which will include consideration of data from observational studies on delamanid. A final policy recommendation on the role of delamanid in MDR-TB treatment will be included in this revision. This process will draw inferences from individual patient data of participants in *Trial 213* as well as ongoing observational studies by several investigators.
 - Until then the current interim and conditional guidance on delamanid remains in place. **However, national TB programmes and other stakeholders are advised to only add delamanid to a longer MDR-TB regimen when it cannot be composed according to WHO recommendations. When an effective and well-tolerated longer MDR-TB regimen can be otherwise composed, the addition of delamanid may not be warranted.**
 - The decision to use delamanid in such regimens should be made by treating clinicians based on individual patient assessment and well-established considerations for composition of MDR-TB regimens including drug susceptibility profiles, drug intolerance and safety, risk-benefit and ethics.

The inclusion of sufficient medicines to ensure effectiveness and avert acquisition of resistance in such regimens is particularly important. Although the data from *Trial 213* were limited, delamanid may have a protective role in preventing the emergence of additional drug resistance.

- The conditions for delamanid use in individual patients remain the same, i.e. i) careful selection of patients likely to benefit; ii) patient informed consent; iii) adherence to WHO recommendations in designing a longer MDR-TB regimen; iv) close monitoring of clinical treatment response; and v) active TB drug-safety monitoring and management (aDSM).¹
- Use of delamanid in the shorter MDR-TB regimen under programmatic conditions is not recommended by WHO given the lack of data.
- Delamanid should be retained in country guidelines, national essential medicine lists and procurement options. MDR-TB treatment algorithms may need adjustment in view of the *Trial 213* outcomes.
- Research on the role of delamanid in MDR-TB treatment should continue. In particular, the use of delamanid in MDR-TB regimens compromised by drug resistance or drug intolerance should be pursued.

Next steps

- The 2018 comprehensive review of WHO policy guidance on treatment of drug-resistant TB will include updates on the use of bedaquiline and delamanid, the shorter MDR-TB regimen, the role of injectable second-line medicines and a review of the positioning of other second-line agents in MDR-TB regimen composition.
- To this end, data from ongoing studies of delamanid are anticipated soon and several systematic reviews and individual patient data meta-analyses are being commissioned by WHO. **We therefore call on countries, researchers and implementers to submit their data at the earliest opportunity.** For more information please contact the WHO Global Tuberculosis Programme (GTB) (enquiries may be submitted to weyerk@who.int).

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ANNEX 1: SUMMARY OUTCOMES, TRIAL 213

Outcomes	No of patients		Effect	
	Delamanid	no delamanid	Relative (95% CI)	Absolute (95% CI)
Treatment success at 30 months (follow up: range 6 months to 12 months; assessed with: Trial 213; ITT population; MGIT) ^a	263/341 (77.1%)	132/170 (77.6%)	RR 0.993 (0.899 to 1.097)	5 fewer per 1,000 (from 75 more to 78 fewer)
Mortality at 30 months (follow up: range 6 months to 12 months; assessed with: Trial 213; ITT population) ^b	18/341 (5.3%)	8/170 (4.7%)	RR 1.122 (0.498 to 2.527)	6 more per 1,000 (from 24 fewer to 72 more)
Serious Adverse Events (follow up: range 6 months to 12 months; assessed with: Trial 213; ITT population)	89/341 (26.1%) ^c	47/170 (27.6%) ^c	RR 0.944 (0.698 to 1.276) ^d	15 fewer per 1,000 (from 76 more to 83 fewer)
QTcF interval prolongation >60ms from baseline on electrocardiogram over 30 months (follow up: range 6 months to 12 months; assessed with: Trial 213; ITT population) ^{e,f}	35/341 (10.3%)	12/170 (7.1%)	RR 1.454 (0.775 to 2.728) ^g	32 more per 1,000 (from 16 fewer to 122 more)
QTcF interval >500ms (new onset) on electrocardiogram over 30 months (follow up: range 6 months to 12 months; assessed with: Trial 213; ITT population) ^{e,h}	7/341 (2.1%)	2/170 (1.2%)	OR 1.761 (0.362 to 8.568) ^g	9 more per 1,000 (from 7 fewer to 81 more)
Acquired resistance to delamanid up to 26 weeks (assessed with: Trial 213; ITT population; MGIT or solid media culture) ^{i,j}	4/341 (1.2%) ^k	0/170 (0.0%)	not estimable	
Time to sputum culture conversion by 6 months (assessed with: Trial 213; MITT population; MGIT)	198/226 (87.6%)	87/101 (86.1%)	HR 1.17 (0.91 to 1.51)	40 more per 1,000 (from 27 fewer to 88 more)
<u>Primary analysis:</u> All time points with missing culture data assumed to be positive until sputum culture conversion achieved	51 days	57 days	p=0.0562	
<u>Last observation carried forward (LOCF):</u> All time points with missing culture data assumed to be the same as the last observed result	44 days	57 days	p=0.0281	
<u>Bookended:</u> All time points with missing culture data assumed to be negative if previous and following time point negative and solid culture for time points negative, contaminated or not done	51 days	64 days	p=0.0052	
Sputum culture conversion at 2 months (assessed with: Trial 213; MITT population; MGIT) ^m	132/226 (58.4%)	54/101 (53.5%)	RR 1.096 (0.889 to 1.352)	51 more per 1,000 (from 59 fewer to 188 more)
Sputum culture conversion at 6 months (assessed with: Trial 213; MITT population; MGIT) ⁿ	198/226 (87.6%)	87/101 (86.1%)	RR 1.017 (0.927 to 1.115)	15 more per 1,000 (from 63 fewer to 99 more)

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio; HR: Hazard Ratio

Footnotes

a. Treatment success: defined as per Trial 213, sustained sputum culture conversion (SCC) by week 26, completing the trial out to month 30 visit with SCC and staying alive at the last contact for follow-up per trial (CT-5.10.1.2 in page 2042 of Clinical Study Report PROTOCOL 242-09-213). Results with solid media obtain lead to similar estimates of effects RR=1.008 (95%CL: 0.916, 1.110) (CT-5.10.2.2 of PROTOCOL 242-09-213; page 2051). RRs using results at different time points (18 and 24 months) are very similar to the value shown here (CT-CT-5.8.1.2 in page 2026 of Clinical Study Report PROTOCOL 242-09-213). XDR-TB cases were excluded and many patients received combination chemotherapy in the 30 days before treatment (see

Table CT-4.4.1 in page 1840 of Clinical Study Report PROTOCOL 242-09-213); otherwise the study population relates closely to adult patients in whom this medicine is likely to be indicated. The Expert Panel did not downgrade for the exclusion of children in the trial, because it considered that any recommendation for individuals under 18 years of age would be based on the same principles used to develop the interim policy for 6-17 year olds in 2016, i.e. that efficacy in paediatric TB patients can be inferred from adult data, and that adult PK/PD data coupled with paediatric PK data can inform about what drug dosages in children will achieve adult PK targets, so the extrapolation of delamanid recommendations from adults to children was reasonable (see WHO guidelines at apps.who.int/iris/bitstream/10665/250614/1/9789241549899-eng.pdf)

b. All-cause mortality assessed during the whole 30 months (see CT-5.11.1 in page 2055 of Clinical Study Report PROTOCOL 242-09-213)

c. As per serious Treatment Emergent Adverse Events (see CT-8.1.1 in page 2227 of Clinical Study Report PROTOCOL 242-09-213)

d. Calculated using the values in Table CT-8.1.1

e. As per Table CT-11.4.1 of PROTOCOL 242-09-213; page 5002

f. 8 of 35 cases with QTcF prolongation in the delamanid group and 5/12 of the placebo group happened after 6 months.

g. Calculated manually using values in Table CT-11.4.1 of PROTOCOL 242-09-213; page 5002

h. 3 of 7 cases with QTcF prolongation in the delamanid group and 2/2 of the placebo group happened after 6 months.

i. Delamanid susceptibility is not available for all of the 511 subjects (in page 379 of Clinical Study Report PROTOCOL 242-09-213 a denominator of 502 is reported). The calculation is done for the 341 patients exposed to delamanid (retaining in the denominator the 2 cases found to be delamanid resistant at baseline). The DST methodology used only assessed resistance at baseline and week 26 and not on the last isolate, and therefore this is likely to be a minimum estimate

j. DST was not systematically done on the last positive culture for patients receiving delamanid (testing was done at 26 weeks and acquired resistance may thus have been underestimated). Resistance only emerged in patients on 3-drug regimens.

k. 95% binomial confidence intervals (exact) : 0.3-3%

l. Number of cases converting by 6 months (as per CT-5.1.1.1 in page 1954 of Clinical Study Report PROTOCOL 242-09-213); the primary analysis used a 2-sided stratified Peto-Peto modification of Gehan's Wilcoxon rank sum test to compare the survival distribution curves of time to SCC as per regulatory requirement. A protocol-specified sensitivity analysis using "last observation carried forward" (LOCF) resulted in a HR of 1.24 (95%CI 0.96-1.6) and a HR of 1.33 (95%CI 1.03-1.74) using the "bookended" method (ST-16.1 in page 6024 of Clinical Study Report PROTOCOL 242-09-213). Median times to SCC were: (i) ITT analysis 51 days vs 57 days (P-value 0.056) ; (ii) LOCF 44 days vs 57 days (P-value 0.0281); (iii) "bookended" 51 days vs 64 days (P-value 0.0052). Other analysis for sustained conversion shows a reduced effect.

m. RR was estimated using PROC FREQ (SAS) and the Cochran-Mantel-Haenszel general association test (see CT-5.2.1.1 in page 1964 of Clinical Study Report PROTOCOL 242-09-213). Using LOCF (CT-5.2.1.2), the RR was 1.069 (95%CI: 0.875-1.305) and the "bookended" (ST-16.3) RR was 1.172 (95%CI : 0.946-1.453)

n. RR was estimated using PROC FREQ (SAS) and the Cochran-Mantel-Haenszel general association test (see CT-5.3.1.1 in page 1972 of Clinical Study Report PROTOCOL 242-09-213). Using LOCF (CT-5.3.1.2), the RR 1.034 (95%CI: 0.941-1.137) and the "bookended" (ST-16.2) RR was 1.070 (95%CI: 0.950-1.204).