New Drugs and Treatments for TB

Tuberculosis Symposium – Eastern Europe and Central Asia
New treatments and approaches to Tuberculosis

_Yerevan, 17th February 2015_

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World Health Organization
Geneva, Switzerland
Overview of the presentation

- Background
- New Drugs for TB – the pipeline
- The WHO Strategic Plan for rational introduction of new TB drugs and regimens in countries
  - A working example: Developing interim guidance on bedaquiline
- From new TB drugs to new TB regimens
- The WHO Policy Implementation Package
  - A working example: Introduction of bedaquiline in countries
QUALITY TUBERCULOSIS (TB) CARE FOR MILLIONS WORLDWIDE HAS DRIVEN DOWN TB DEATHS BUT TB REMAINS THE SECOND BIGGEST KILLER DISEASE FROM A SINGLE INFECTIOUS AGENT

9 MILLION
PEOPLE FELL ILL WITH TB IN 2013 INCLUDING 1.1 MILLION PEOPLE LIVING WITH HIV

1.5 MILLION
PEOPLE DIED IN 2013 INCLUDING 360 000 PEOPLE WHO WERE HIV POSITIVE

480 000
PEOPLE ESTIMATED TO HAVE DEVELOPED MULTIDRUG-RESISTANT TB (MDR-TB) IN 2013.

Improved TB data from countries are revealing that the burden of the disease is higher than previously estimated.
Global TB Drug Pipeline

Discovery

Preclinical Development

Clinical Development

Lead Optimization

Early Stage Development

GLP Tox.

Phase I

Phase II

Phase III

Cyclopeptides
Diarylquinolines
DprE Inhibitors
InhA Inhibitor, Indazoles
LeuRS Inhibitors, Ureas
Macrolides, Azaindoles
Mycobacterial Gyrase Inhibitors
Pyrazinamide Analogs
Ruthenium(II) Complexes
Spectinamides SPR-10199
Translocase-1 Inhibitors

CPZEN-45
BTZ043
DC-159a
SQ609
SQ641
TBI-166

AZD5847
Bedaquiline
Linezolid
Novel Regimens
PA-824
Rifapentine for DS-TB
SQ-109
Sutezolid (PNU-100480)

Delamanid
Gatifloxacin*
Moxifloxacin*
Rifapentine for LBTI

New TB drugs - currently in the regulatory review process

Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php

Combination regimens: NC-001-(J-M-Pa-Z), phase 2a, NCT01215851; NC-002-(M-Pa-Z), phase 2b, NCT01498419; NC-003-(C-J-Pa-Z), phase 2a, NCT01691534; PanACEA-MAMS-TB-01-(H-R-Z-E-Q-M), phase 2b, NCT01785186

Projects that have been completed

Updated: August 2014
New Drugs: 1. Bedaquiline

- First new TB drug class in more than 40 years
- Chemical class: diarylquinolone
- Novel target: ATP synthase inhibitor
- Phase IIb data: placebo-controlled trial of BDQ in combination with background MDR-TB therapy (BT)
  - Showed greater efficacy of BT + BDQ than BT + placebo at 6 months
- Approved by FDA (accelerated procedure) in December 2012 "as part of combination therapy to treat adults with multi-drug resistant tuberculosis when other alternatives are not available"
New Drugs: 2. Delamanid

- Chemical class: nitroimidazole
- Phase IIb data: placebo-controlled trial of delamanid in combination with optimized background therapy (OBT)
  - 2 test arms: (i) Delamanid (100mg bid) + OBT
    (ii) Delamanid (200mg bid) + OBT
  - Greater efficacy of OBT + Delamanid than OBT + placebo at 2 months
- Phase III trial launched in September 2011
- Approved in April 2014 by the European Medicines Agency (EMA) "as part of an appropriate combination regimen for pulmonary multi-drug resistant tuberculosis in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability."
New Drugs: 3. Pretomanid

- Chemical class: nitroimidazole (nitroimidazo-oxazine sub-class)
- active against drug-sensitive and multidrug-resistant strains of *M. tuberculosis*
- Potent bactericidal activity against replicating and static bacilli
- Several Phase I studies completed - no significant food effect at anticipated clinical dose; not a significant inhibitor/inducer of CYP3A4
- Phase II: Two 14-day EBA studies in patients with newly diagnosed, smear +, drug sensitive pulmonary TB
- 14 days EBA study of a new combination: PA-824 + Moxi + PZA showing promising results
Public health challenges of introduction of new TB drugs in countries

Implications for TB control programmes:

– determine *optimal regimens* for use of newly developed and/or repurposed drugs for treatment of DS- and DR-TB under programmatic conditions;

– evaluate requirements for patients’ eligibility;

– assess programmatic feasibility;

– evaluate cost-effectiveness of newly-developed treatments;

– ensure proper surveillance and pharmacovigilance;

– ensure responsible use (appropriate indication, doses, drug combination(s), and treatment duration) – prevent off-label use and amplification of resistance;
The WHO Strategic Plan for rational introduction of new TB drugs and regimens in countries

Describes key elements of a process aimed at:

- producing policy recommendations for the treatment of TB (all forms), according to progress made in the development of new drugs or combinations of drugs,

and

- assisting countries in the implementation of these recommendations

WHAT? WHO Policy Development Framework

1. Development of new TB drugs or new regimens
   • Partners (industry, researchers, consortia, …)
   • Body of evidence available (publications, SRA approval)

2. Reviewing the evidence
   • Collection of data on pre-clinical and clinical development phases
   • Cost-effectiveness analysis

3. Convening an Expert Group
   • Experts, methodologists, end-users
   • Guidelines Review Committee
   • GRADE process for evidence synthesis

4. Developing policy proposal and recommendations
   • Peer-review by ERC
   • Strategic and Technical Advisory Group
   • Endorsement/revision/addition
   • Advise to WHO to proceed/not with policy

5. Formulating and disseminating policy
   • Guidelines Review Committee
   • Dissemination to Member States
   • Promotion with stakeholders & funders
   • Phased implementation & scale-up plan
Involves two fundamental determinations:

- **Quality of evidence**: reflects the extent to which confidence in an estimate of the effect is adequate to support recommendations.

- **Strength of recommendation**: reflects the extent to which we can, across the range of patients for whom the recommendations are intended, be confident that the desirable effects of an intervention outweigh the undesirable effects.
Procedure:

Review of data:
• Data available from FDA public website
• Request for additional specific data to Janssen
• Independent consultant contracted to prepare a concise summary report of the publicly available evidence (B. Fourie, Sth Africa)

Two technical resource consultants requested to develop specific documents to assist the Expert Group in their evaluation of the product:
• an assessment of the validity of sputum culture conversion at 6 months and time to culture conversion as surrogate markers of MDR-TB treatment outcomes (E. Kurbatova, CDC);
• a cost-effectiveness analysis based on modeling (A. Vassall, LSHTM).
Expert Group Meeting

- The **overall objective** of the Expert Group meeting was to evaluate the added benefit of bedaquiline for the treatment of MDR-TB and, if appropriate, to provide recommendations to WHO for interim guidance to countries on its use in conjunction with other second-line drugs used in MDR-TB treatment.

- The **specific objectives** were:
  - To evaluate the efficacy and safety of bedaquiline in addition to currently WHO recommended MDR-TB treatment;
  - To evaluate the balance between harms and benefits of the drug, its potential cost-effectiveness, patient- and provider preferences and concerns, and the feasibility of introducing the drug in MDR-TB programmes;
  - To provide, as appropriate, recommendations on the use of the drug as part of WHO-recommended MDR-TB treatment regimens, including attention to concerns/constraints relevant to the potential use of a new drug for which Phase III clinical trial data are not yet available.
Procedures

- Review using GRADE Procedures

- PICO question:
  - “In MDR-TB patients, does the addition of bedaquiline to a background regimen based on WHO-recommendations safely improve patient outcomes?”

- Selected outcomes
  1. Cure by 120 weeks
  2. Serious adverse events during investigational 24 weeks treatment phase
  3. Mortality
  4. Time to culture conversion over 24 weeks
  5. Culture conversion at 24 weeks
  6. Acquired resistance to second-line drugs (fluoroquinolones, amino-glycosides and capreomycin) at 72 weeks
Brief summary of main data reviewed for assessment of role of bedaquiline in the treatment of MDR-TB
C208 Stage 2: Time to Culture Conversion (Wk 24 – mITT)

Primary endpoint (difference in TtC):

\[ p = <0.0001 \]

<table>
<thead>
<tr>
<th>Time to Culture Conversion (Weeks)</th>
<th>BDQ/BR (N=66)</th>
<th>Placebo/BR (N=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>61</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>53</td>
<td>37</td>
</tr>
<tr>
<td>8</td>
<td>53</td>
<td>37</td>
</tr>
<tr>
<td>12</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td>16</td>
<td>30</td>
<td>25</td>
</tr>
<tr>
<td>20</td>
<td>22</td>
<td>12</td>
</tr>
<tr>
<td>24</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>83d</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>125d</td>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>
| Median time to culture conversion was 12 weeks in the BDQ group and 18 weeks in the placebo group\[ p\-value from Cox proportional model adjusting for strata \]
Week 24, Week 72 and Week 120 (end of study) culture conversion proportions (mITT)

<table>
<thead>
<tr>
<th>Time-point</th>
<th>Bedaquiline</th>
<th>Placebo</th>
<th>Diff [95% CI] P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 24</td>
<td>52/66 (79%)</td>
<td>38/66 (58%)</td>
<td>21.2% [5.6%, 36.8%] 0.008</td>
</tr>
<tr>
<td>Week 72</td>
<td>47/66 (71%)</td>
<td>37/66 (56%)</td>
<td>15.2% [-1.2%, 31.5%] 0.069</td>
</tr>
<tr>
<td>Week 120</td>
<td>41/66 (62%)</td>
<td>29/66 (44%)</td>
<td>18.2% [1.3%, 35.1%] 0.035</td>
</tr>
</tbody>
</table>
### Pooled, Controlled Phase IIb Trials: Adverse Events of Interest – Hepatic Safety Reported Events

<table>
<thead>
<tr>
<th>Preferred term</th>
<th>Investigational Treatment Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BDQ N = 102</td>
</tr>
<tr>
<td></td>
<td>9 (8.8)</td>
</tr>
<tr>
<td>Transaminases increased</td>
<td>4 (3.9)</td>
</tr>
<tr>
<td>AST increased</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>2 (2.0)</td>
</tr>
<tr>
<td>GGT abnormal</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>PT prolonged</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>GGT increased</td>
<td>0</td>
</tr>
</tbody>
</table>

N = number of ITT subjects with data; n = number of ITT subjects with this observation

*^1* Based on Standardized MedDRA Queries for Drug-related hepatic disorders
Trial C208: QTcF changes from reference (ITT population)

Week 24 = End of Investigational Treatment Phase

BDQ/BR: 76 71 68 64 63 62 60 59 58 60 58 56 55 51
Placebo/BR: 78 73 73 72 70 64 59 59 60 58 56 53 49 50

QTcF: QT interval corrected for heart rate according to the Fridericia method
## Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Type of study</th>
<th>Bedaquiline</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 Deaths</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Phase 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study C202*</td>
<td>Randomised, open-label, doz ranging, EBA study</td>
<td>N=45</td>
<td>N=30</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td>2 (4.4%)</td>
<td>0</td>
</tr>
<tr>
<td>Trial C208 Stage 1</td>
<td>Randomised, placebo-controlled, 8 week exposure</td>
<td>N=23</td>
<td>N=24</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td>2 (8.7%)</td>
<td>2 (8.3%)</td>
</tr>
<tr>
<td>Trial C208 Stage 2</td>
<td>Randomised, placebo-controlled, 24 week exposure</td>
<td>N=79</td>
<td>N=81</td>
</tr>
<tr>
<td>Deaths**</td>
<td></td>
<td>10 (12.7%)</td>
<td>2 (2.5%)</td>
</tr>
<tr>
<td>Trial C209</td>
<td>Open label, uncontrolled, 24 week exposure</td>
<td>N=233</td>
<td>n/a</td>
</tr>
<tr>
<td>Deaths</td>
<td></td>
<td>16 (6.9%)</td>
<td></td>
</tr>
</tbody>
</table>

* Reference drugs: INH+RMP, not placebo

** Relative Risk 5.1 (p=0.017)
"Bedaquiline may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB, under five specific conditions"

"conditional recommendation, very low confidence in estimates of effect"


WHO – June 2013
Interim policy guidance on the use of bedaquiline

5 conditions:

1. Proper selection of patients
2. Patient informed consent required
3. Treatment design based on WHO recommendations
4. Close monitoring conditions
5. Active pharmacovigilance and management of AEs
From new TB drugs to new TB treatment regimens: key questions

What would be the added value and best impact of the new regimen considering its characteristics and the variability of national contexts?

- Evaluation of efficacy and safety aspects
- Evaluation of harms vs. benefits in comparison with current SOC
- Evaluation of feasibility (programmatic aspects)
- Evaluation of values (patients aspects)
- Variable scenarios according to the epidemiological context:
  - TB epidemics
  - burden and pattern of resistance
  - high-risk/vulnerable groups
From new TB drugs to new TB treatment regimens: key questions

What population would benefit most of the new regimen(s)?

- Depends on the regimen's characteristics and indications:
  - Patients with susceptible TB?
  - Patients with MDR-TB?
  - MDR-TB patients with additional FQ and/or INJ resistance?
  - Only recourse regimen?

- Consider high-risk groups:
  - HIV infected population: high vs. low HIV prevalence in TB cases
  - Respective proportions of new vs. re-treatment in MDR-TB cases

What are the possibilities of optimal deployment of new regimens in countries?

- High variability of situation according to countries
- Feasibility and acceptability
<table>
<thead>
<tr>
<th>Trial Name (funding source)</th>
<th>Duration of Experimental regimen (months)</th>
<th>Comparator</th>
<th>Experimental Arm(s)</th>
<th>GOAL Shorten</th>
<th>All-oral</th>
<th>Improve tolerability</th>
<th>Improve cure rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>C 213/Phase 3 Delamanid (Otsuka)</td>
<td>24</td>
<td>WHO Std</td>
<td>DLM+OBT</td>
<td>X</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>NeXT (MRC-SA)</td>
<td>6-9</td>
<td>SA Std</td>
<td>BDQ+LZD+LFX+ETA/ INH₄+PZA</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>End-TB (UNITAID)</td>
<td>9</td>
<td>None</td>
<td>BDQ+LZD+MXF+PZA BDQ+CFZ+LZD+CFZ+PZA BDQ+CFZ+LFX+PZA DLM+LZD+MXF+PZA DLM+CFZ+LZD+LFX+PZA DLM+CFZ+LFX+PZA</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>TB-PRACTICAL (MSF)</td>
<td>6</td>
<td>WHO Std</td>
<td>BDQ+PRT+LZD+MXF BDQ+PRT+LZD+CFZ BDQ+PRT+LZD</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>STREAM Stage 1 (USAID+)</td>
<td>9</td>
<td>WHO Std</td>
<td>CFZ+EMB+MFX+PZA+4(KM+INH₄+PTO)</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>STREAM Stage 2 (USAID+)</td>
<td>6: 9:</td>
<td>WHO std / 9 mo. regimen</td>
<td>BDQ+LFX+CFZ+PZA+2(INH₄+KM) BDQ+CFZ+EMB+LFX+PZA+4(INH₄+PTO)</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>NC-005* (GATB)</td>
<td>2 (followed by OBT)</td>
<td>None for MDR Arm</td>
<td>BDQ+PRT+MFX+PZA</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>NIX-TB (GATB)</td>
<td>6-9</td>
<td>None</td>
<td>BDQ+PRT+LZD</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>STAND* (GATB)</td>
<td>4-6 months</td>
<td>None for MDR ARM</td>
<td>PRT+MFX+PZA</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Novartis</td>
<td>24</td>
<td>WHO Std</td>
<td>CFZ+OBT</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The **goal** is to support countries in preparing for introduction of new TB drugs and/or regimens, based on WHO policy guidance, in order to better serve patients and communities in need.

WHO – Oct 2014
WHO Policy Implementation Package for Rational Introduction of New TB Drugs or Drug Regimens in Countries

1. Minimum requirements for country preparedness and planning.

2. Implementation plan for introduction of new TB drugs or regimens.

3. Pharmacovigilance and drug resistance surveillance.

4. Private sector engagement.

5. Systems approach for ensuring uninterrupted supply of quality-assured medicines.

6. Operational research.
Guidance on the use of new TB drugs

- Expert consultations to evaluate new TB drugs/regimens coming out of the pipeline and revise/update treatment guidelines as appropriate
- Led to the development of interim guidance for the use of bedaquiline and for the use of delamanid
- Backed-up by the Companion Handbook on WHO guidelines for PMDT
Implementation Plan for introduction of bedaquiline in countries

- Step 1: Establish the framework for the introduction of bedaquiline at country level
- Step 2: Meet the minimal requirements for introduction of bedaquiline
  - checklist to assist in country preparedness
- Step 3: Develop a national plan for introduction of bedaquiline
- Step 4: Implement the introduction of bedaquiline in pilot sites
- Step 5: Generate evidence for scale up

Developed with the assistance of Marina Tadolini & Jennifer Furin
Work with early implementing countries

- A group of countries have expressed interest in working with WHO for *introduction of bedaquiline in programme conditions, following WHO recommendations*
Work with early implementing countries

- Initial workshop involving all key stakeholders (NTP, MoH, NRA, NPV, etc.) and TA bodies/donors (GF, USAID, B&MGF, KNCV, etc..)
  - Outline of a country-specific National Implementation Plan
  - Establishment of national framework
  - Identification of pilot sites
  - Determination of target cohort
  - Laboratory aspects
  - Monitoring – including recording and reporting
  - Establishment of active PV in conjunction with key stakeholders
  - Discussion with NRAs on regulatory aspects and drug procurement
  - Timeline of activities
- Follow-up of activities at country-level
Key aspects for WHO/GTB are:

• to engage with and support national authorities and stakeholders early in the preparation of policies for introduction of new TB drugs and regimens at programmatic level (including quality, procurement aspects, etc.);

• to ensure that new TB drugs are introduced in an optimal way and in appropriate combination regimens to protect patients from misuse and prevent emergence of resistance;

• to ensure that introduction of new TB drugs and regimens follows policy recommendations and appropriate plans are made to ensure feasibility and inform policy-making.
Acknowledgements

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• **Observers**: Richard Hafner, Michael Kimerling, Ya-Diul Mukadi.

• **WHO**: Dennis Falzon, Ernesto Jaramillo, Joel Keravec, Mario Raviglione, Fraser Wares, Diana Weil & Karin Weyer.

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• **Support from B&MGF and USAID**.
Thank you for your attention!
Back-up slides
WHO’s strategy and guidance for new TB drug introduction

2. WHO Policy Development Framework

- Development of new TB drugs or new regimens
- Reviewing the evidence
- Consulting an Expert Group
- Developing policy proposals and recommendations
- Formulating and disseminating policy

- Partners (include researchers, clinicians,...)
- Body of evidence available (publications, SRAs, approval)
- Collection of data on pre-clinical and clinical development phases
- Cost-effectiveness analysis
- Experts, methodologists, and users
- Guidelines Review Committee
- CANMIE process for evidence synthesis
- Peer review by ERC
- Strategic Technical Advisory Group
- Enablers and barriers
- Advice to WHO on pre-adoption policy

- Guidelines and implementation
- Dissemination to Member States
- Promotion with stakeholders & funders
- Phased implementation & scale-up plan

Strategic Plan for New TB Drug Introduction

WHO Task Force on New Drug Policy Development April 2012 - 2014

Standard Policy Development Framework

Expert Reviews

Interim guidance

Policy implementation Package

Support to Country Roll-out

Bedaquiline (Jan 2013)
Delamanid (April 2014)

WHO’s strategy and guidance for new TB drug introduction

New Drugs: 2. Delamanid

• Phase IIb trial: placebo-controlled safety, efficacy, and PK of delamanid combined with optimized background therapy (OBT)

• 2 test arms:
  (i) delamanid (100mg BID) + OBT ;
  (ii) delamanid (200mg BID) + OBT

• Primary endpoint: 2-month sputum culture conversion

Survival Analysis of Days to Sputum-Culture Conversion
Two-month SCC in Trial 204 - MGIT

Proportion of patients treated with delamanid + OBR achieving SCC by Day 57 using the MGIT system compared with placebo + OBR

Source: Gler et al, 2012
Summary of efficacy endpoints in Trial 204

Forest plots summarizing the relative efficacy of the delamanid groups compared to the placebo group in the randomized, controlled Trial 204

*N = Number of patients; RR = Risk ratio; LL = Lower Limit; UL = Upper Limit*
Sustained SCC – Proportion of patients with no positive culture results after SCC is achieved

(Source: Otsuka's summary efficacy analysis - document submitted to WHO February 2014)
Final Treatment Outcome - Combined analysis of patients in Trial 204, Trial 208 and Study 116

<table>
<thead>
<tr>
<th>Delamanid Exposure</th>
<th>Total ITT Patients</th>
<th>24-Month Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Favorable</td>
</tr>
<tr>
<td>≥ 6 Months</td>
<td>192</td>
<td>143 (74.5)</td>
</tr>
<tr>
<td>≤ 2 Months</td>
<td>229</td>
<td>126 (55.0)</td>
</tr>
<tr>
<td>No delamanid</td>
<td>73</td>
<td>42 (57.5)</td>
</tr>
</tbody>
</table>

a Patients participating in 208 and treated with delamanid or placebo in 204.
b Patients not participating in 208 Patients treated with delamanid or placebo in 204.

RR 1.35 (95% CI: 1.03 to 1.63)  
(Source: Otsuka's summary efficacy analysis – document submitted to WHO February 2014)
Outcome at 24 months for patients in Trial 204, Trial 208 and Study 116 using WHO treatment outcome categories (N=421)

<table>
<thead>
<tr>
<th>Trial 204 Assignment (2 months DLM+OBR or OBR alone)</th>
<th>Trial 208 Participation (6 months DLM+OBR or OBR alone)</th>
<th>ITT patients in Trial 116 (N)</th>
<th>Cured</th>
<th>Completed</th>
<th>Failed</th>
<th>Died</th>
<th>Defaulted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>100-BID</td>
<td>1</td>
<td>100-BID</td>
<td>38</td>
<td>24</td>
<td>63%</td>
<td>9</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>200-BID</td>
<td>21</td>
<td>13</td>
<td>62%</td>
<td>2</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>No</td>
<td>80</td>
<td>31</td>
<td>39%</td>
<td>17</td>
<td>21%</td>
</tr>
<tr>
<td>200-BID</td>
<td>4</td>
<td>100-BID</td>
<td>45</td>
<td>25</td>
<td>56%</td>
<td>16</td>
<td>36%</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>200-BID</td>
<td>22</td>
<td>15</td>
<td>68%</td>
<td>3</td>
<td>14%</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>No</td>
<td>76</td>
<td>36</td>
<td>47%</td>
<td>14</td>
<td>18%</td>
</tr>
<tr>
<td>Placebo</td>
<td>7</td>
<td>100-BID</td>
<td>39</td>
<td>27</td>
<td>69%</td>
<td>7</td>
<td>18%</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>200-BID</td>
<td>27</td>
<td>18</td>
<td>67%</td>
<td>2</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>No</td>
<td>73</td>
<td>33</td>
<td>45%</td>
<td>12</td>
<td>16%</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>421</td>
<td>222</td>
<td>53%</td>
<td>82</td>
<td>19%</td>
</tr>
</tbody>
</table>

Patients treated with delamanid 100-BID or 200-BID + OBR for 2, 6, or 8 months or with OBR alone

Data submitted to WHO by the company.
"Delamanid may be added to a WHO-recommended regimen in adult patients with pulmonary MDR-TB, under **five** specific conditions"

"conditional recommendation, very low confidence in estimates of effect"

WHO – Oct 2014
Interim policy guidance on the use of delamanid

5 conditions:

1. Proper selection of patients
2. Adherence to the principles of designing a WHO-recommended MDR-TB regimen
3. Treatment under close monitoring
4. Active pharmacovigilance
5. Patient informed consent required