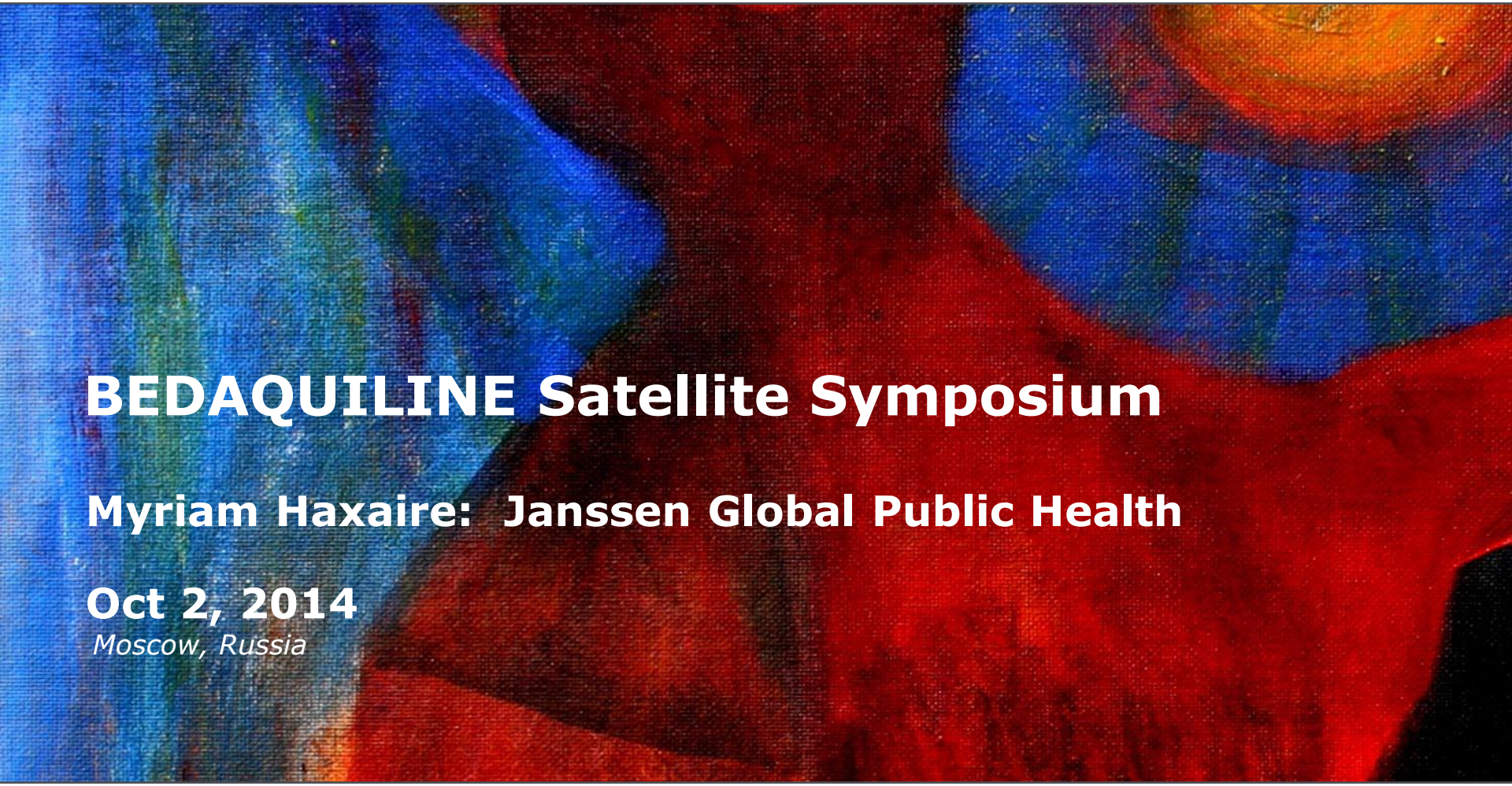

BEDAQUILINE Satellite Symposium

Myriam Haxaire: Janssen Global Public Health

Oct 2, 2014

Moscow, Russia

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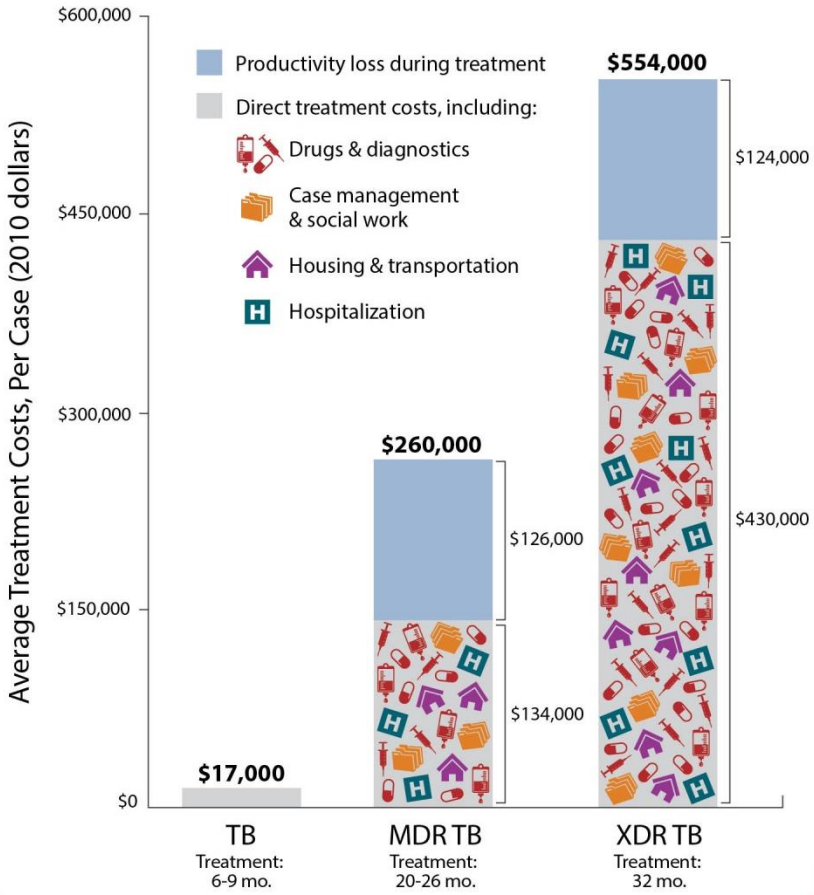
THE COSTLY BURDEN OF DRUG-RESISTANT TB IN THE U.S.

Multidrug-resistant (MDR) tuberculosis is a major health threat globally. Nearly half a million MDR TB[1] cases are estimated to occur worldwide annually, including cases that are extensively drug-resistant (XDR).[2]

While MDR and XDR TB are relatively rare in the U.S., their treatment comes at a terrible price – it is very expensive, takes a long time, disrupts lives, and has potentially life-threatening side effects.

The Outsized Financial Toll of MDR and XDR TB

Cost increases with greater resistance:

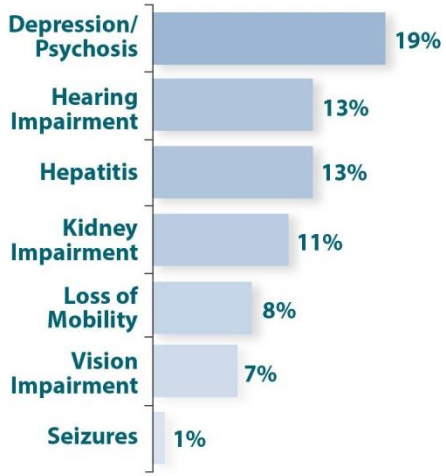


A Major Human Cost

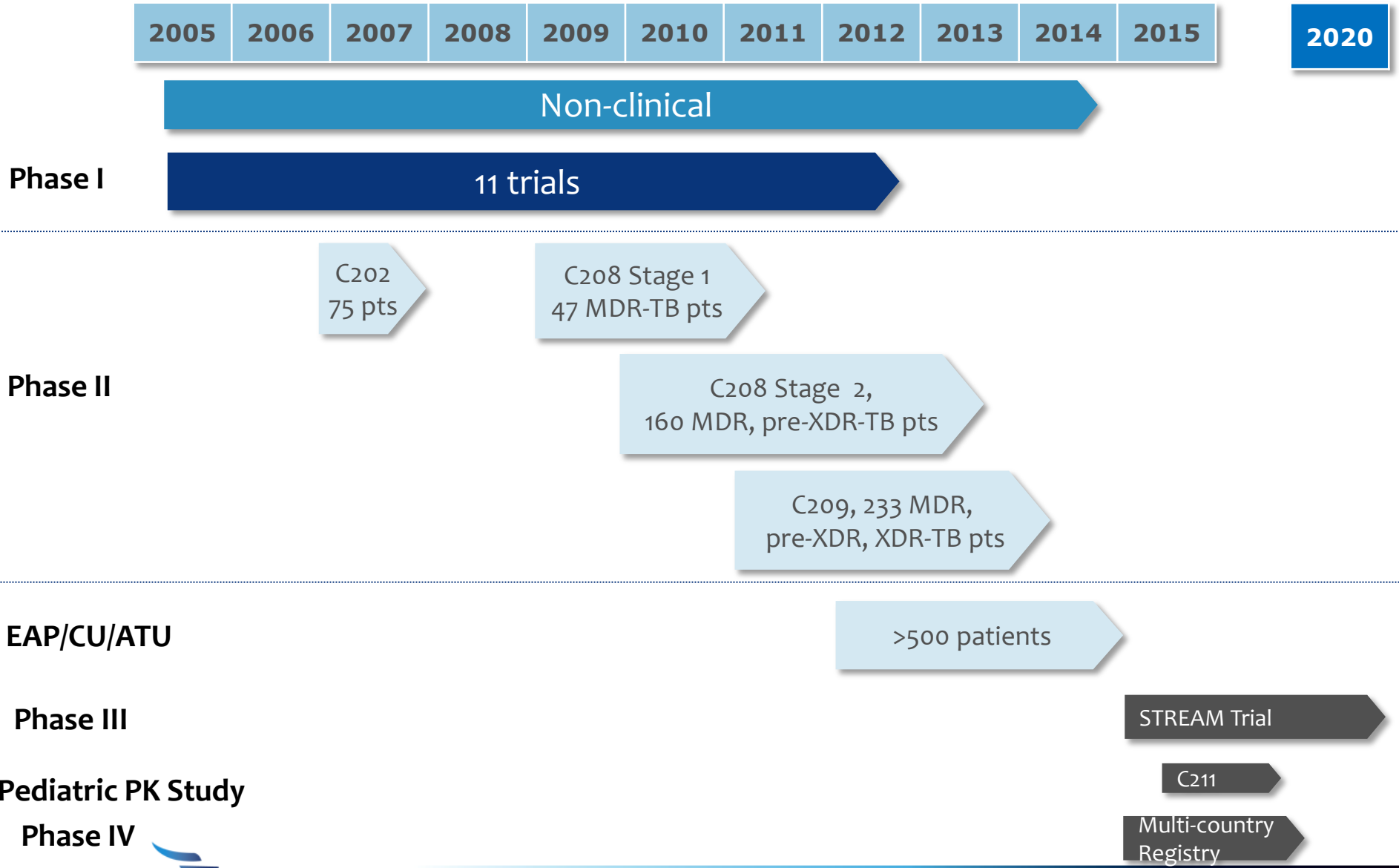
Of those treated for drug-resistant TB:

- **9%** Die During Treatment
- **27%** Stop Working
- **73%** Hospitalized
- **37%** Require Home Isolation

Severe Treatment Side Effects



Bedaquiline Development Program



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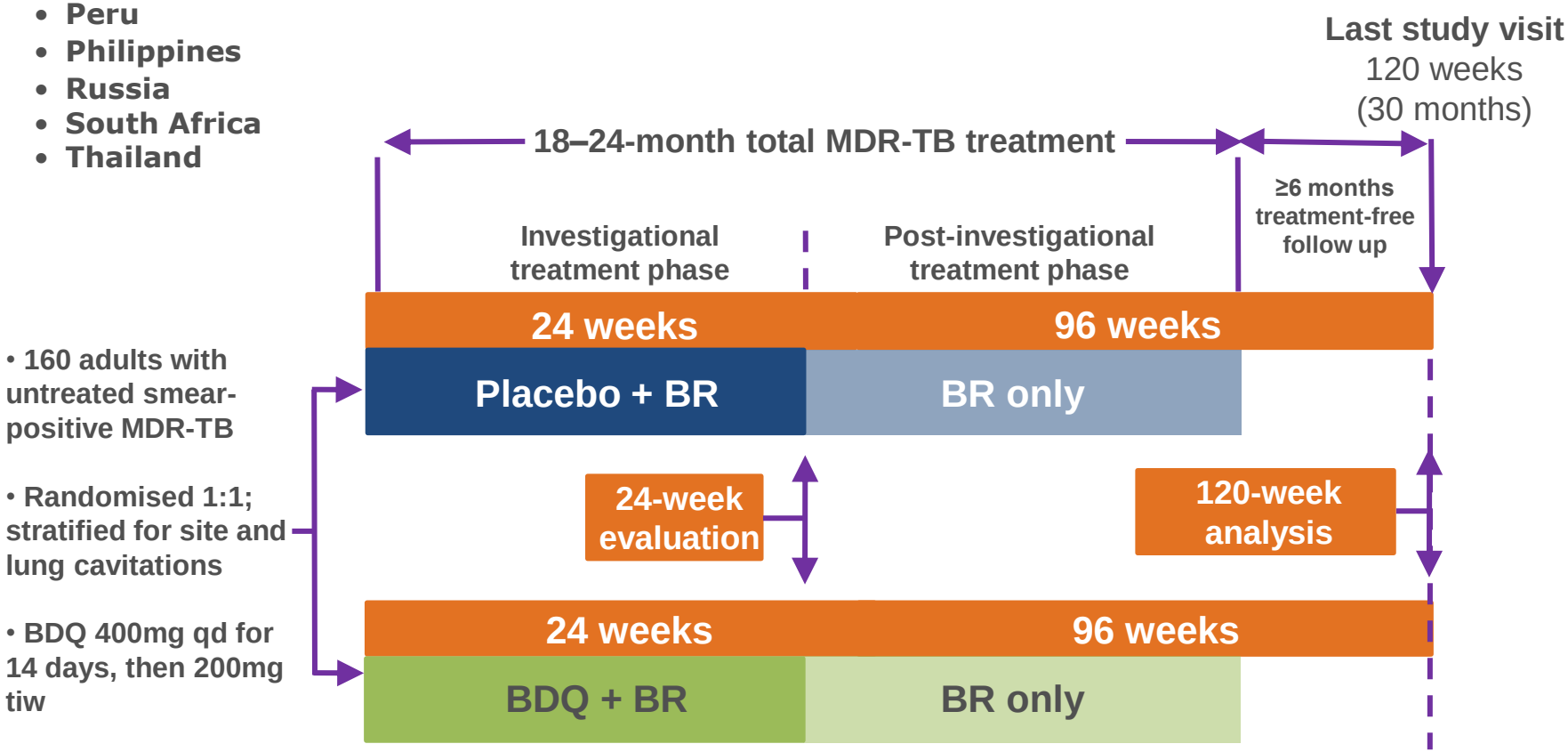
Countries

- Brazil
- India
- Latvia
- Peru
- Philippines
- Russia
- South Africa
- Thailand

Study design

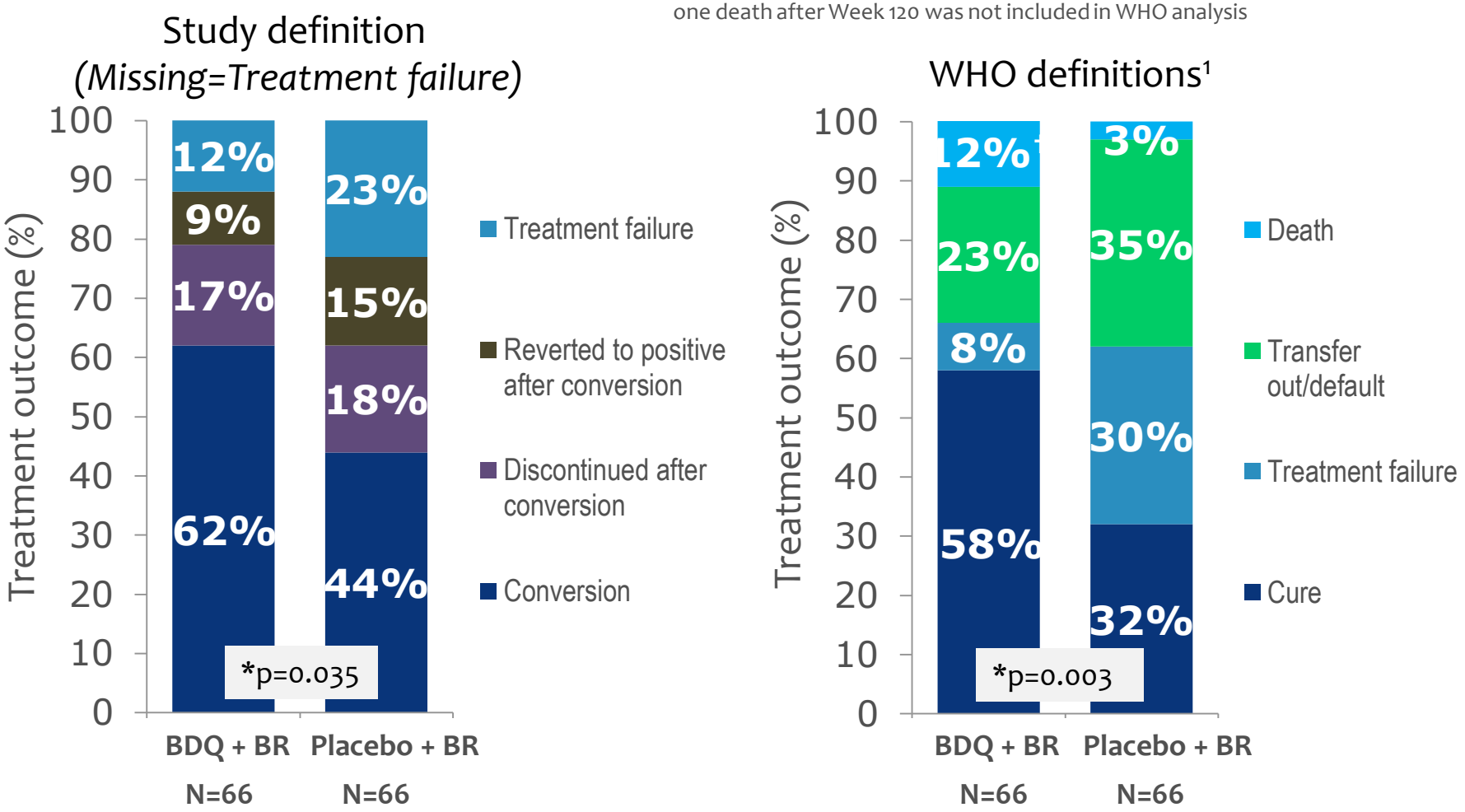


Objective: Demonstrate superiority of BDQ vs placebo at 24 weeks in the mITT population

PhII: *C208 Outcome at study end (120 weeks; mITT)*

- Median duration of overall treatment phase: BDQ 92 weeks vs placebo 94 weeks

†Only 8 of 10 deaths included: one death not included in mITT population; one death after Week 120 was not included in WHO analysis



Language in the European label: The imbalance in deaths is unexplained; no evidence has been found for a causal relationship with bedaquiline treatment.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Multidrug-Resistant Tuberculosis and Culture Conversion with Bedaquiline

Andreas H. Diacon, M.D., Ph.D., Alexander Pym, M.D., Ph.D., Martin P. Grobusch, M.D., Ph.D., Jorge M. de los Rios, M.D., Eduardo Gotuzzo, M.D., Irina Vasilyeva, M.D., Ph.D., Vaira Leimane, M.D., Koen Andries, D.V.M., Ph.D., Nyasha Bakare, M.D., M.P.H., Tine De Marez, Ph.D., Myriam Haxaire-Theeuwes, D.D.S., Nacer Lounis, Ph.D., Paul Meyvisch, M.Sc., Els De Paepe, M.Sc., Rolf P.G. van Heeswijk, Pharm.D., Ph.D., and Brian Dannemann, M.D., for the TMC207-C208 Study Group*

- The overall incidence of adverse events was similar in the two groups.
- The most frequent adverse events were nausea, arthralgia, and vomiting.
- In addition, mortality in the placebo group was surprisingly low, as compared with mortality in a meta-analysis involving 9153 patients with multidrugresistant tuberculosis (15%)[16] and in an open-label, phase 2 trial of bedaquiline involving 233 patients with newly diagnosed or previously treated multidrug-resistant tuberculosis (7%).

The NEW ENGLAND JOURNAL of MEDICINE

Perspective

AUGUST 21, 2014

FDA Approval of Bedaquiline — The Benefit–Risk Balance for Drug-Resistant Tuberculosis

Edward Cox, M.D., M.P.H., and Katherine Laessig, M.D.

Related article, p. 723

- Among sputum-smear–positive cases of pulmonary tuberculosis in HIV negative patients, the estimated **10-year case fatality** rate is **70%.**[4]

- The limited indication of use for bedaquiline identifies a patient population for which there is considerable unmet need and a positive benefit– risk balance.[1]

Preapproval Access & Compassionate Use Activities

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Bedaquiline Early Access Programs

Aim: Make bedaquiline available to patients ***with extensively drug resistant (XDR) or pre-XDR Tuberculosis infection*** *(TB), who have limited to no treatment options.*

No proactive recruitment or promotion are permitted

Program(s) cease at the time in which marketing authorization and/or reimbursement is secured. Patients then transitioned to commercial supply.

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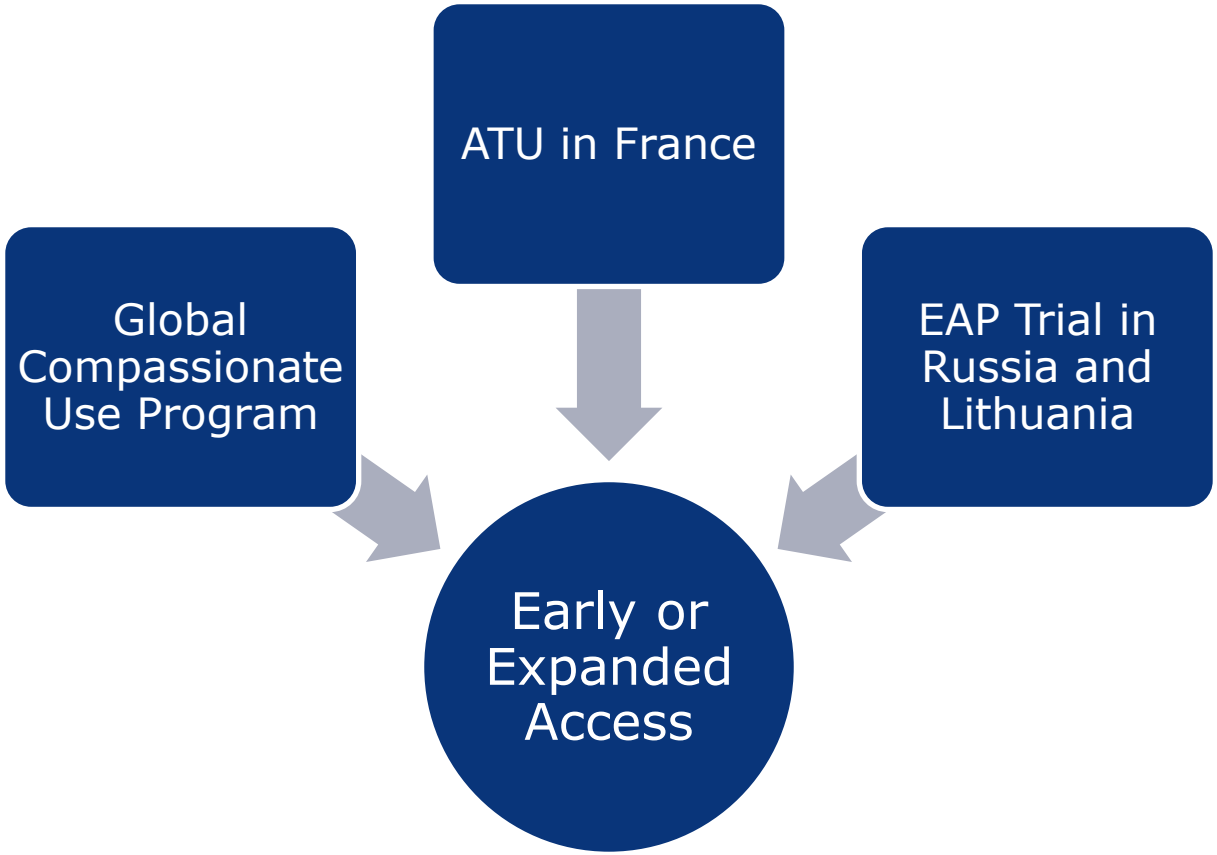
Early access/expanded access programs



All 3 limited to (pre) XDR TB

Participating Countries in Compassionate Use Program

Argentina	Germany	Nepal	Taiwan
Armenia	Georgia	Netherlands	USA
Australia	Greece	Niger	UK
Austria	India	Nigeria	(France-ATU)
Bangladesh	Italy	Norway	
Belgium	Ireland	Peru	
Botswana	Kenia	PNG	
Canada	Latvia	Romania	
Denmark	Lebanon	South Africa	
Estonia	Lesotho	Sweden	
Ethiopia	Mongolia	Switzerland	

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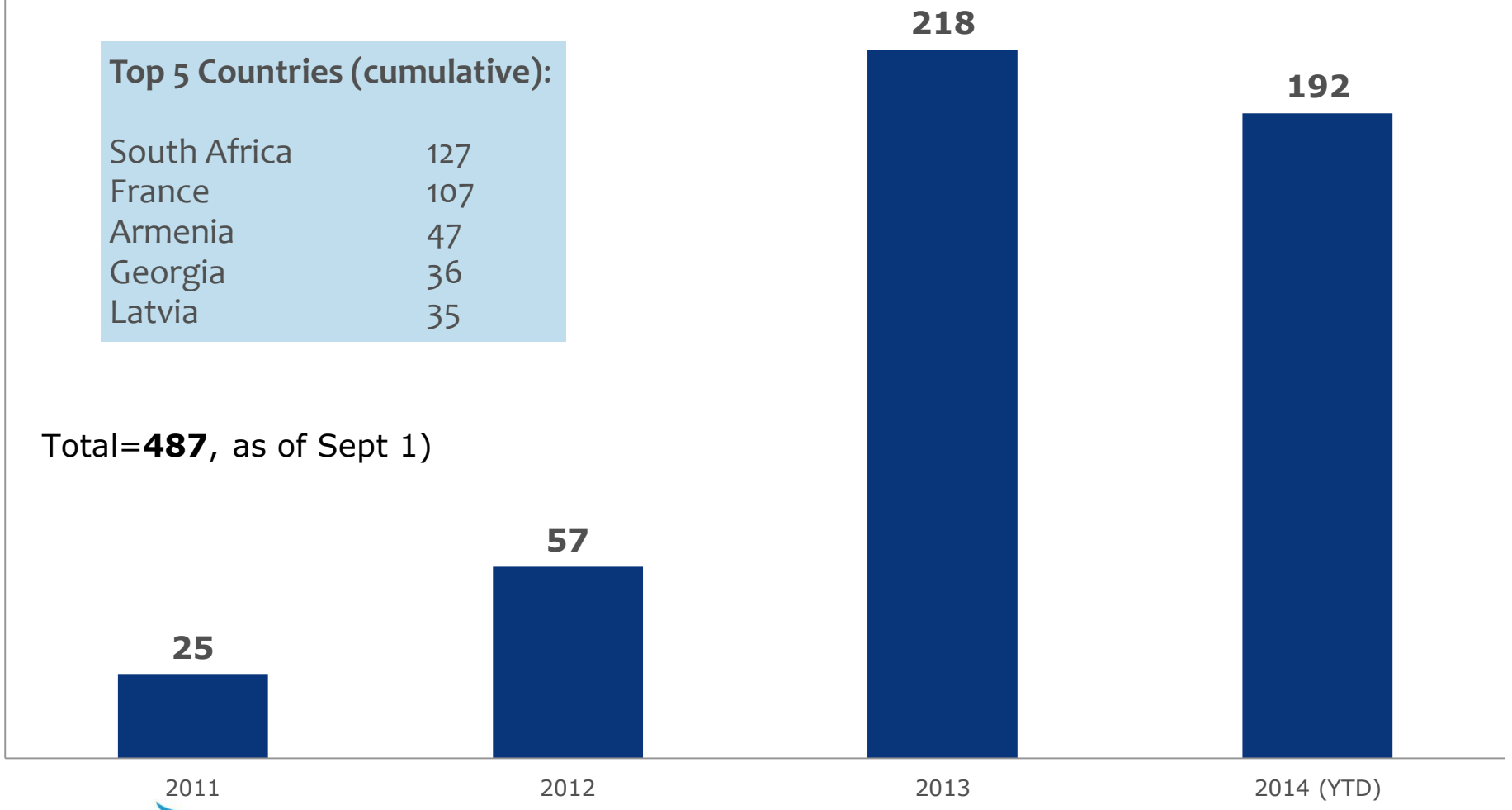
Numbers of patients who have received bedaquiline in compassionate use programs, 2011-2014

Top 5 Countries (cumulative):

South Africa	127
France	107
Armenia	47
Georgia	36
Latvia	35

Total=**487**, as of Sept 1)



TMC207 EAP- CT Status Update

Lithuania:

First Patient In (FPI)	11/1/2012
# patients screened	4
# patients approved/enrolled	3

Recruitment terminated – LPO expected Nov 2014

Russia:

FPI	11/1/ 2012
# patients screened	57
# patients approved/enrolled	54

Bedaquiline is now commercially available in Russia. Enrolment was closed on 14 Jul 2014
LPO expected Nov 2016

Cumulative reported deaths in expanded access programs, 2011-2014

Program	Number exposed to bedaquiline, N	Cumulative number of deaths, n (%)
Global Compassionate Use program	380	**7 (1.8%)**
ATU Program in France	107	**5 (4.7%)**
EAP Trial (Russia and Lithuania)	57	**2 (3.5%)**

Source: Janssen Safety Database

Safety Conclusions

- Based on the medical evaluation of the additional safety data collected in the C208 Stage 2 and C209 trials (including the Week 120 final analyses), and the 3 ongoing programs for expanded access/compassionate use, there were no new safety signals identified.

- Important adverse drug reactions for TMC207, as previously reported, include QT prolongation and transaminase increases.

- Both can be measured in the clinical setting and will continue to be monitored in clinical trials.

- The long-term effect of TMC207 on mortality will be evaluated further in the planned Stage 2 of the randomized and controlled STREAM trial, and in the Multi-Country MDR-TB Registry cohort study.

Phase III

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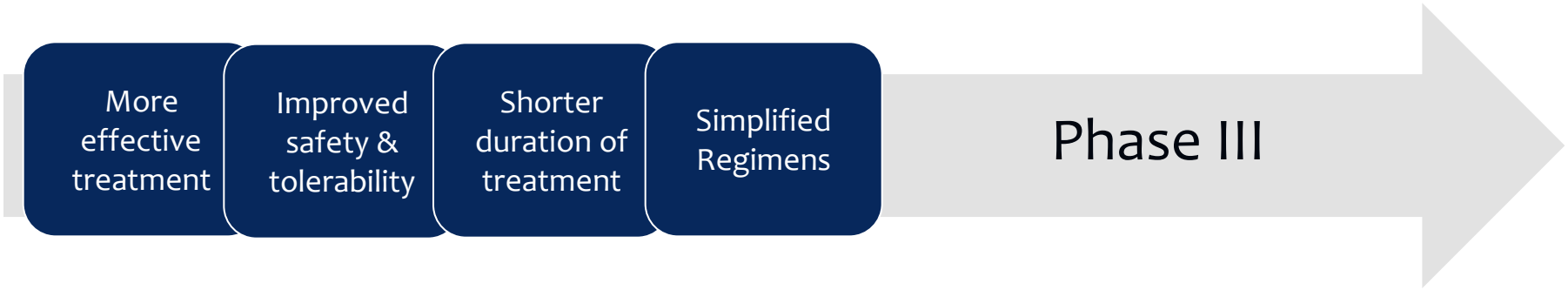

- 9-month Bangladesh regimen vs. WHO SOC:
  - Trial is ongoing
  - Sites in S. Africa, Vietnam, Ethiopia, Mongolia… (TBD)
- Janssen (bedaquiline) arms:
  - Sponsor: *International Union against TB & Lung Disease*
  - **6 mos of bedaquiline** on top of a 6-mo Bangladesh regimen
  - **9 mos of bedaquiline** on top of a 9-mo Bangladesh regimen **w/o injectable**
  - **FPI: Q1 2015; Final analysis: 2020**

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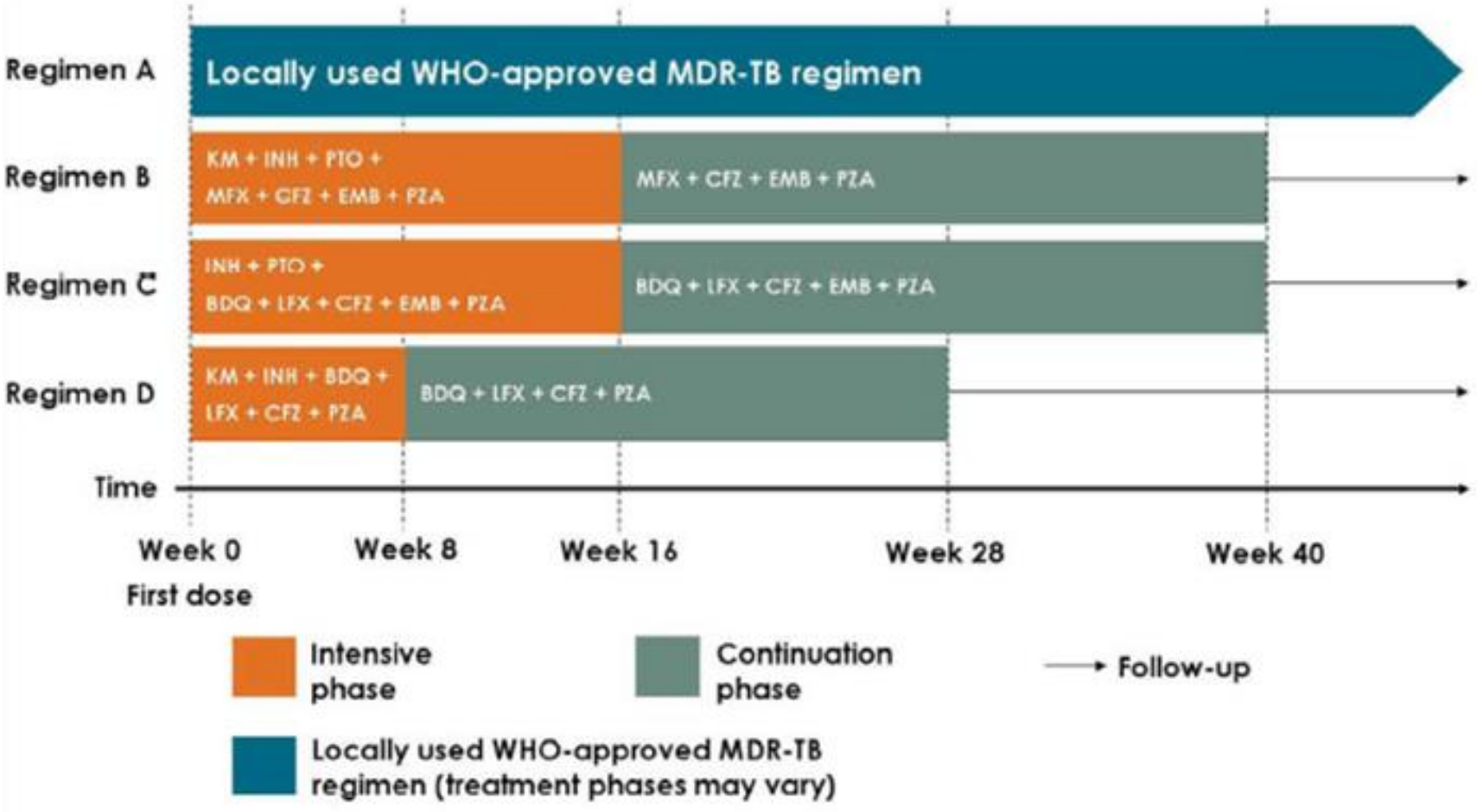
Phase III: STREAM Stage 2 Trial Design



N = 1,155 MDR-TB patients

Registries

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More effective treatment | Improved safety & tolerability | Shorter duration of treatment | Simplified Regimens | Real World Data Generation

Multi-Country MDR-TB Registry

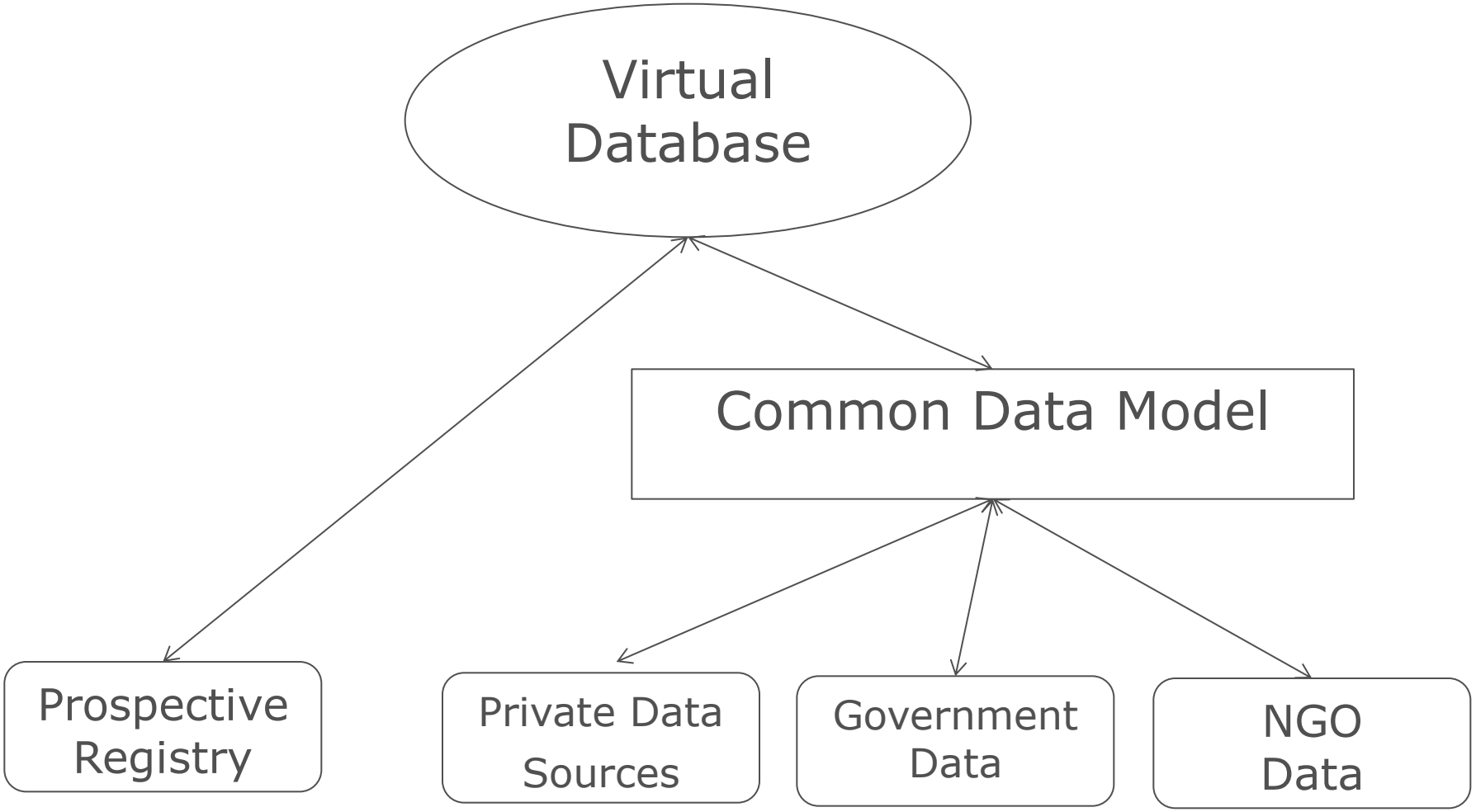
- Describe BDQ drug utilization data:
  - Indication, dose/duration, and type of treating site
- Describe adverse events among BDQ-treated patients, including deaths
- To compare the treatment outcomes between BDQ-treated patients and patients not treated with BDQ
- *Countries targeted as 'early adopters': South Africa, Vietnam, Philippines, Indonesia, Korea, Peru*
- *FPI: Q1 2015*

A public / private collaboration to track the introduction and use of bedaquiline and to capture treatment outcomes

Multi-Country MDR-TB Disease Registry

- Multi-Country Prospective Multi-Drug Resistant Tuberculosis Patient Registry to Monitor Bedaquiline Safety, Utilization, and Emergence of Resistance
- Supplements a post marketing commitment relative to the accelerated approval of Bedaquiline (BDQ) by the United States (U.S) Food and Drug Administration (FDA) and the European Medicines Agency (EMA). It is a requirement in Korea.
- Allows for more rapid collection of real-world data to evaluate the risks and benefits of BDQ treatment, to supplement Phase II data earlier than planned Ph III data availability
  - Larger patient population
  - Representative of target population for BDQ treatment

Data Sources

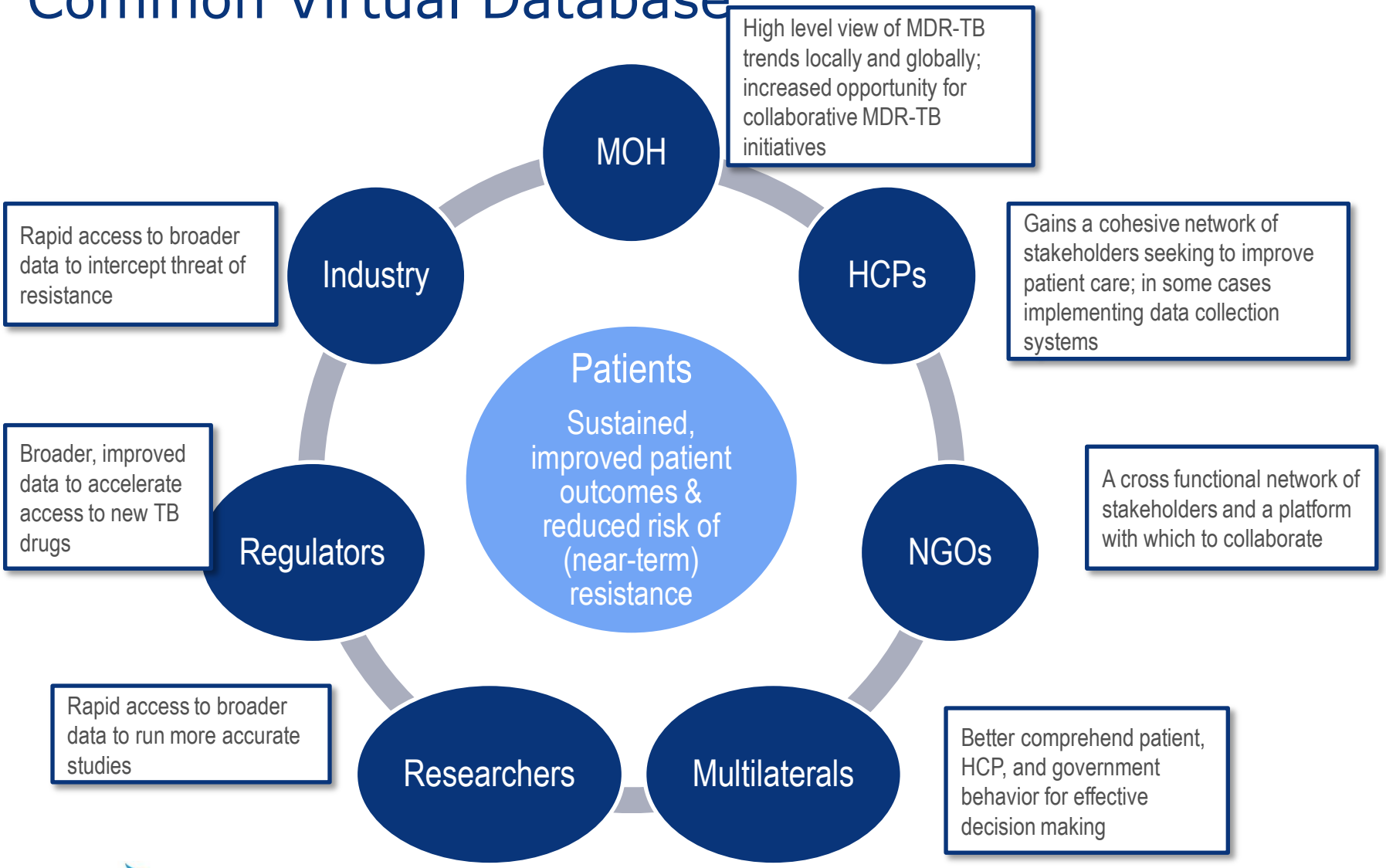


Note: data providers maintain autonomy of their own data

COMMON DATA MODEL

- Goal: to provide opportunity for countries and organizations not directly participating in the registry to submit data for analysis.
- Focuses on core set of data variables used to assess clinical care and outcomes of MDR-TB patients
- Reviews and recodes variable values to a set of common definitions where possible (“male”, “m”, “1”, etc. recoded to “M”).
- Transformed data are merged with recoded values for analyses with variable indicating source cohort to assess any clustering issues.

Benefits of Public-Private Partnerships and Common Virtual Database



Steering Committee Representatives

- Representative of stringent national regulatory authorities (SNRA),
- Representatives of health technical agencies involved in tuberculosis (eg CDC, The Union, KNCV, PIH, MSF, among others)
- Representatives of multilaterals, such as WHO, The World Bank, The Global Find to Fight AIDS, Tuberculosis and Malaria, the Stop TB Partnership, or others
- Representatives from TB Affected Communities
- Representatives from TB Affected Countries participating in the registry or in the common data model
- Representative from Foundations/Donors
- Representatives from the research community (e.g. US NIH, UK MRC, academia)
- Representative from the private sector (Sponsors)

Steering Committee Governance

- Directs the Registry's work and planning
- Advises what issues are appropriate for analysis using the Registry and the scope of the analysis
- Review of AEs
- Review submitted protocols for data analysis
- Ensure publication quality
- Awareness campaign
- Sustainability and Scale-up: beyond five year horizon (other companies, countries)

Access: *Where Needed Most*

By end of 2014 Bedaquiline will have been filed in countries that represent > 60% of the global MDR-TB burden

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Janssen Global Public Health

The Janssen Global Public Health (Janssen GPH) group complements the groundbreaking science of the Janssen Pharmaceutical companies of Johnson & Johnson with innovative strategies that improve access to medicines, foster collaborations, and support public health solutions to sustainably advance health care worldwide.

Current focus includes multi-drug resistant tuberculosis (MDR-TB); human immunodeficiency virus (HIV); elephantiasis and river blindness; intestinal worms; and use of mobile technologies (mHealth) to improve health outcomes.

Acknowledgements

- The patients and volunteers who participated in our studies

- Our Investigators: Andreas Diacon,[1] Alexander Pym,[2] Martin Grobusch,[3] Jorge de los Rios,[4] Eduardo Gotuzzo,[5] Irina Vasilyeva,[6] Vaira Leimane,[7] Francesca Conradie,[3] Shen-Jie Tang,[4]

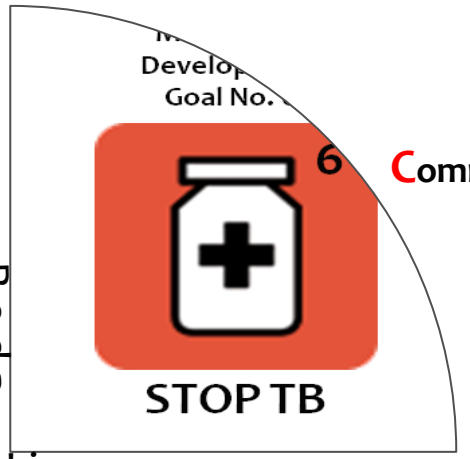
[1]Stellenbosch University, Cape Town, South Africa; [2]Medical Research Council and Kwazulu Research Institute for Tuberculosis and HIV (K-RITH), Durban, South Africa; [3]University of Amsterdam, Amsterdam, The Netherlands; [4]Hospital María Auxiliadora, Lima, Perú; [5]Cayetano Heredia University, Lima, Perú; [6]Russian Academy of Medical Sciences, Moscow, Russian Federation; [7]Riga East University Hospital, Riga, Latvia; [3]University of the Witwatersrand, Johannesburg, South Africa; [4]Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China;

Thank-you

Bedaquiline: *A World of Promise*

Collaborate to do more

Commit to eradicate

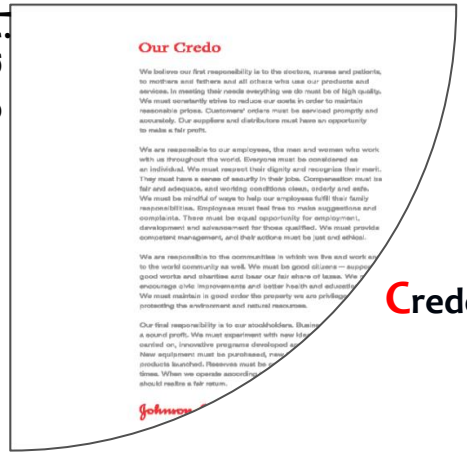


bedaquiline

Bedaquiline

Challenge to help more

Credo is our compass



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