TRAITEMENT DE *MYCOBACTERIUM TUBERCULOSIS* MULTIRÉSISTANT

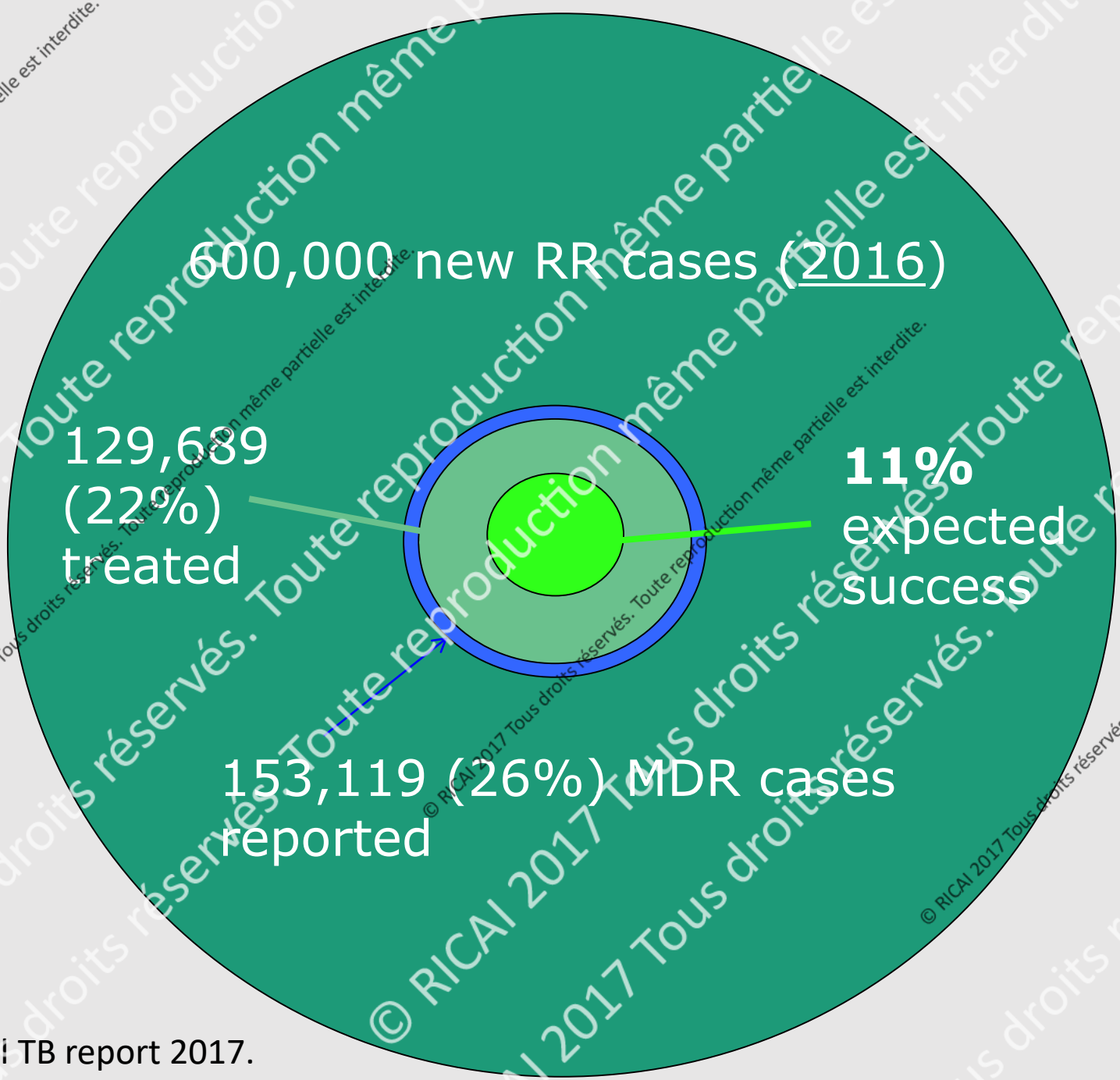
LORENZO GUGLIELMETTI

RICAI, 18 DÉCEMBRE 2017

CNR des Mycobactéries

OUTLINE

- Introduction
- New regimens and new drugs
- New drugs in France
- Future perspectives



WHO. Global TB report 2017.

MDR-TB TREATMENT

LONG

20 to 24 months according to WHO

POORLY TOLERATED

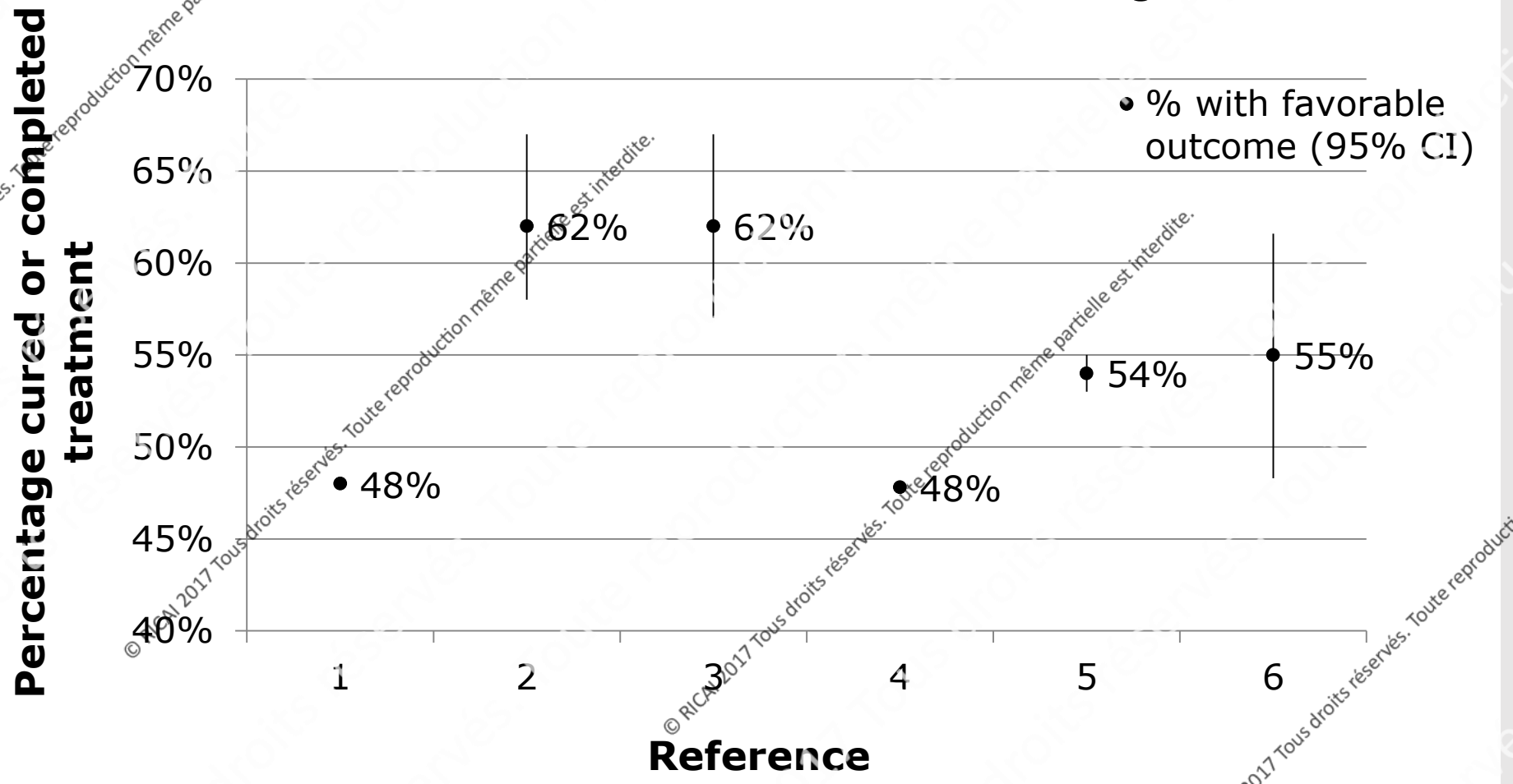
14600 pills + injections + adverse events

EXPENSIVE[1]

MDR-TB: 23.272 €; XDR-TB: 93.962 €

1. Gunther et al, Eur Resp J 2014.

Success on Conventional MDR-TB Treatment without new drugs



[1]WHO Global Report, 2013 [2]Orenstein, Lancet, 2009*; [3]Johnston, PLoS, 2009*; [4]Diacon, AAC, 2012; [5]Ahuja, PLoS, 2012*; [6]Skripconoka, ERJ, 2013

Courtesy of Carole Mitnick.

OUTLINE

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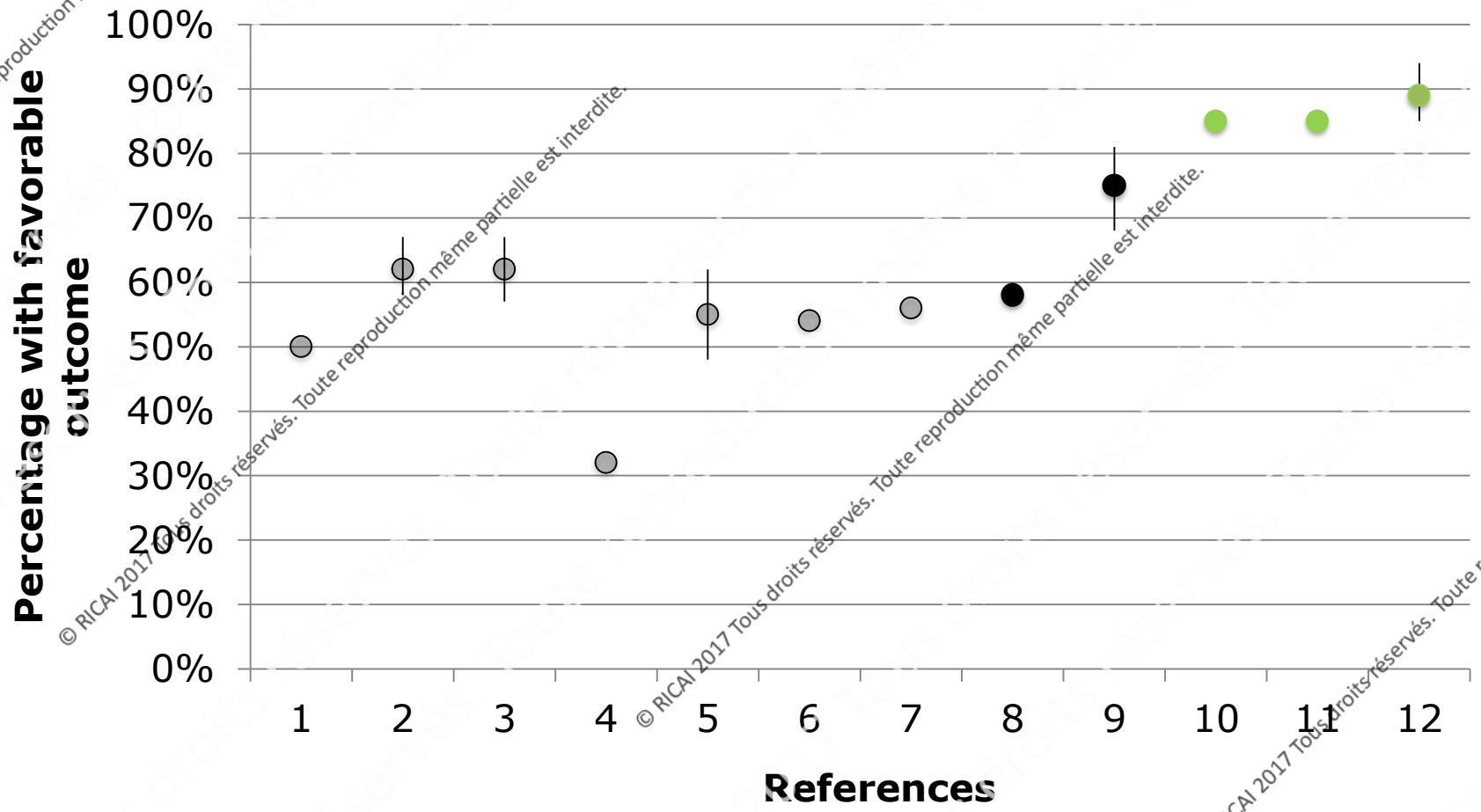
Success of Conventional, Novel, and Short MDR-TB treatments



[1]WHO Global Report, 2014; [2]Orenstein, Lancet, 2009*; [3]Johnston, PLoS, 2009*; [4]Diacon, NEJM, 2014-P; [5]Skriponoca, ERJ, 2013-P; [6]Ahuja, PLoS, 2012*; [7]Bonnet, IJTLD, 2016; [8]Diacon, NEJM, 2014-A; [9]Skriponoca, ERJ, 2013-A; [10] Aung, IJTLD, 2014; [11] Piubello, IJTLD, 2015;[12] Kuaban, IJTLD, 2014;

Courtesy of Carole Mitnick.

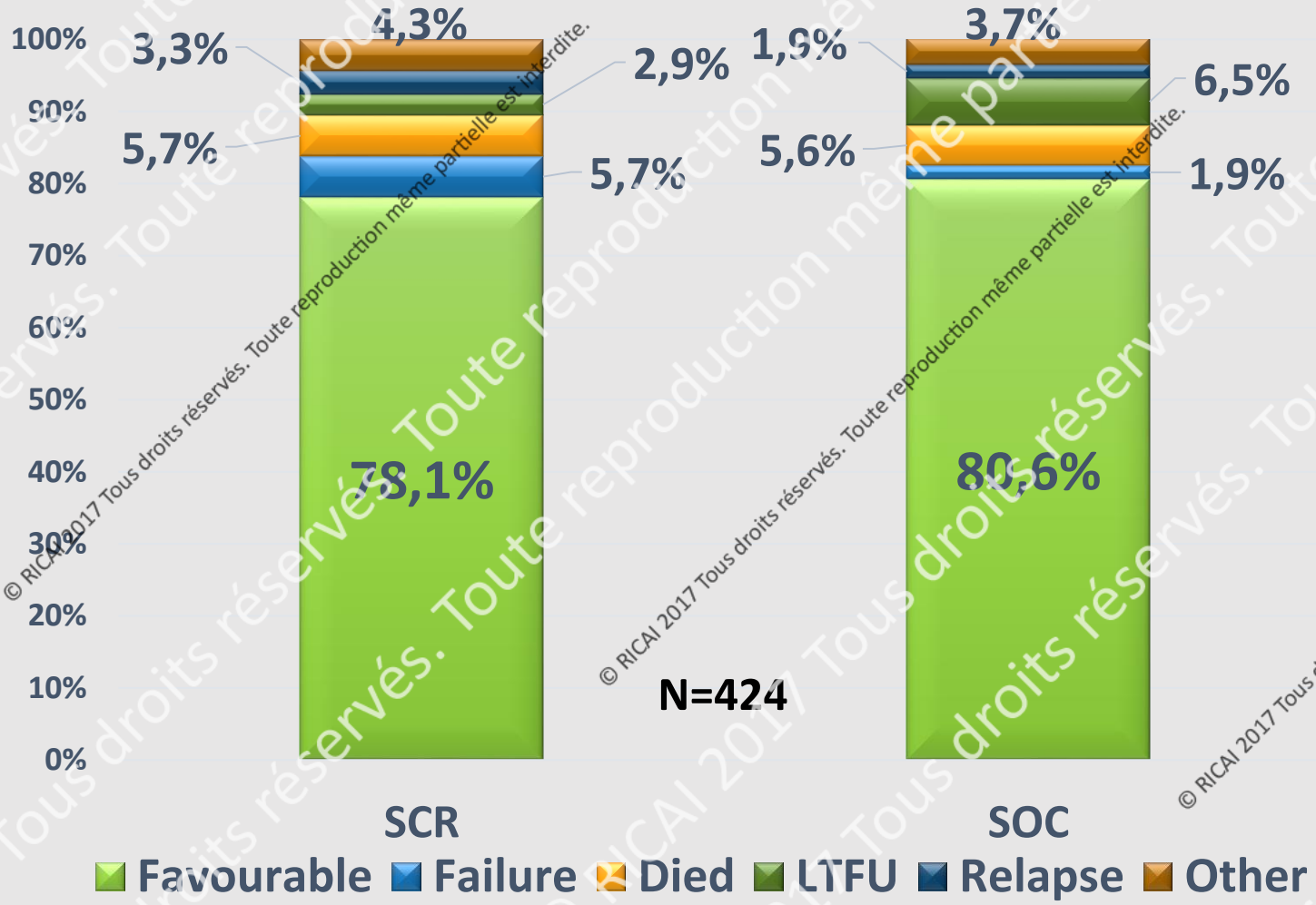
Shortcourse “Bangladesh” MDR-TB regimen

4-6 Km-Mfx-Pto-Cfz-Z-$H_{high-dose}$-E / 5 Mfx-Cfz-Z-E

Intensive phase
Duration: 4-6 months
Composition: 4 second-line drugs

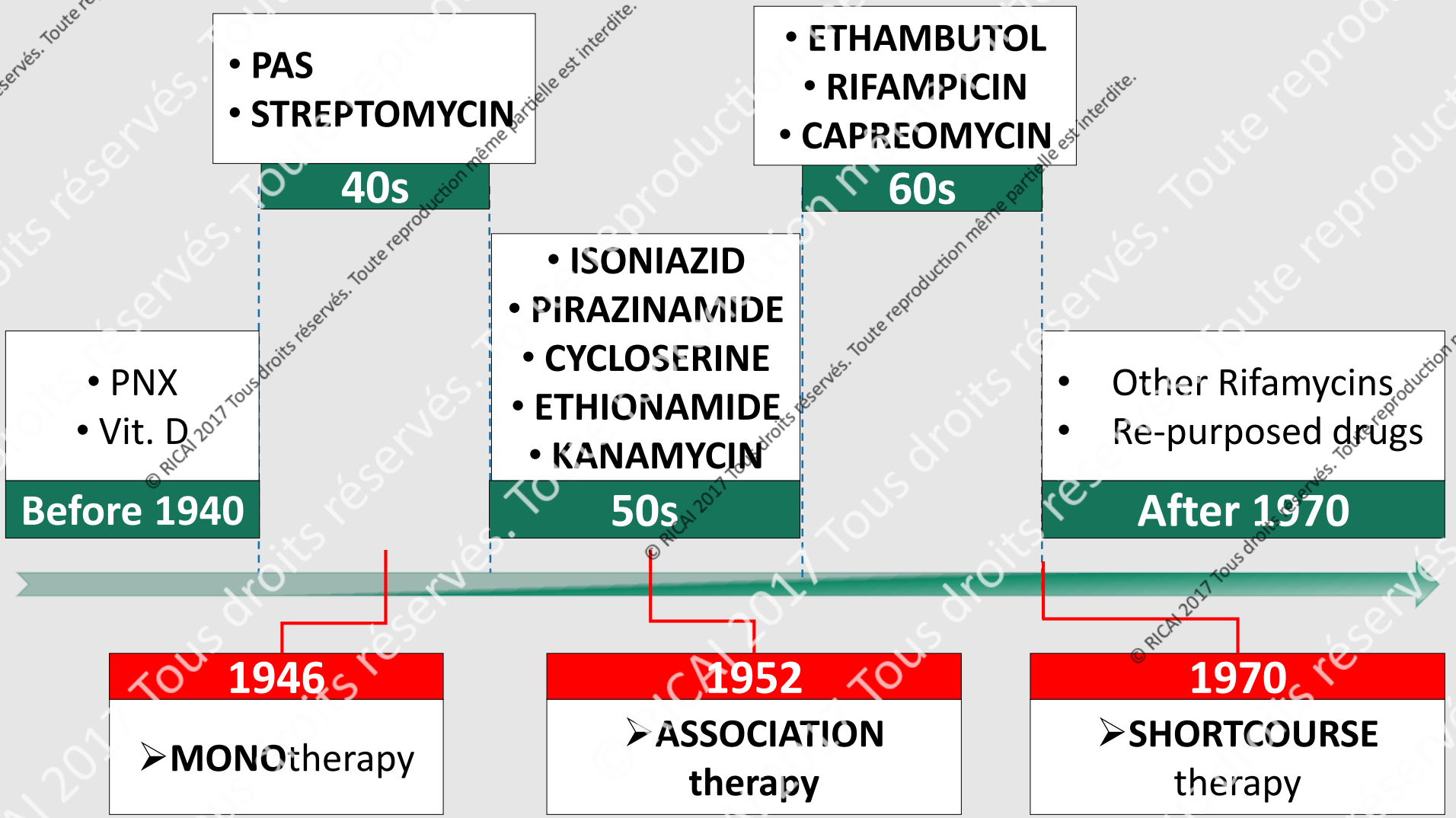
Continuation phase
Duration: 5 months
Composition: 2 second-line drugs

Shortcourse treatment: STREAM I



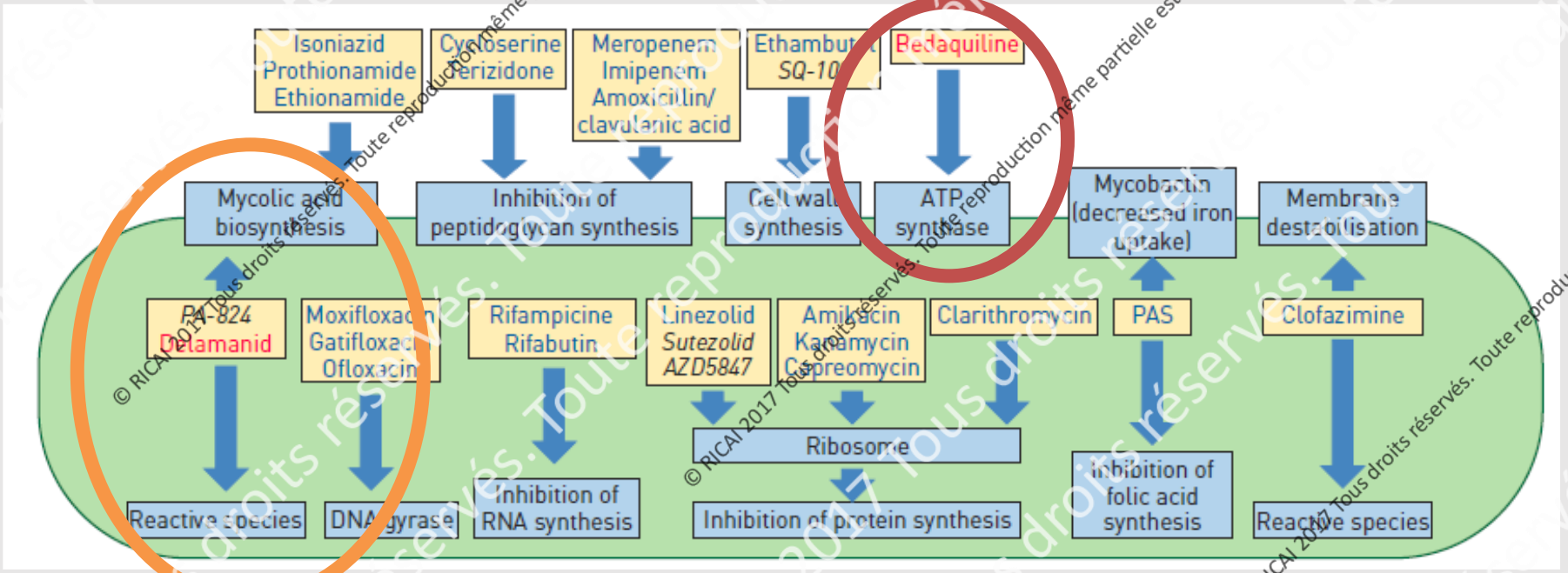
Nunn A. Union World Conference on Lung Health, Satellite Session, October 12 ,2017

Discovery of TB drugs



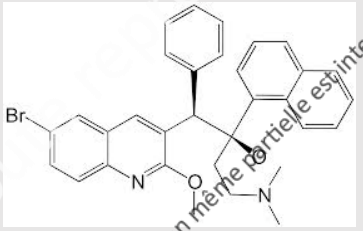
New TB drugs

2012 (FDA)
2013 (EMA)

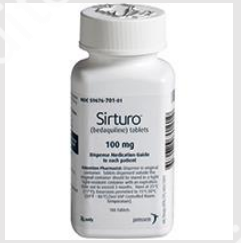


2014 (EMA)

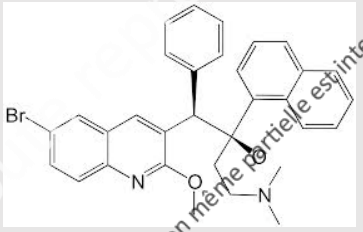
Image from Olaru et al, Eur Resp J 2014.



BEDAQUILINE (Bdq)



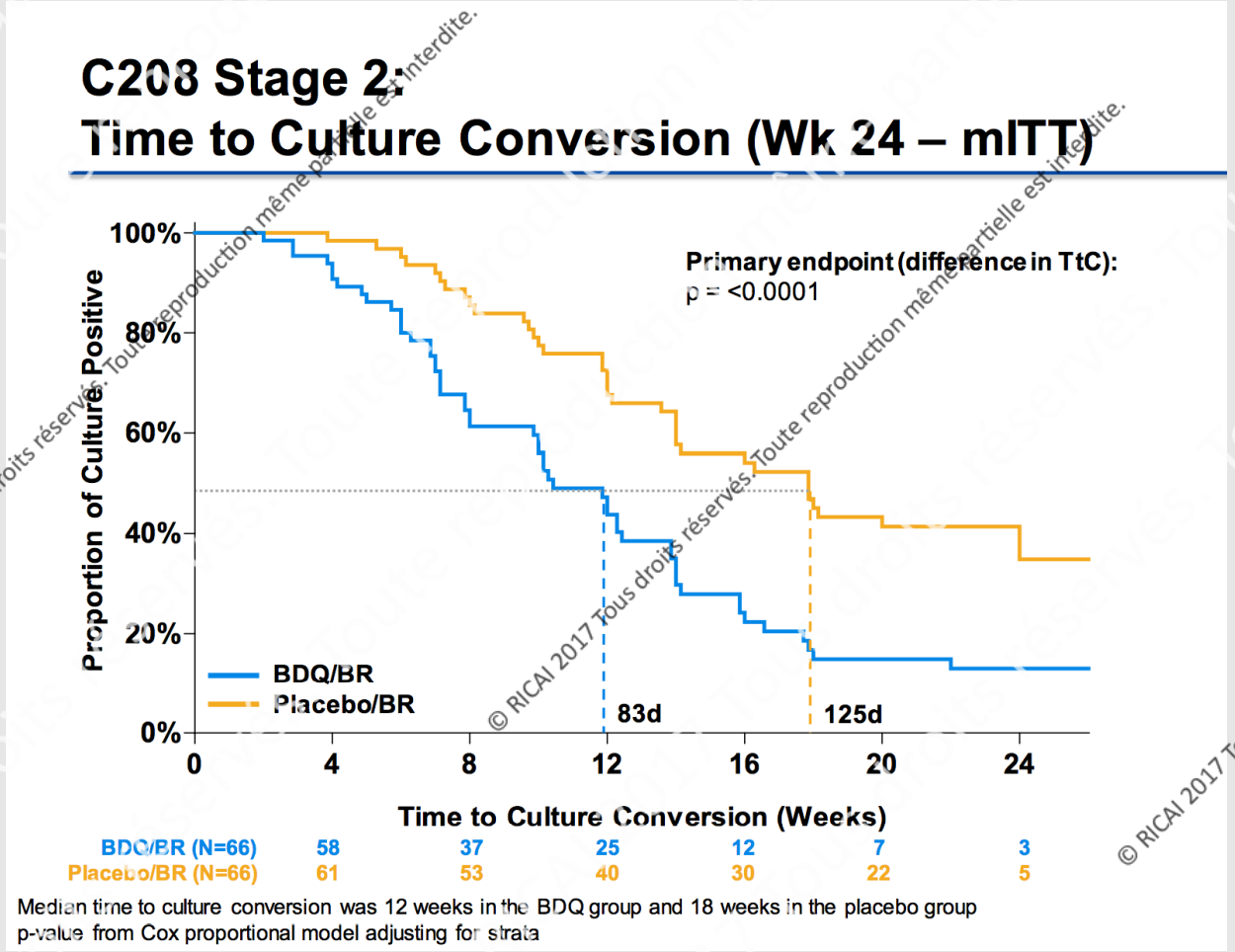
- Diarylquinoline
- Inhibitor of the mycobacterial ATP synthase
- PK: good oral bioavailability, terminal elimination half-life: 5,5 months
- Dosage: 400 mg/d for 14 d, then 200 mg thrice/w



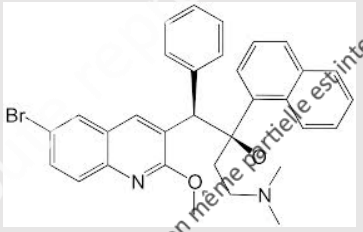
Bdq: C208 Stage 2

Phase IIa

N=160

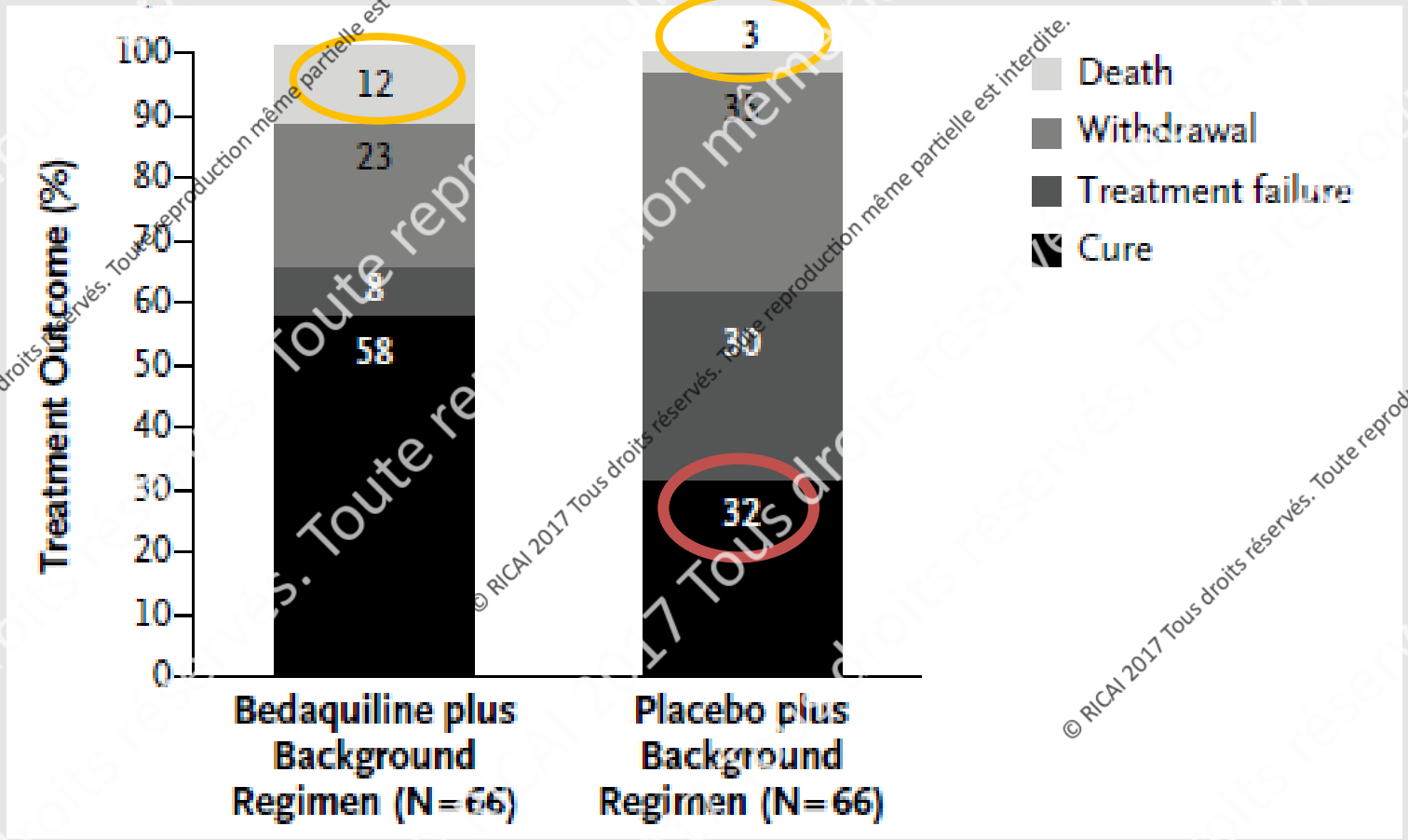


Diacon et al, NEJM 2014

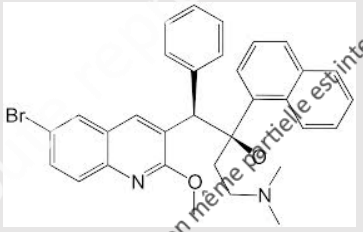


Bdq: C208 Stage 2

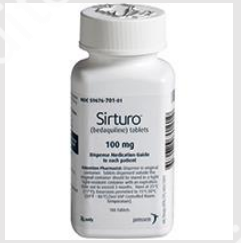
N=132



Diacon et al, NEJM 2014



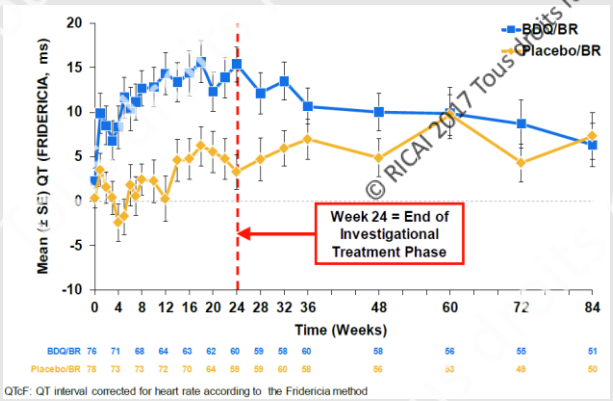
Bdq: Safety



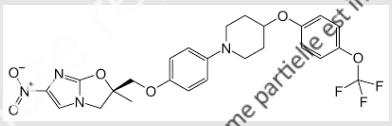
Data from the pooled RCT population (N = 207)

Bdq arm:

- Higher incidence of hepatic events (9% vs. 2%)
- Higher incidence of severe adverse events (7% vs. 2%)
- Higher rate of QT interval prolongation



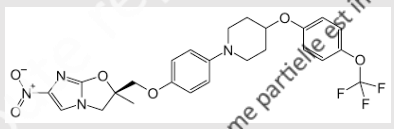
Diacon et al, NEJM 2009; Diacon et al, NEJM 2014.

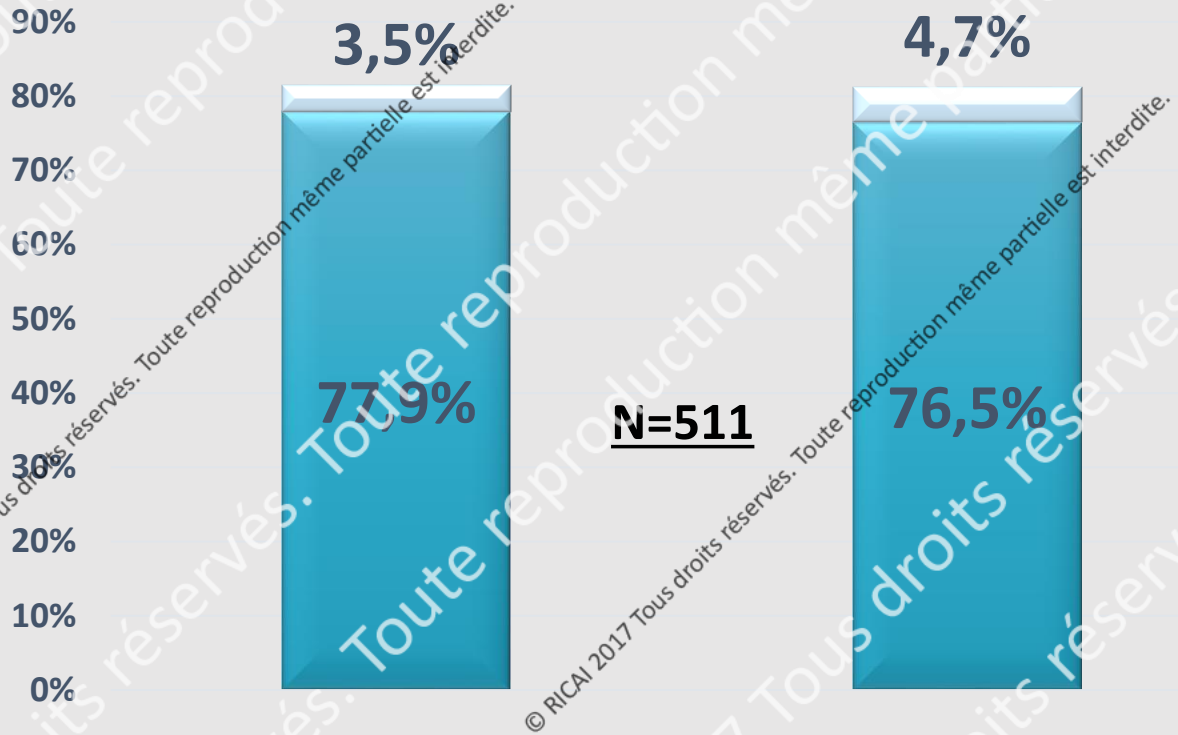


DELAMANID (Dlm)

- Nitroimidazole
- Inhibitor of mycolic acid synthesis
- PK: good oral bioavailability – enhanced with food, half-life: 30 hours
- Dosage: 100 mg bid

Dlm: Phase III trial (213)

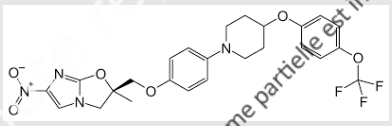




Primary outcome: SCC in mITT

6 days faster in Dlm arm (p=0.056)

Geiter L. Union World Conference on Lung Health, Satellite Session, October 12 ,2017

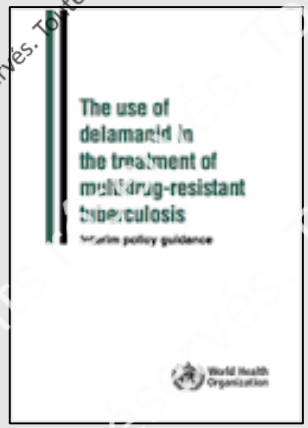


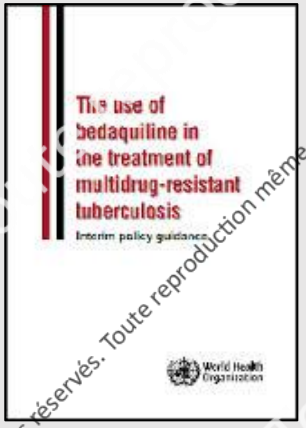
Dim: Safety

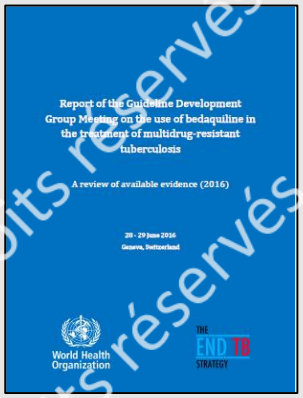
Data from Trial 213

- Dim arm: Increased rate of GI and QT AEs
- QTcF prolongation: max 5.3 at W8, decrease at W26
- No difference in other AEs/SAEs

New drugs: Recommendations







Adult MDR-TB patients:

- when an effective treatment cannot be designed;
- resistance *(or intolerance)* to any FQ or injectable;
- risk factors for poor outcome

Dlm+Bdq: only "if no other options"

Treatment duration: <u>24 weeks</u>

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Cohort of MDR-TB patients treated with Bdq in France – **microbiological efficacy** and safety

45 MDR-TB patients

Sputum culture conversion and safety

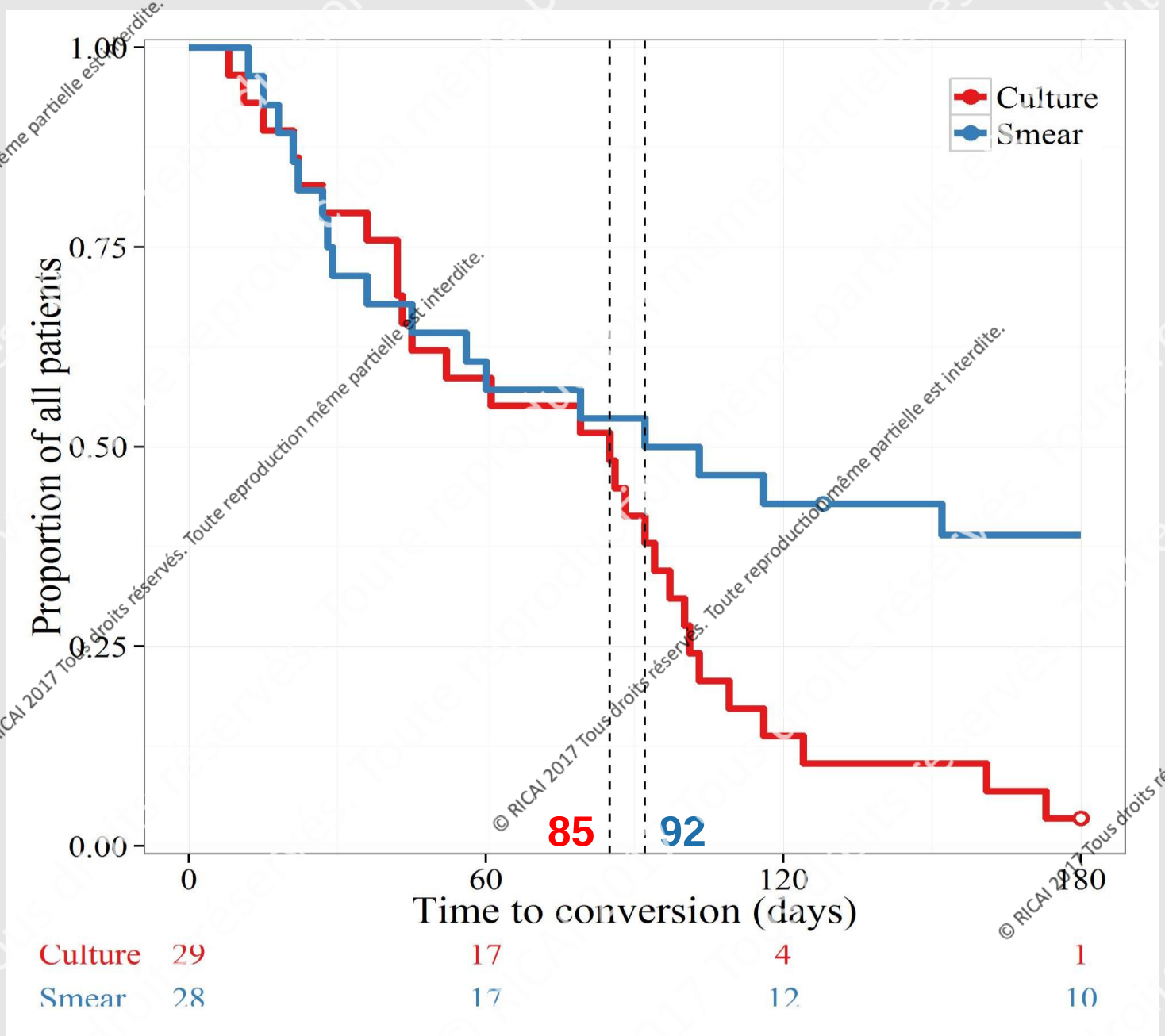
1

3 centres
Retrospective cohort

2

6 months endpoint:
96% culture conversion
Good safety

Guglielmetti et al. Clin Inf Dis 2015.



Guglielmetti et al. Clin Inf Dis 2015.

Cohort of MDR-TB patients treated with Bdq in France – **treatment outcome** and safety

45 MDR-TB patients

Sputum culture conversion and safety

Treatment outcome and safety

1 — 3 centres
Retrospective cohort

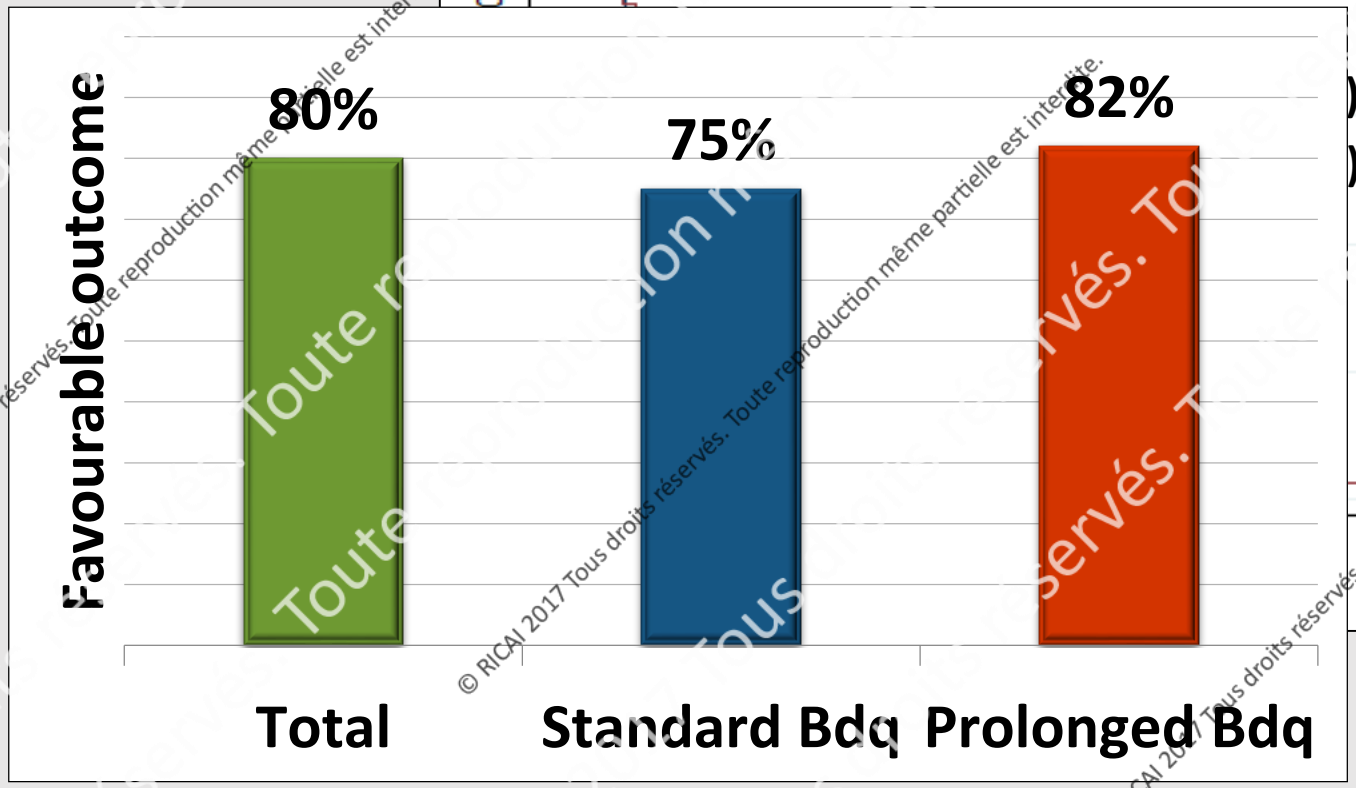
2 — **6 months** endpoint:
96% culture conversion
Good safety

3 — Follow-up **> 36 months**
(18-24 treatment + 12-24 FU)
80% de succès
Toxicité fréquente

Guglielmetti et al. Eur Resp J, 2017.

Comparing prolonged and standard Bdq duration

Efficacy:



Guglielmetti et al. Eur Resp J, 2017.

Comparing prolonged and standard Bdq duration

Safety:

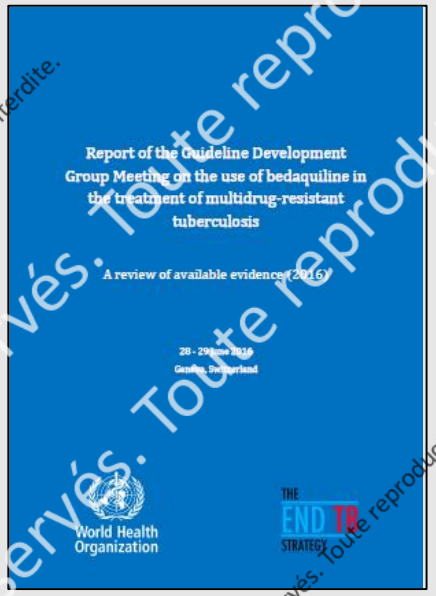
	Standard	Prolonged	p
Any adverse event (AE)	100 %	97 %	NS
Severe AE	42 %	70 %	NS
Serious AE	8 %	21 %	NS
Liver enzymes elevation	50 %	33 %	NS
QT >500ms	17 %	18 %	NS
Bdq stopped due to AE	8 %	6 %	NS

Guglielmetti et al. Eur Resp J, 2017.

Update of WHO recommendations (2017)

"…Data from the French cohort allowed to assess whether the duration of bedaquiline treatment had an effect on QTc prolongation. Data seemed to indicate an absence of effect of duration of bedaquiline exposure [higher than six months] on QTc prolongation >480 ms.

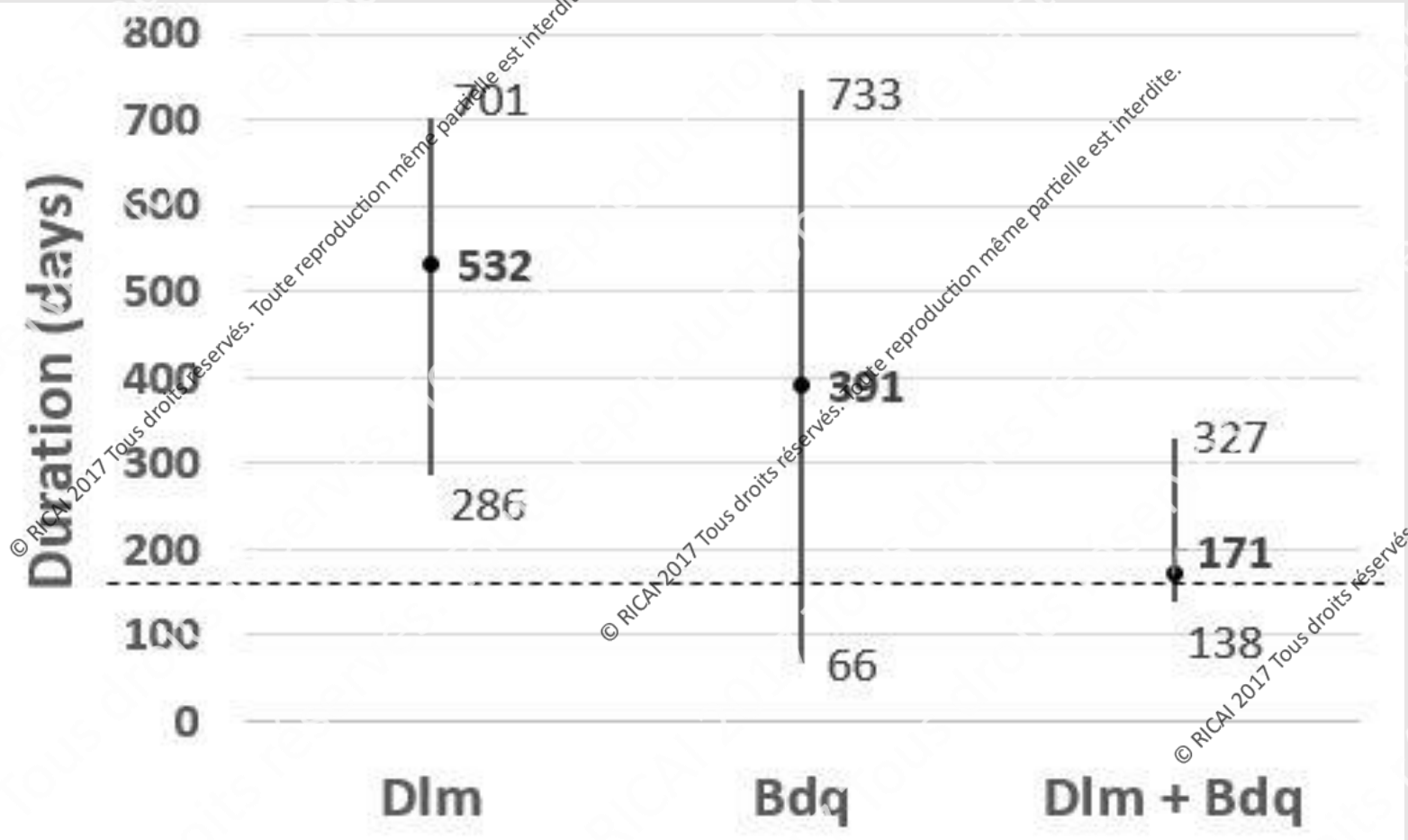
…However, the very limited sample size needs to be noted."



Conclusion: There is limited evidence, so far, to warrant its use beyond 6 months.

Guglielmetti et al. Eur Resp J, 2017.

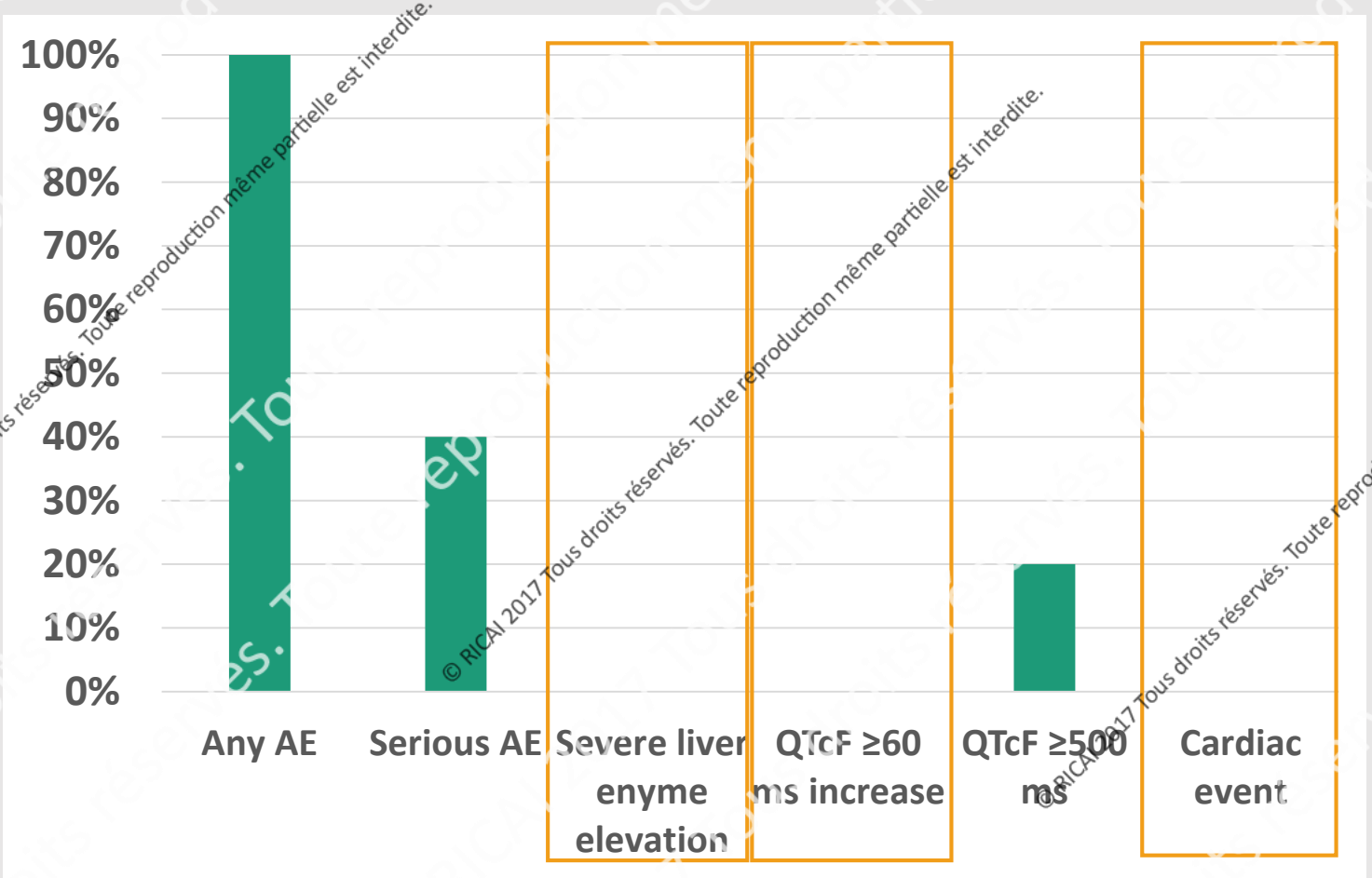
Bedaquiline – Delamanid combination



Guglielmetti et al. Eur Resp J – in revision.

Bedaquiline – Delamanid combination

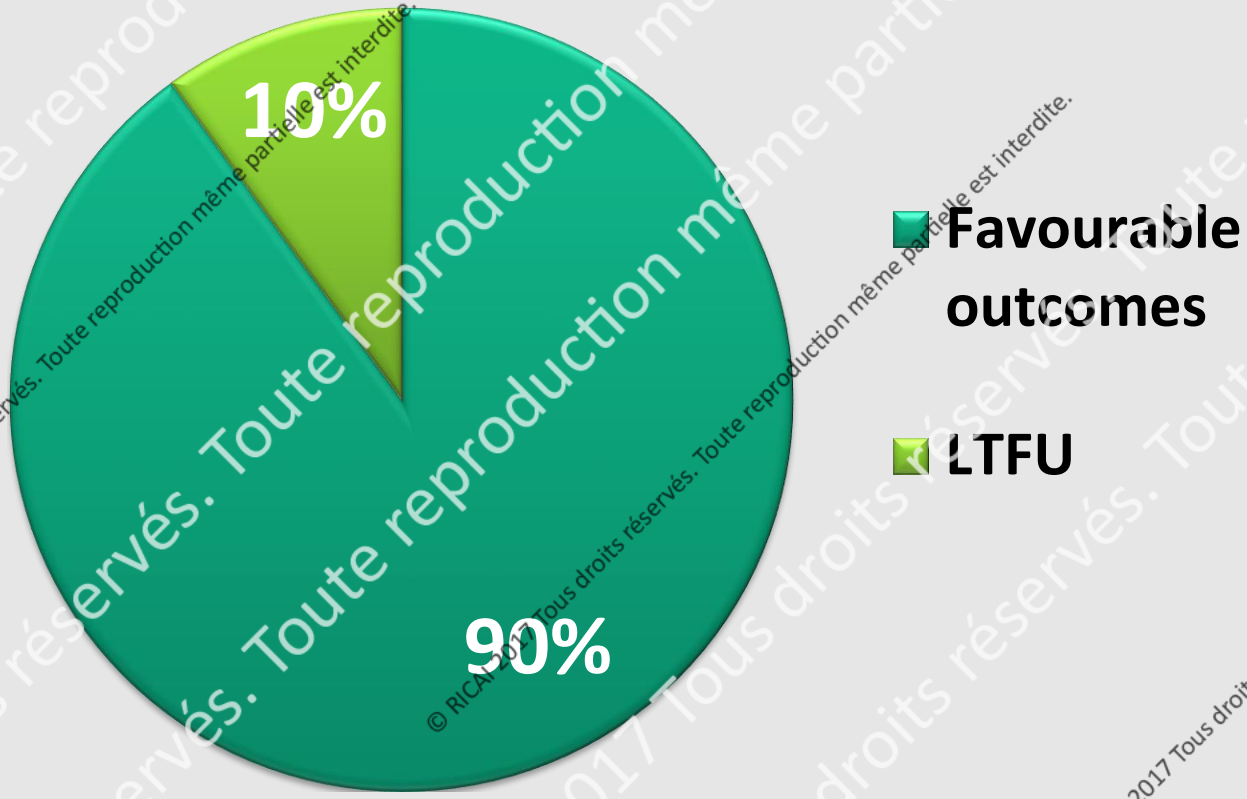
Safety:



Guglielmetti et al. Eur Resp J – in revision.

Bedaquiline – Delamanid combination

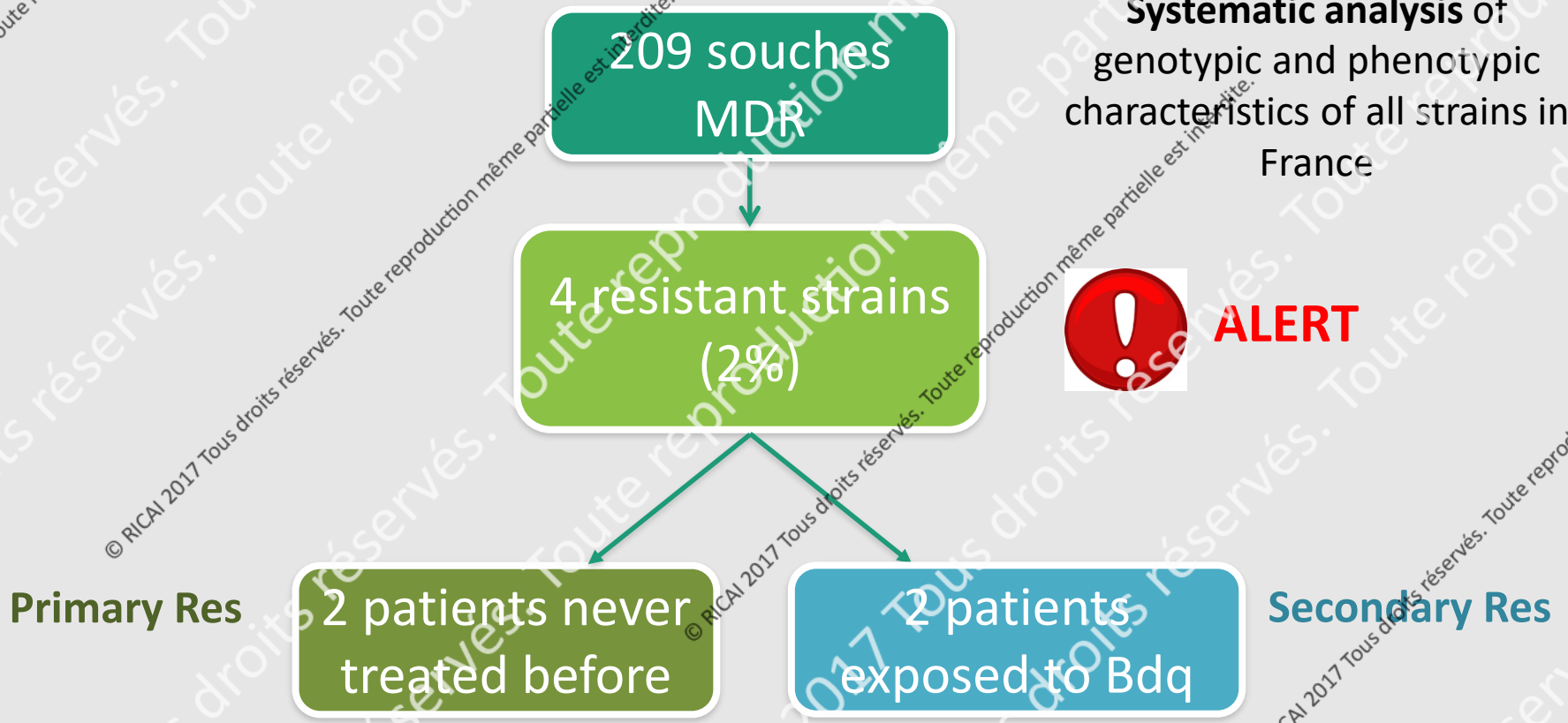
Efficacy:



Time to sputum culture conversion (median, IQR)	77 (43-88)

Guglielmetti et al. Eur Resp J – in revision.

Bdq resistance surveillance (CNR Lab, 2014-2015)



Conclusion: rapid resistance selection!

Veziris N, et al. Eur Resp J, 2017.

OUTLINE

- Introduction
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Global New TB Drug Pipeline [1]

Preclinical Development | **Clinical Development**

Early Stage	GMP/ GLP Tox	Phase 1	Phase 2	Phase 3
Caprazen nucleoside CPZEN-45*	BTZ-043*	OPC-167832*	Delpazolid (LCB01-0371)	Bedaquiline* (TMC-207)
Cyclopeptide SATB082*	TBAJ-587	Q203*	Sutezolid (PNU100480)	Delamanid* (OPC-67683)
Spectinamide 1810*	TBI-166	GSK-070*	Contezolid MRX-4/MRX-1	Pretomanid* (PA-824)
Gyrase inhibitor SPR-720 (pVXc-486)*	TBI-223	TBA-7371*	SQ-109*	
Pyrazolo pyridine carboxamide TB-47*			PBTZ169*	

New chemical class* Known chemical classes for any indication are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone, imidazopyridine amide.

[1] New Molecular Entities not yet approved, being developed for TB or only conditionally approved for TB. Showing most advanced stage reported for each. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

Ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline/discovery

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated: September 2017

Global TB Drug and Regimen Clinical Research [1]

Ongoing Clinical Development Research: Strategy/Optimization/Regimen Development

Phase 2

Bedaquiline-Delamanid (ACTG 5343)

Bedaquiline - Pretomanid - Pyrazinamide (BPaZ) (NC-005)

Bedaquiline - Pretomanid – Moxifloxacin - Pyrazinamide (BPaMZ) (NC-005)

Levofloxacin with OBR for MDR-TB (OPTI-Q)

Linezolid Dose-Ranging

Clofazimine

Nitazoxanide

High Dose Rifampicin (PANACEA)

TB PRACTECAL - regimens with Bedaquiline-Pretomanid-Linezolid

Phase 3 Regimens

Bedaquiline-STREAM MDR-TB Trial Stage 2 with oral OBR (9 mo) or OBR with injectables (6 mo)

Bedaquiline-Pretomanid-Linezolid (NiX-TB)

Delamanid (OPC-67683) with OBR for MDR-TB

High Dose Rifampicin for DS-TB (RIFASHORT)

Rifapentine - Moxifloxacin for DS-TB

Pretomanid-Moxifloxacin-Pyrazinamide (STAND)

Optimization/Post Market

Bedaquiline-Linezolid with OBR for MDR-TB (NExT Trial)

endTB 5-Regimen Trial for MDR TB

PredictTB – PET/CT, biomarkers DS-TB, 4 mo

Known chemical classes are color coded: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone , imidazopyridine amide.

[1] Strategy trials, regimen development, open label, repurposed drug studies. Details for projects listed can be found at http://www.newtbdrugs.org/pipeline/clinical

[2] OBR = Optimized Background Regimen

WORKING GROUP ON NEW TB DRUGS

www.newtbdrugs.org

Updated:September 2017

Collaborations, remerciements, financements

COLLABORATIONS :

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Marie LACHATRE
Yazdan YAZDANPANAH

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Linda BARKANE
Liga KUKSA

DIM Malinf

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Diane MARTIN (M2)

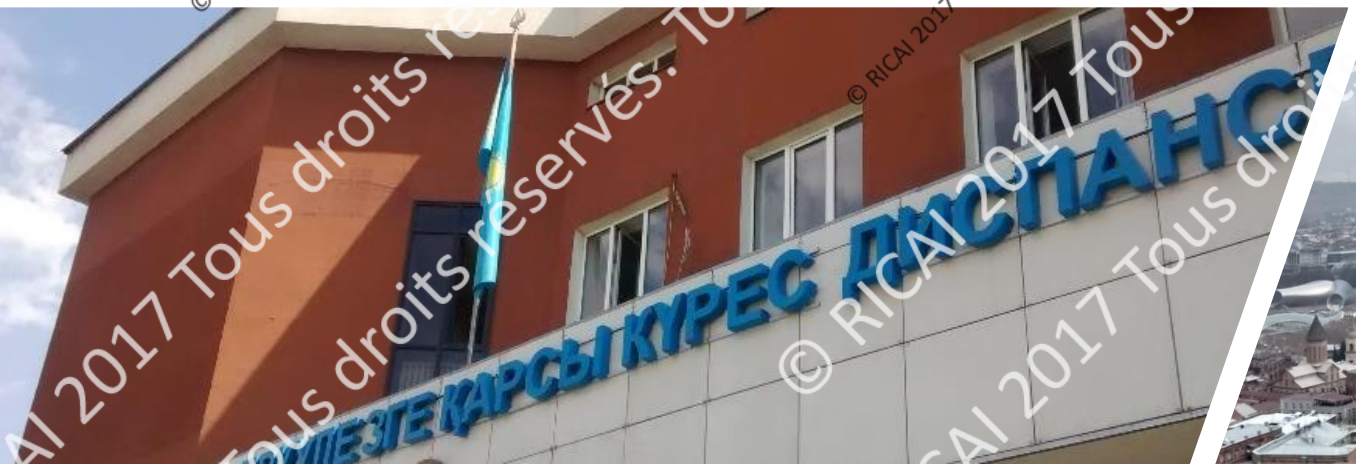
CNR-MyRMA
National reference centre for mycobacteria (Pitié-Salpêtrière)

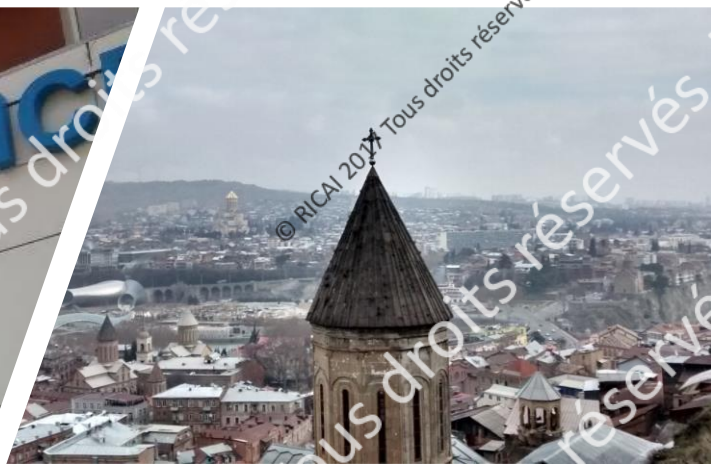
SATT LUTECH

SORBONNE UNIVERSITÉS

Inserm

Merci…





endTB

Sponsor

Médecins Sans Frontières

PI

Carole Mitnick
Lorenzo Guglielmetti

Characteristics

Phase III, Adaptive

Population

R-R, FQ-S

Target

750 patients

Estimated results

September 2020

Bdq + Lzd + Mfx + Z

Bdq + Cfz + Lzd + Lfx + Z

Bdq+Dlm+Lzd +Lfx + Z

Dlm + Cfz + Lzd + Lfx + Z

Dlm + Cfz + Mfx + Z

for 39 weeks

Vs.

Standard of care

Randomization adapted to efficacy at W8 and W39

STREAM Stage 2

Sponsor

Union

PI

Andrew Nunn
Sarah Meredith

Characteristics

Phase III

Population

R-R, FQ- and SLI-S

Target

1155 patients

Estimated results

April 2021

Bdq + Lfx + Cfz + E + Z + (hH + Pto for 16W)

for 40 weeks

Bdq + Lfx + Cfz + Z + (hH + Km for 8W)

for 28 weeks

Vs.

Standard of care

Standard of care: conventional or shorter?

NiX-TB

Sponsor

TB Alliance

PI

Francesca Conradie
Andreas Diacon

Characteristics

Phase III, Uncontrolled

Population

XDR

Target

200 patients

Estimated results

October 2018

Bdq + Pa + Lzd

for 26 to 39 weeks

Linezolid 1200 mg qd

Preliminary results available: 30 pts, 100% culture conversion at 4 mts (excl unfav outcomes), 1 relapse.

NeXT

Sponsor

University of Cape Town

PI

Keertan Dheda

Characteristics

Phase III

Population

R-R, FQ- and SLI-S

Target

300 patients

Estimated results

January 2019

Lzd + Bdq + Lfx + Z + (Eto or hH or Tzd)

for 6 to 9 months

Vs.

Standard of care

Regimen: based on *inhA* / *ethA* rapid molecular testing

Duration: based on sputum smear results

TB-PRACTECAL

Sponsor

Médecins Sans Frontières

PI

Bern Nyang'wa

Characteristics

Phase II/III, MAMS

Population

R-R (MDR+XDR)

Target

630 patients

Estimated results

June 2020

Bdq + Pa + Lzd + Mfx

Bdq + Pa + Lzd + Cfz

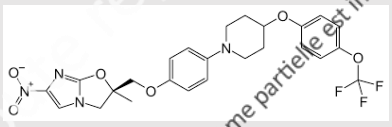
Bdq + Pa + Lzd

for 24 weeks

Vs.

Standard of care

One or two exp arms will be dropped based on culture conversion at 8 weeks



DLM: CLINICAL Phase IIb (208)

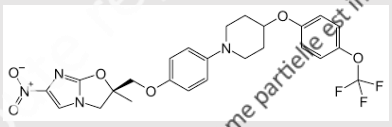
TABLE 2 Long-term (24 month) treatment outcomes after treatment with delamanid in combination with an optimised background treatment regimen: MDR- and XDR-TB patients

Treatment outcome	Long-term treatment[#]	Short-term treatment[¶]	All patients[+]
Favourable	143 (74.5; 67.7–80.5)[§]	126 (55.0; 48.3–61.6)[§]	269 (63.9; 59.1–68.5)
Cured	110 (57.3; 50.0–64.4)	111 (48.5; 41.8–55.1)	221 (52.5; 47.6–57.4)
Completed	33 (17.2; 12.1–23.3)[§]	15 (6.6; 3.7–10.6)[§]	48 (11.4; 8.5–14.8)
Unfavourable	49 (25.5; 19.5–32.3)[§]	103 (45.0; 38.4–51.7)[§]	152 (36.1; 31.5–40.9)
Died	2 (1.0; 0.1–3.7)[§]	19 (8.3; 5.1–12.7)[§]	21 (5.0; 3.1–7.5)
Failed	32 (16.7; 11.7–22.7)	26 (11.4; 7.6–16.2)	58 (13.8; 10.6–17.4)
Defaulted	15 (7.8; 4.4–12.6)[§]	58 (25.3; 19.8–31.5)[§]	73 (17.3; 13.8–21.3)

≥ 6 months Dlm

< 6 months Dlm

Skripconoka et al, Eur Resp J 2013



DLM: CLINICAL Phase IIb (208)

TABLE 2 Long-term (24 month) treatment outcomes after treatment with delamanid in combination with an optimised background treatment regimen: MDR- and XDR-TB patients

Treatment outcome	Long-term treatment[#]	Short-term treatment[¶]	All patients[+]
Favourable	143 (74.5; 67.7–80.5)[§]	126 (55.0; 48.3–61.6)[§]	269 (63.9; 59.1–68.5)
Cured	110 (57.3; 50.0–64.4)	111 (48.5; 41.8–55.1)	221 (52.5; 47.6–57.4)
Completed	33 (17.2; 12.1–23.3)[§]	15 (6.6; 3.7–10.6)[§]	48 (11.4; 8.5–14.8)
Unfavourable	49 (25.5; 19.5–32.3)[§]	103 (45.0; 38.4–51.7)[§]	152 (36.1; 31.5–40.9)
Died	2 (1.0; 0.1–3.7)[§]	19 (8.3; 5.1–12.7)[§]	21 (5.0; 3.1–7.5)
Failed	32 (16.7; 11.7–22.7)	26 (11.4; 7.6–16.2)	58 (13.8; 10.6–17.4)
Defaulted	15 (7.8; 4.4–12.6)[§]	58 (25.3; 19.8–31.5)[§]	73 (17.3; 13.8–21.3)

≥ 6 months Dlm | **< 6 months Dlm**

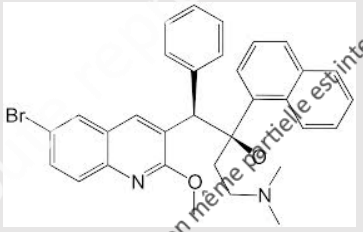
Long-term mortality:

6 (2,9 %) in long-term Dlm vs. 31 (12,0 %) in short-term Dlm

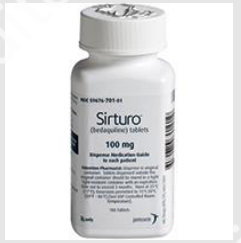
Skripconoka et al, Eur Resp J 2013; Wells et al, Eur Resp J 2015.

STREAM I

- 4 sites (Ethiopia, Mongolia, SA, Vietnam)
- MDR-TB patients with no mutation in *gyrA, rrs*
- 9-11 months regimen vs SOC -> FU 132 weeks
- 424 randomized pts: mITT 383 pts, 33% HIV+
- Good study retention



BDQ: DEATHS IN C208 AND C209



Arm and study	N. of deaths (%)	Timing	TB-related	Related to cardiac events
Bdq arm (C208 stage 1&2)	12 (12%)	11 out of 12 after stopping Bdq (average 425 days after last dose)	4	0
Placebo arm (C208 stage 1&2)	4 (4%)		3	0

Diacon et al, NEJM 2009; Diacon et al, NEJM 2014; Pym et al, Eur Resp J 2015.