HOW MUCH DOES IT COST TO DEVELOP A NEW MEDICINE?

PUBLIC VERSUS PRIVATE INVESTMENTS IN THE TB DRUG **BEDAQUILINE**

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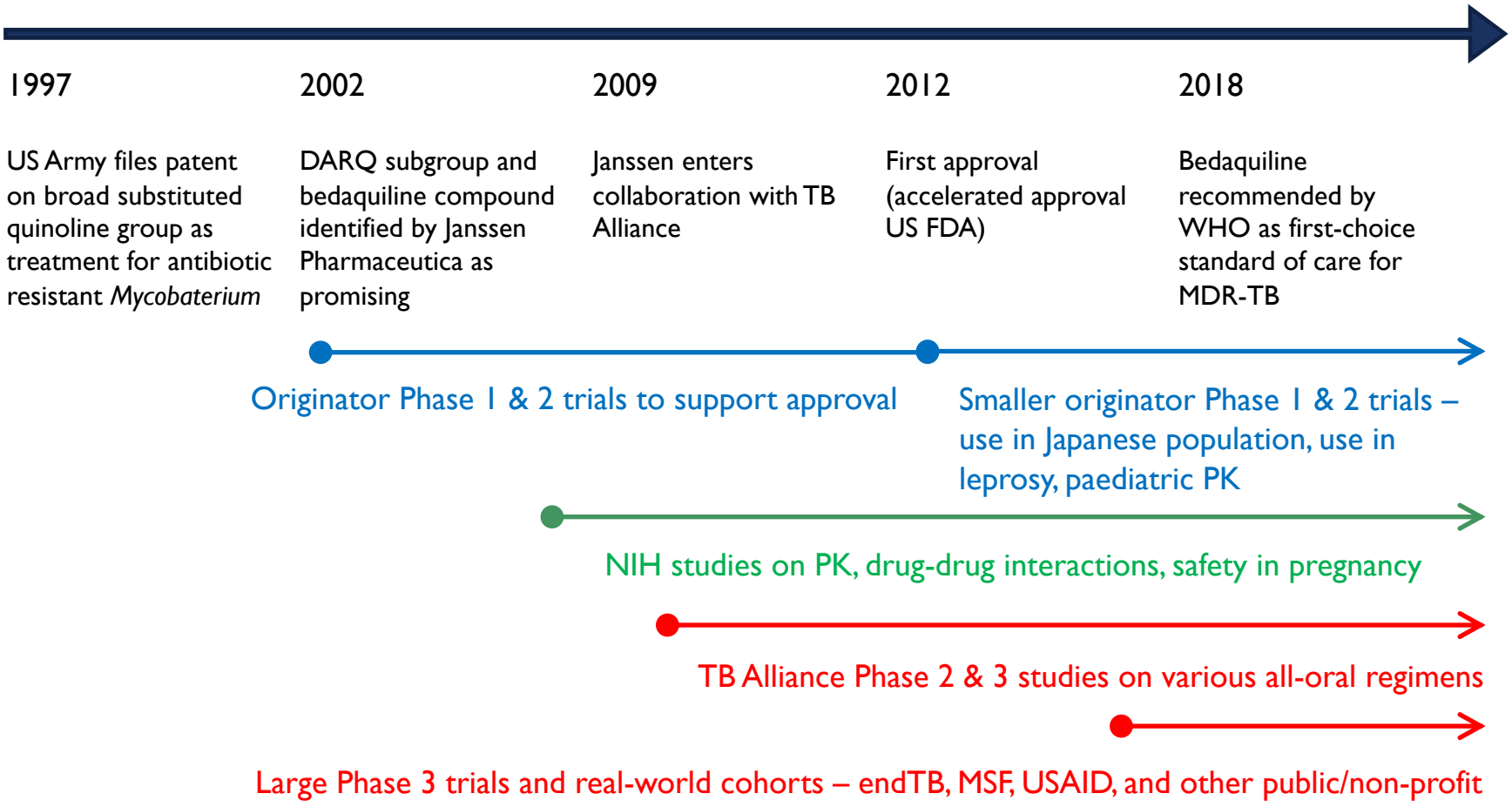
WEBINAR PRESENTATION

KNOWLEDGE NETWORK ON INNOVATION AND ACCESS TO MEDICINES

BACKGROUND OF THE STUDY

- In 2012, bedaquiline became the first new treatment from a novel class to be approved for tuberculosis in nearly five decades and it is now a core component of the standard of care for multidrug-resistant tuberculosis.
- Commissioned by Treatment Action Group (TAG) to quantify in monetary terms public sector contributions to the clinical development of bedaquiline.
- For simplicity, in this analysis 'public' is taken to mean governments and non-profit organizations.
- Previously presented at the Union conference 2019, full paper under review at PLOS ONE.

BEDAQUILINE DEVELOPMENT TIMELINE



AREAS OF WORK AND SOURCES OF FUNDING FOR BEDAQUILINE R&D AND ROLL-OUT

Captured in our analysis:

- Direct public funding of clinical trials
- Tax incentives to originator
- Priority review voucher
- Public funding of roll-out/early use

Not captured in our analysis:

- Pre-clinical development
- Operational expenses (e.g. MSF costs in projects trialling bedaquiline use)

PUBLICLY FUNDED CLINICAL TRIALS

Trial phase	Short title	Sponsor(s)	Dates	Trial cost (2018 US$ million)**
1	ACTG 5267	NIAID	2009-10	0.4
1	TMC207-CL002	TB Alliance	2010-10	4.9*
1	TMC207 +/- Rifabutin/Rifampin	NIAID	2011-12	4.9*
1	TASK-002	IMPAACT, NIAID, NICHD, NIMH	2016-17	0.2
1/2	IMPAACT 1108	NIAID	2017-22	1.0
2	TMC207-CL001	TB Alliance	2010-10	16.5*
2	NC-001	TB Alliance	2010-11	16.5*
2	NC-003	TB Alliance	2012-13	16.5*
2	NC-005	TB Alliance	2014-18	16.5*
2	ACTG 5343	NIAID	2016-20	2.2
2	Janssen C211	Janssen, Unitaid	2016-25	1.5
2	IMPAACT P1108	NIAID, NICHD	2017-22	1.0
2	SimpliciTB (B-Pa-M-Z) NC-008	TB Alliance	2018-22	21.6*
2/3	NEXT	UCT, UoL, WSU, UoS, UCTLI	2015-19	3.8
2/3	TB-PRACTECAL	MSF, TB Alliance, DNDi, others	2017-21	8.0
2/3	TRUNCATE-TB	UCL, NUHS, SCRI	2018-22	7.4
3	NiX-TB	TB Alliance	2015-21	26.6*
3	STREAM Stage 2	The Union, UK MRC	2016-21	40.0
3	endTB interventional	MSF, PIH, others	2016-21	19.9
3	ZeNix (B-Pa-L) NC-007	TB Alliance	2017-22	26.6*
3	endTB-Q	MSF, PIH, others	2019-22	13.1
4	endTB observational	MSF, PIH, others	2016-20	31.0

*Costs not provided by sponsor, estimated using trial cost averages reported in Sertkaya et al. 2016.

**Costs shown here do not include adjustments for lower LMIC trial costs, or 'bedaquiline-attributable' portion of trial costs (see later).

PUBLICLY FUNDED CLINICAL TRIALS

- Where respondents did not provide data (TB Alliance, and one Phase I NIAID-sponsored trial), we estimated trial costs based on published average trial costs (Sertkaya et al. 2016).
- Overall we estimate that public funding of clinical trials for bedaquiline is US$120-279 million, where the bottom end of the range is adjusted for 'bedaquiline-attributable portion'
- We explored including real-world cohorts – e.g. the French cohort, MSF cohorts in South Africa, India, Georgia, Armenia.
  But discussion with study leads revealed that costs attributable to the research aspect alone were very low, as secondary analysis of data collected routinely as part of clinical operations.

*Sertkaya A, Wong H-H, Jessup A, Beleche T. Key cost drivers of pharmaceutical clinical trials in the United States. Clin Trials 2016; 13: 117–26.

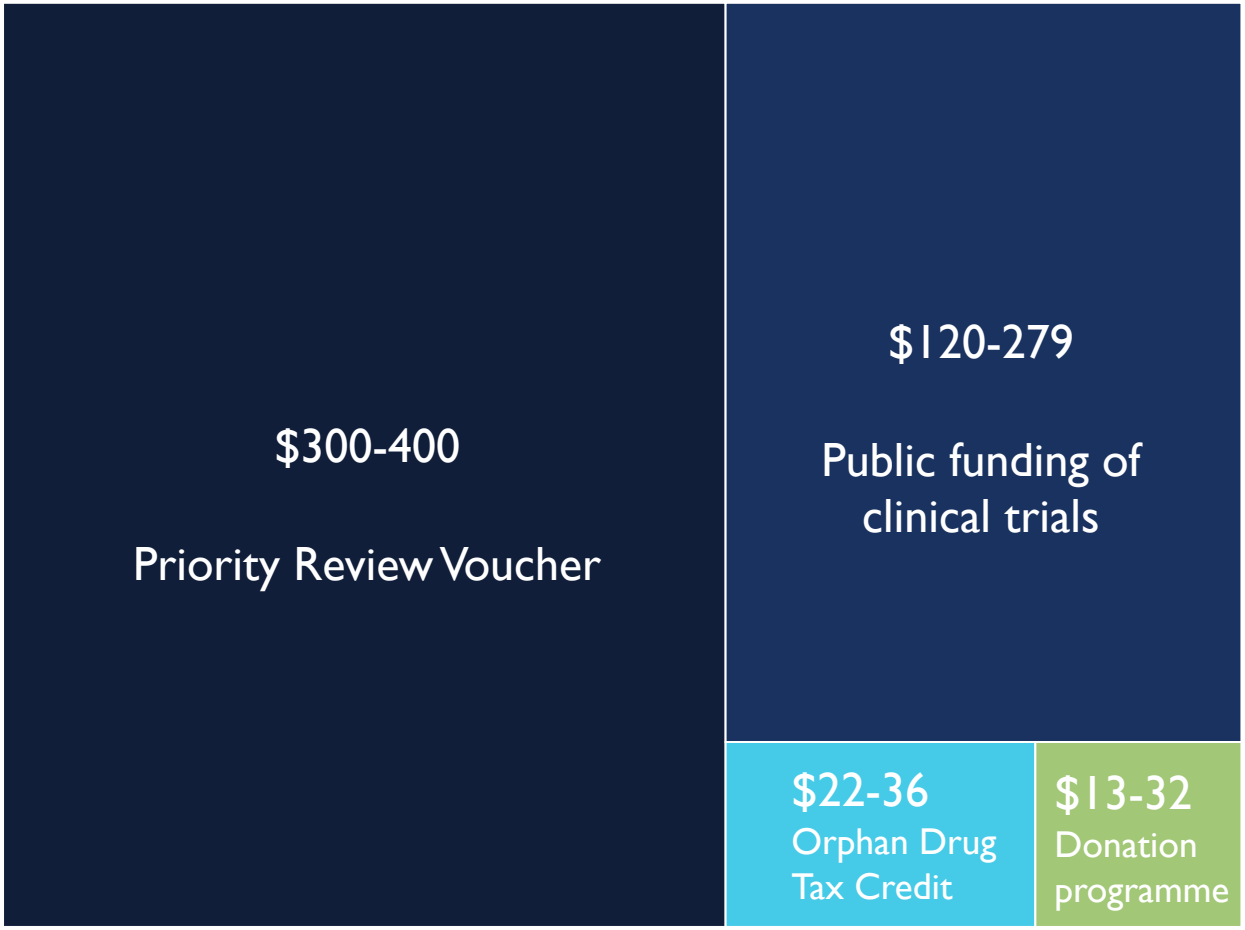
OTHER PUBLIC FUNDING FOR BDQ R&D:

- **Orphan drug tax credits**
  - 50% of qualifying research expenditures, 2005–2012; estimated average clinical trial cost by phase to estimate total research expenditures = $43–72M → **$22–36M tax credits**
- **Tax deductions for bedaquiline donations** (2015–2019)
  - Not public, so estimated based on cost of manufacture for bedaquiline, as reported by a Janssen representative (deductible expense is twice the cost of making the product*); $266 per course x 105,000 treatment courses = the deductible expense claimed after inflation adjustment: 28.3M → **$8.4M reduction in tax bill**
  - Estimated deductions based on reports on charitable contributions published by Janssen; deductible expenses for BDQ claimed in 2015 and 2016: $76.5M → **$26.7M reduction in tax bill** (this is probably a conservative estimate)
- **Priority review voucher (PRV)** – granted to Janssen for bedaquiline, later used to expedite FDA review of guselkumab (for plaque psoriasis)
  - Used simplified Ridley 2016 model to estimate PRV value: **US$300-400 million**
- **Technical assistance**
  - USAID **US$5 million** for administration of the donation programme.

*Deductible amount is twice the 'cost basis' – or the midpoint between cost basis and 'fair market value', whichever is lower. The 'cost basis' is often considered to represent the manufacturing cost, but depending on the company's accounting practices, this value could be much higher than the cost basis we have assumed.

* Ridley DB, Régnier SA. The Commercial Market For Priority Review Vouchers. *Health Aff (Millwood)* 2016; **35**: 776–83.

MONETARY CONTRIBUTIONS TO THE CLINICAL DEVELOPMENT OF BEDAQUILINE (US$ MILLIONS)



Total:

US$455–747 mil

(US$155-347 mil without PRV)

COMPARING PRIVATE AND PUBLIC EXPENDITURES: WHAT DID JANSSEN SPEND ON R&D?

- Adrian Thomas, (Vice President, Johnson & Johnson), stated that their R&D expenses for bedaquiline were US$500 million, though not much detail on what exactly is included in this.
- In order to examine this claim, we estimated Janssen's clinical R&D expenses.

Remarks by Adrian Thomas (Vice President, Access, Programs & Policy, Global Public Health, Johnson & Johnson) at the UN High-Level Meeting on Tuberculosis. 24 Sep 2018.

Sertkaya A, Wong H-H, Jessup A, Beleche T. Key cost drivers of pharmaceutical clinical trials in the United States. Clin Trials 2016; 13: 117–26.

ESTIMATING CLINICAL TRIAL COSTS

- For the originator trials and where no response from public sector (TB Alliance)
- Average clinical trial cost estimates by using Sertkaya, 2016:
  - Phase I: US$ 4.9 million
  - Phase II: US$ 16.5 million
  - Phase III: US$ 26.6 million
- We additionally calculated a lower estimate to account for
  - lower clinical trial costs in LMICs compared to the US (40% lower (Frost, 2016))
  - the proportion of costs attributable to bedaquiline development (e.g. for trials where bedaquiline and delamanid are both tested, 50%)
  - for the originator, savings due to the orphan drug tax credit.

Frost & Sullivan. Asia: preferred destination for clinical trials. https://novotech-cro.com/sites/default/files/170217_FrostSullivan_Asia%20white%20paper_full.pdf (accessed Jan 14, 2019).

KEY CONCEPTS FOR COMPARING PRIVATE AND PUBLIC EXPENDITURES

"out-of-pocket" (OOP) expenditures – the $ amount that was spent on the activity when it was undertaken

"capitalized" expenditure – the OOP amount adjusted for the 'opportunity cost' of not having instead invested this amount. Standard assumption, and the one used here, is of ~10% annual returns. Capitalization exponentially increases expenses that occurred further in the past.

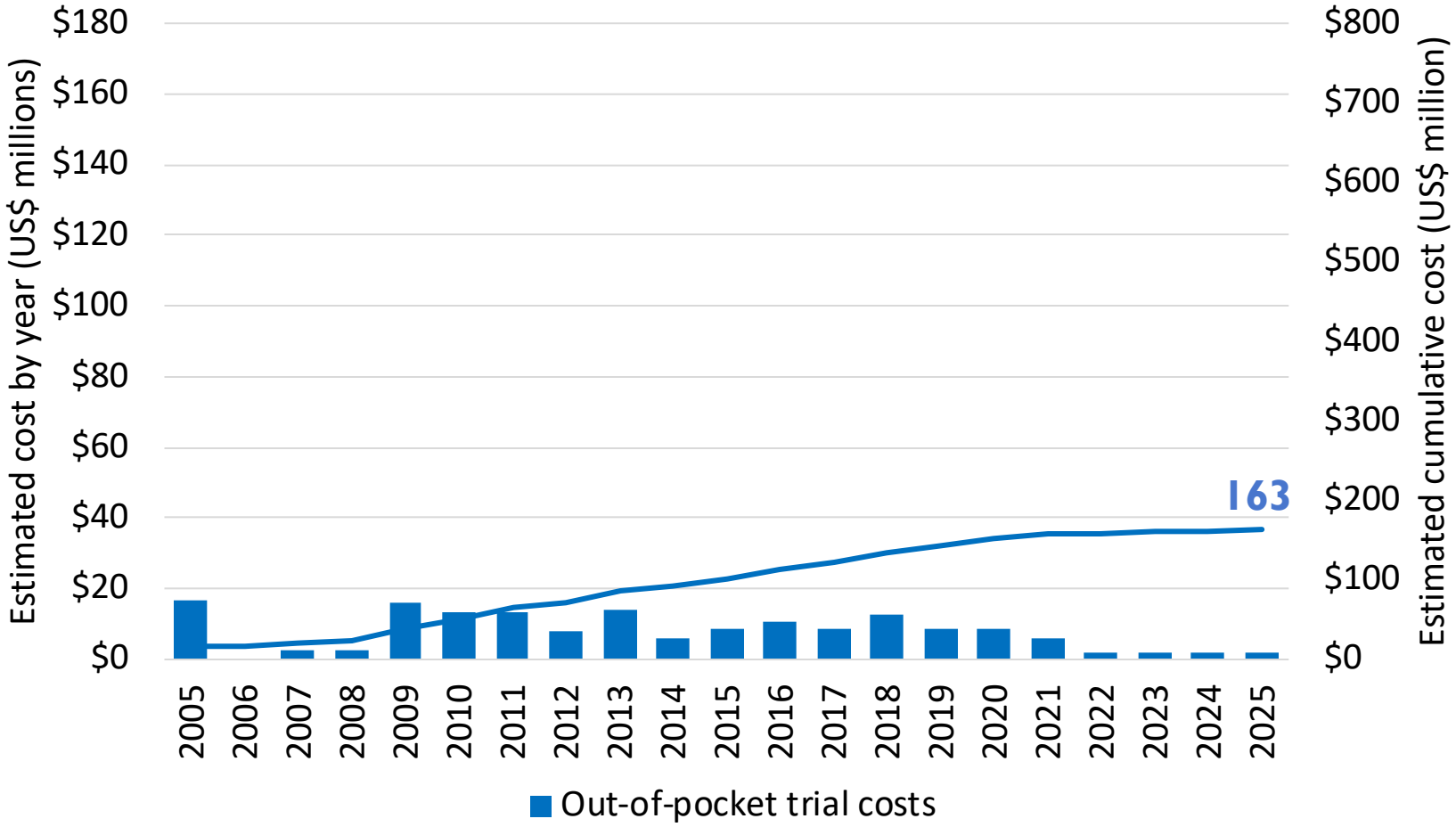
"risk-adjusted" expenditure – adjusted for the theoretical cost of other trials that were searching for an effective compound but failed.

US$100 spent on a Phase 2 trial in 2004:

- OOP expenditures: US$100
- Capitalized expenditures: US$459
- Risk-adjusted expenditures: US$244
- Capitalized **and** risk-adjusted: **US$1,121**

*Assuming likelihood of success for Phase II trial = 41%. Sertkaya et al. 2016.

ESTIMATING JANSSEN'S CLINICAL TRIAL EXPENDITURES



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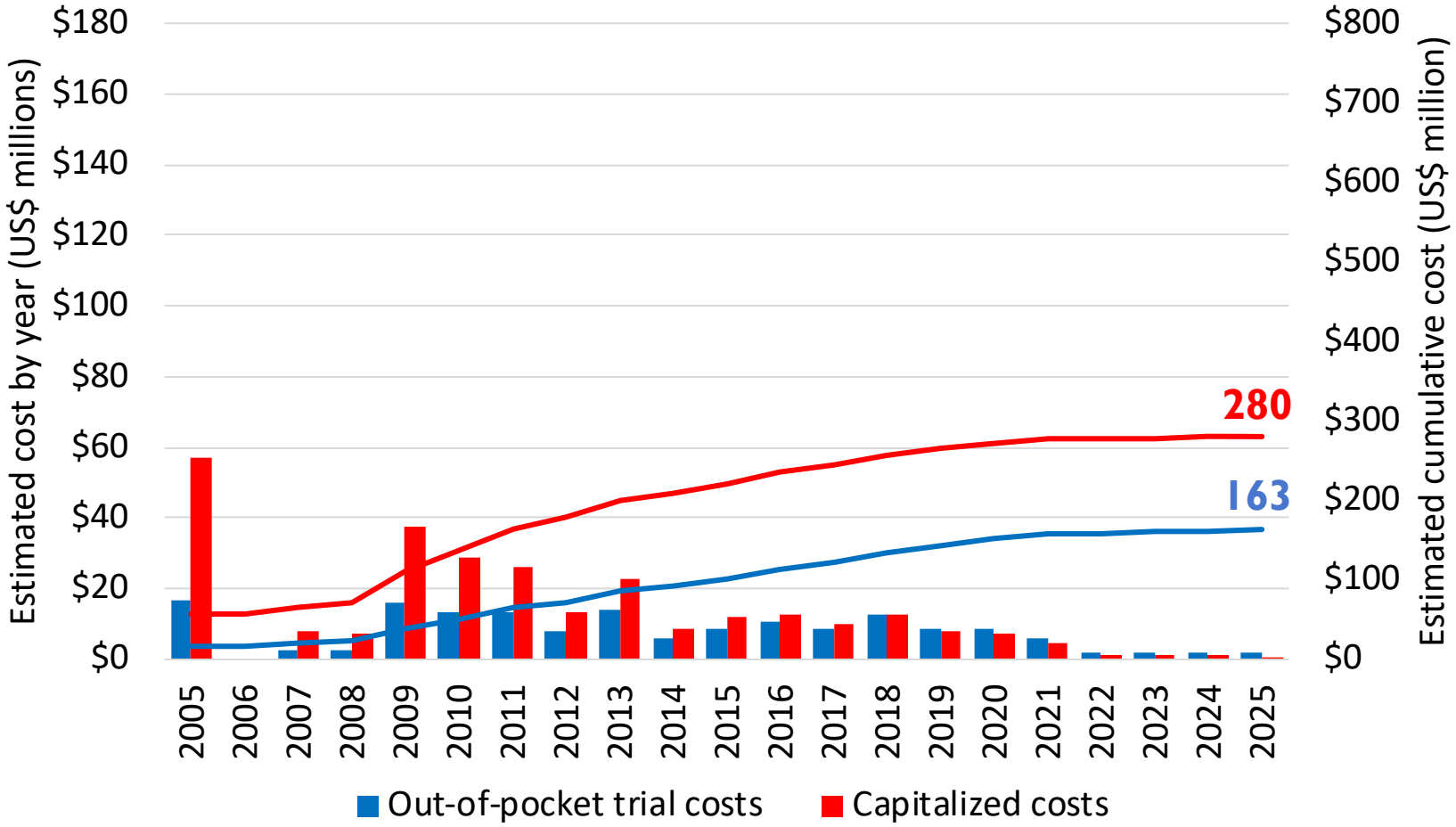

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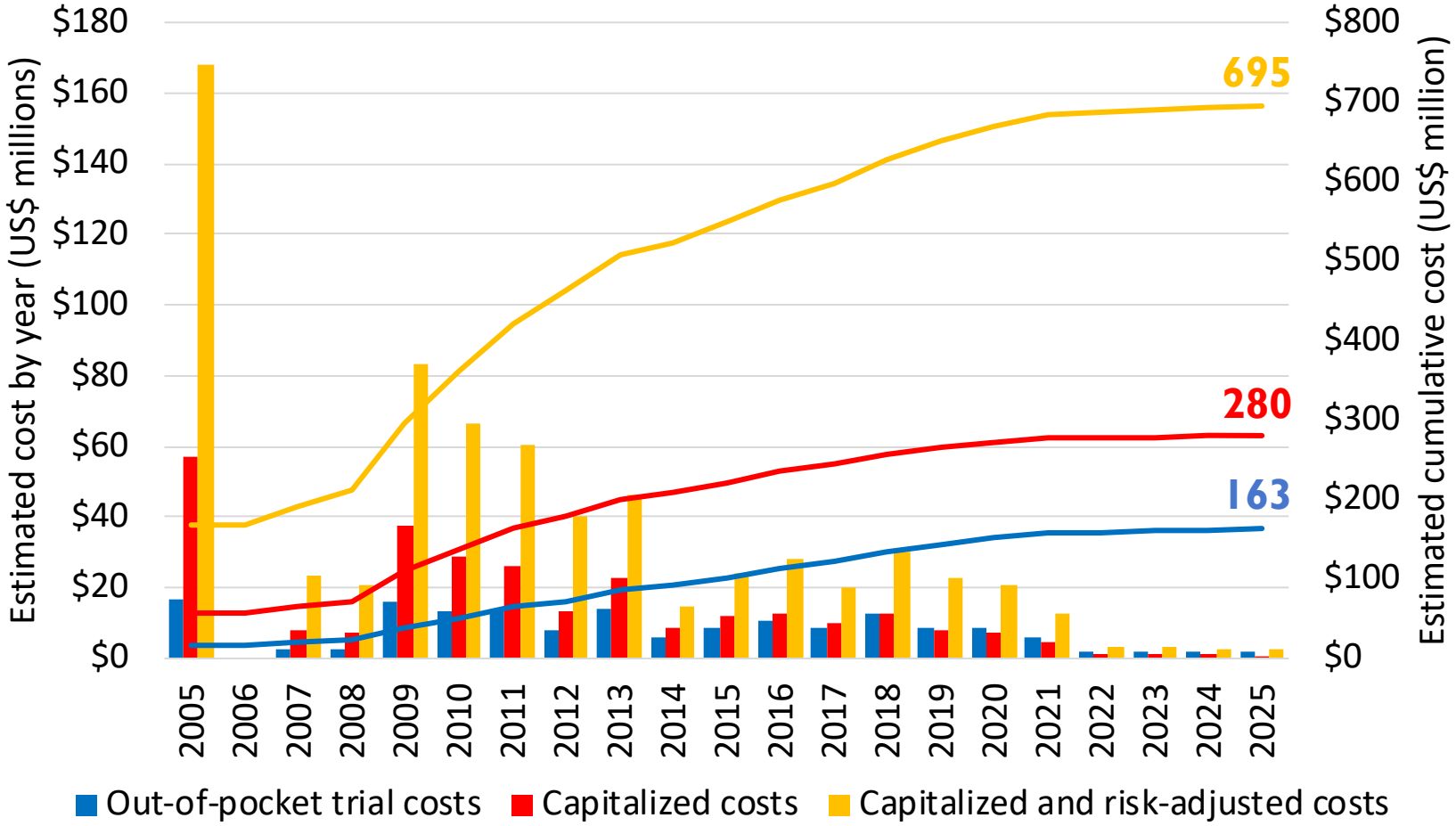

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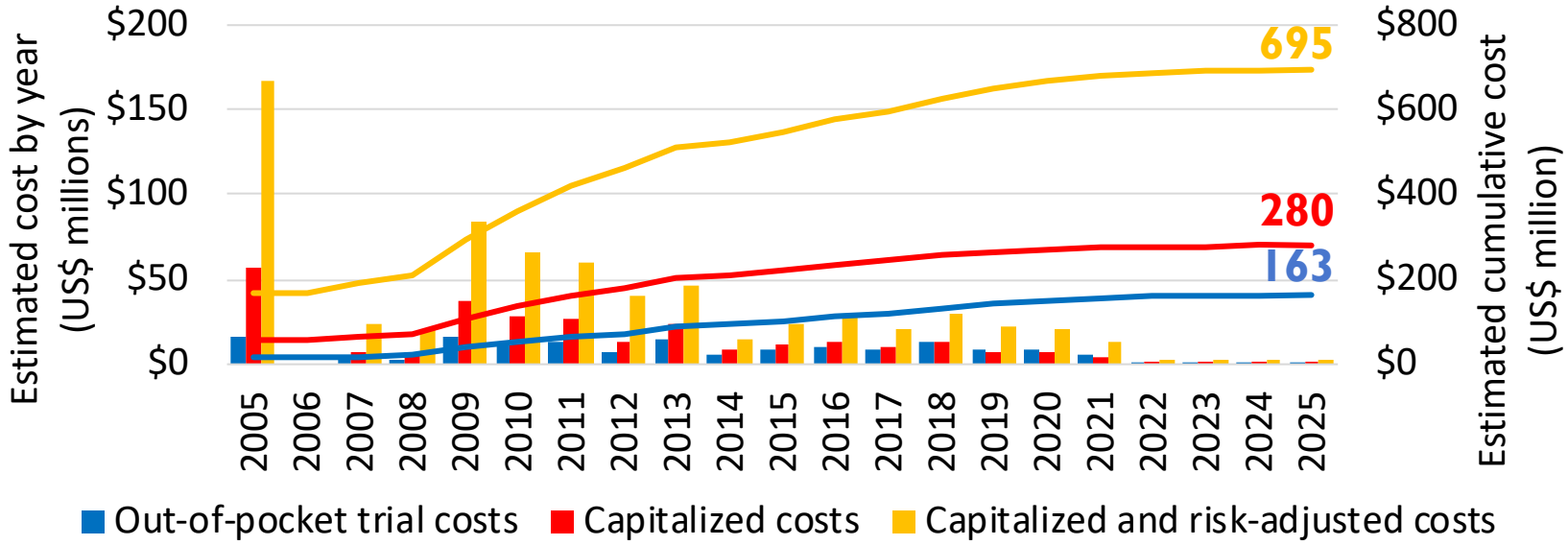
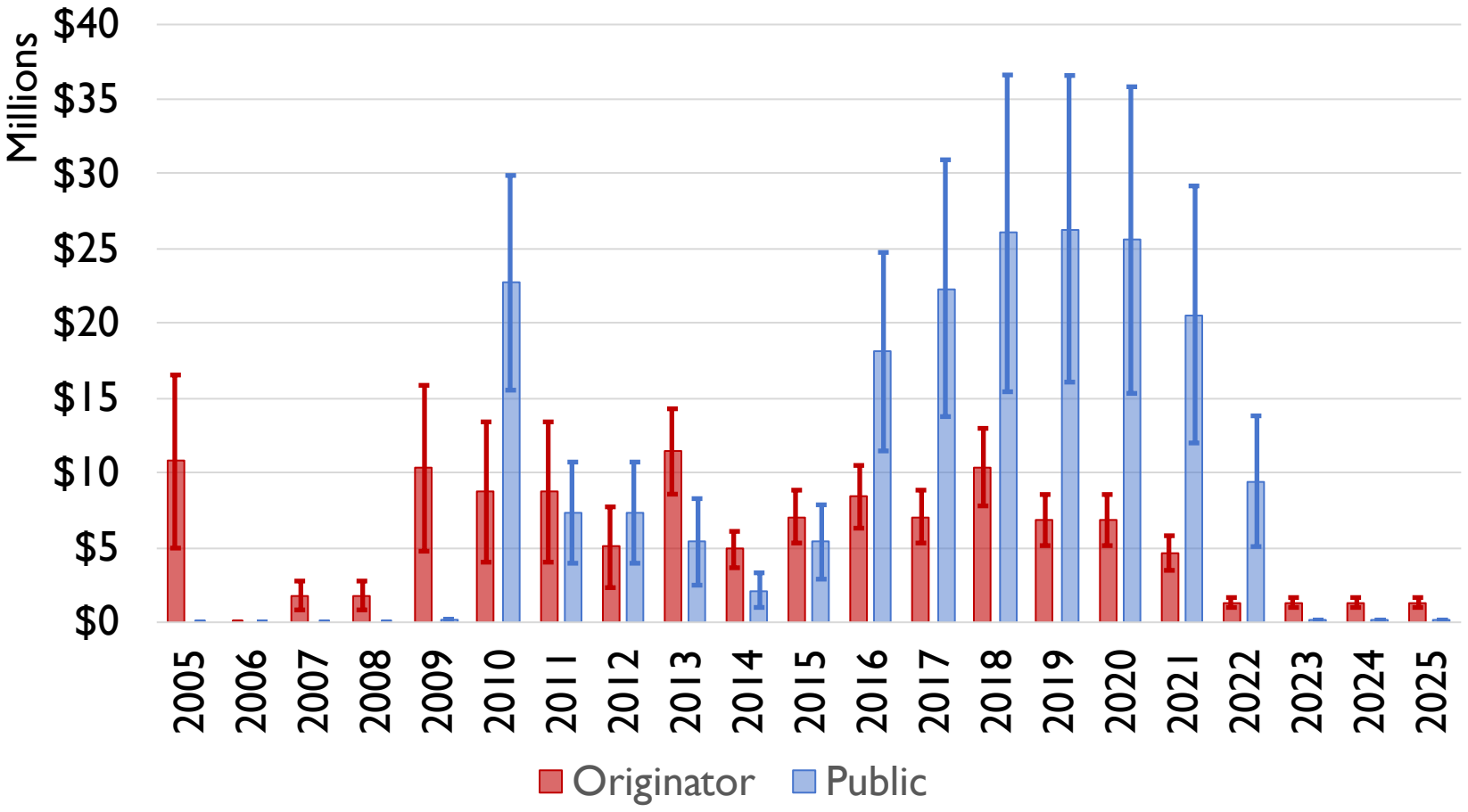


- Out-of-pocket: **US$163 million**. Net of Orphan Drug Tax Credits: **US$127 million.**
- Capitalised and risk-adjusted costs are > 4x crude expenditure.
- Risk-adjustment implies that there were failed drug candidates that 'had to be tested in order to ultimately find bedaquiline'. Where there?

PUBLIC vs PRIVATE EXPENDITURES ON BEDAQUILINE CLINICAL TRIALS



Error bars represent the range of estimates. Out-of-pocket expenditures (not risk-adjusted, not capitalized).

COMPARING ESTIMATED EXPENDITURES: PUBLIC VS PRIVATE – OUT OF POCKET

	Public	Originator	Ratio of public to originator expenditures*
Clinical trials (out of pocket)	120-279	76-163	1.6-1.7
Funding through PRV	300-400	-	-
Orphan drug tax credit	22-36	-	-
Bedaquiline donation program	13-32†	14-77	0.4-0.9
Total out-of-pocket expenditures	**455-747**	**90-240**	**3.1-5.0**

*Ranges for ratios are calculated as the bottom of the range for public funding divided by bottom of the range for Janssen funding, and top of the range for public funding divided by top of the range for originator funding.
†Composed of US$8-27 million through tax deductions for originator and US$5 million through public funding of administration of the donation programme.

COMPARING ESTIMATED EXPENDITURES: PUBLIC VS PRIVATE – ADDING CAPITALIZATION/RISK ADJUSTMENT

	Public	Originator	Ratio of public to originator expenditures*
Clinical trials			
Out of pocket	120-279	76-163	1.6-1.7
Capitalized	142-328	115-280	0.9-1.2
Capitalized and risk-adjusted	312-733	278-695	1.05-1.12
PRV, tax credits, donation program	[not shown for simplicity]		
Totals			
Out-of-pocket expenditures	**455-747**	**90-240**	**3.1-5.0**
Capitalized and risk-adjusted expenditures	**647-1,201**	**292-772**	**1.6-2.2**

*Ranges for ratios are calculated as the bottom of the range for public funding divided by bottom of the range for Janssen funding, and top of the range for public funding divided by top of the range for originator funding.
†Composed of US$8-27 million through tax deductions for originator and US$5 million through public funding of administration of the donation programme.

CONCLUSIONS

- We estimated that total **public expenditures have been 3.1–5.0 times those of the originator (US$455-747 million versus US$90-240 million),** or 1.6–2.2 (US$647-1,201 million versus US$292-772 million) when the cost of failures and costs of forgoing other investment opportunities are counted.
- The largest 'route' for public contributions was through the priority review voucher.
- Findings imply bulk of Janssen's investments – even after capitalization and risk-adjustment – have likely been covered through PRV & tax benefits.
- Quantifying these investments can contribute to debates concerning the price of bedaquiline, the role of the public sector in pharmaceutical research and development (R&D), and the costs of bringing a novel medicine to market.
- Our analysis provides a methodology that may be adapted to estimate public investments in the development of other TB medicines, such as pretomanid and rifapentine, and beyond TB.

LIMITATIONS

- Pre-clinical investments were not assessed.
- Our estimates rely on estimated overall trial costs reported by study sponsors or lead investigators.
- Our estimates also rely, in part, on average clinical trial costs reported by a US-based industry analysis group (Sertkaya et al., 2016). Other trial cost averages could have been used.
- Estimated average costs were phase-specific and adjusted for potentially lower trial costs in LMICs and proportion attributable to bedaquiline, but costs were not adjusted to take into account different trial characteristics such as enrolment numbers or duration of treatment and/or follow up.
- Public investments in technical assistance work and cohort studies were not captured.

ACKNOWLEDGEMENTS

- Thanks to Treatment Action Group for funding and collaboration.
- Thanks to experts who provided thoughtful comments on drafts of this analysis:
  - Jennifer Reid (Médecins Sans Frontières)
  - Katy Athersuch (Médecins Sans Frontières)
  - Suerie Moon (Graduate Institute Geneva)
  - Manuel Martin (Médecins Sans Frontières)
  - Nicholas Lusiani (Oxfam America)
- We are also grateful to the respondents who provided expenditure data.

THANK YOU

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EXTRA SLIDES

ORPHAN DRUG TAX CREDIT

- 'Orphan diseases' is a term given to rare diseases. Multiple incentives were created in the 80s in the US, and a bit later in EU and elsewhere, for orphan medicines.
- Bedaquiline was granted orphan drug designation due to MDR-TB prevalence in the US of <200,000.
- Most importantly for bedaquiline, 'orphan' designation allows the proprietor to claim up to 50% of relevant clinical trial expenditures up to approval*.
- As Janssen has not shared data on trial expenditures, we assumed trial costs based on published averages.**
- Resulting estimated tax credit: **US$22-36 million over 2005-2012**
- Orphan designation offers other benefits in the US, but these were considered unlikely to be relevant for bedaquiline
  - Accelerated approval (~6 months FDA review instead of 10 months)
  - 7 years' marketing exclusivity

*reduced to 25% in 2018, but this is not relevant for bedaquiline due to approval in 2012.

** Sertkaya A, Wong H-H, Jessup A, Beleche T. Key cost drivers of pharmaceutical clinical trials in the United States. Clin Trials 2016; 13: 117–26.

TAX DEDUCTIONS FOR DONATIONS (1)

- The Janssen/USAID/GDF donation programme has donated **105,000 treatment courses** of bedaquiline over 2015-2019
- In the US, donations are tax-deductible at the smaller amount of: A) twice the cost of production and B) the midpoint between the cost of production and 'fair market value'. Assumed **twice the cost of production** is the applicable amount.
- **Cost of production per 6-month course was assumed to be US$133** based on public remarks by Adrian Thomas (J&J), which is similar to independent estimates of cost of producton*
- Estimated resulting reduction in **tax bill: US$8.4 million** over 2015-2020.

* Gotham D, Fortunak J, Pozniak A, *et al.* Estimated generic prices for novel treatments for drug-resistant tuberculosis. *Journal of Antimicrobial Chemotherapy* 2017; **72**. And statements by Adrian Thomas (Vice President, Access, Programs & Policy, Global Public Health, Johnson & Johnson) at the UN High-Level Meeting on Tuberculosis. 2018.

TAX DEDUCTIONS FOR DONATIONS (1) - TABLE

Year	Assumed number of donated treatment courses for which deductible expenses claimed	Assumed deductible expense claimed before inflation adjustment	Inflation adjustment factor (to 2018 USD)	Assumed deductible expense claimed after inflation adjustment	Reduction in tax bill*
2015	21,000	$5,586,000	1·04216102	$5,821,511	$2,037,529
2016	21,000	$5,586,000	1·03098073	$5,759,058	$2,015,670
2017	21,000	$5,586,000	1·01799317	$5,686,510	$1,990,278
2018	21,000	$5,586,000	1	$5,586,000	$1,173,060
2019	21,000	$5,586,000	0·98232486	$5,487,267	$1,152,326
Total	105,000	$27,930,000		$28,340,346	$8,368,864

*Calculated by multiplying assumed deductible expense claimed after inflation adjustment by the corporate tax rate in the respective year: 35% for fiscal years 2015, 2016, and 2017, and 21% for fiscal years 2018 and 2019.

TAX DEDUCTIONS FOR DONATIONS (11)

- Janssen documents report donations of bedaquiline to USAID equivalent to 'payment amounts' of US$ 1,000,000 on 23 of October 2015, 500,000 on the 5th of August 2016, and US$ 29,310,000 to USAID on the 17th of December 2015 and US$ 44,580,000 on the 1st of December 2016.*
- The expected tax deductions, assuming deductions were claimed for these full amounts, and using inflation adjustment and corporate tax rates as in the Table below, would be **US$27 million**.
- We consider this a conservative (low) estimate, as tax deductions could be higher if Janssen has claimed further product donations in addition to those shown in the Table above.
- In addition, Janssen is reported to have made bedaquiline donations after 2016, which are not included here. Janssen has reported additional 'product donations' to USAID, including one with a 'payment amount' of US$18,992,000 on the 29th of November 2018, but these do not specify bedaquiline.

* Senate Committee on Finance Questions for the Record Drug Pricing in America: A Prescription for Change, Part II. February 26, 2019. Questions for: Jennifer Taubert, Executive Vice President, Worldwide Chairman, Janssen Pharmaceuticals Johnson & Johnson. Spending on Advertising/Marketing vs. Research and Development. Available from: https://www.finance.senate.gov/imo/media/doc/Johnson%20and%20Johnson%20Responses.pdf

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PRIORITY REVIEW VOUCHER (I)

- Priority Review Vouchers (PRVs) are a regulatory incentive mechanism created in the US in 2007. The concept was to award a PRV to companies that gain approval for a new neglected disease treatment. The PRV can then be 'cashed in' for any drug filing, to reduce review time from 10 to 6 months.
- PRVs can be used by the holder or sold. Previous PRVs have sold for US$68–350 million.
- Janssen was awarded a for PRV bedaquiline, and chose not to sell it, but use it for guselkumab, a new treatment for psoriasis. Guselkumab is expected to be a blockbuster, expected to have revenues of US$1.6 billion in 2022 alone.
- A model is available for estimating the value of a PRV*
- Resulting estimate in the case of Janssen's PRV: **US$300-400 million**

* Ridley DB, Régnier SA. The Commercial Market For Priority Review Vouchers. *Health Aff (Millwood)* 2016; **35**: 776–83.

PRIORITY REVIEW VOUCHER (II) – SENSITIVITY

- As a sensitivity analysis, we calculated the net present value for an additional 4 months of sales at the level projected for guselkumab in its fifth year.
- Fifth-year (2022) sales are projected to be US$1.6 billion, 4 months of sales at this level would equal approximately US$533 million.
- Applying discounting of 10.5%/year (the level suggested in Ridley and Régnier) yields a net present value in 2018 of US$342 million – a value very similar to that given by the Ridley and Régnier model.

* Ridley DB, Régnier SA. The Commercial Market For Priority Review Vouchers. *Health Aff (Millwood)* 2016; **35**: 776–83.

% OF TRIAL COSTS ATTRIBUTABLE TO BEDAQUILINE (EXAMPLES)

Trial	% attributed to bedaquiline	Rationale
NEXT	100%	Bedaquiline is the key investigational drug in this study
endTB observational	50%	Bedaquiline and delamanid are both primary investigational medicines in this study
endTB interventional	50%	Bedaquiline and delamanid are both primary investigational medicines in this study
endTB-Q	50%	Bedaquiline and delamanid are both primary investigational medicines in this study
ACTG 5343	50%	Bedaquiline and delamanid are both primary investigational medicines in this study
STREAM	50%	The study has two key areas of focus: the use of a shortened regimen without bedaquiline, and the use of shortened regimens including bedaquiline. Bedaquiline is included in two of the three experimental arms in this study.