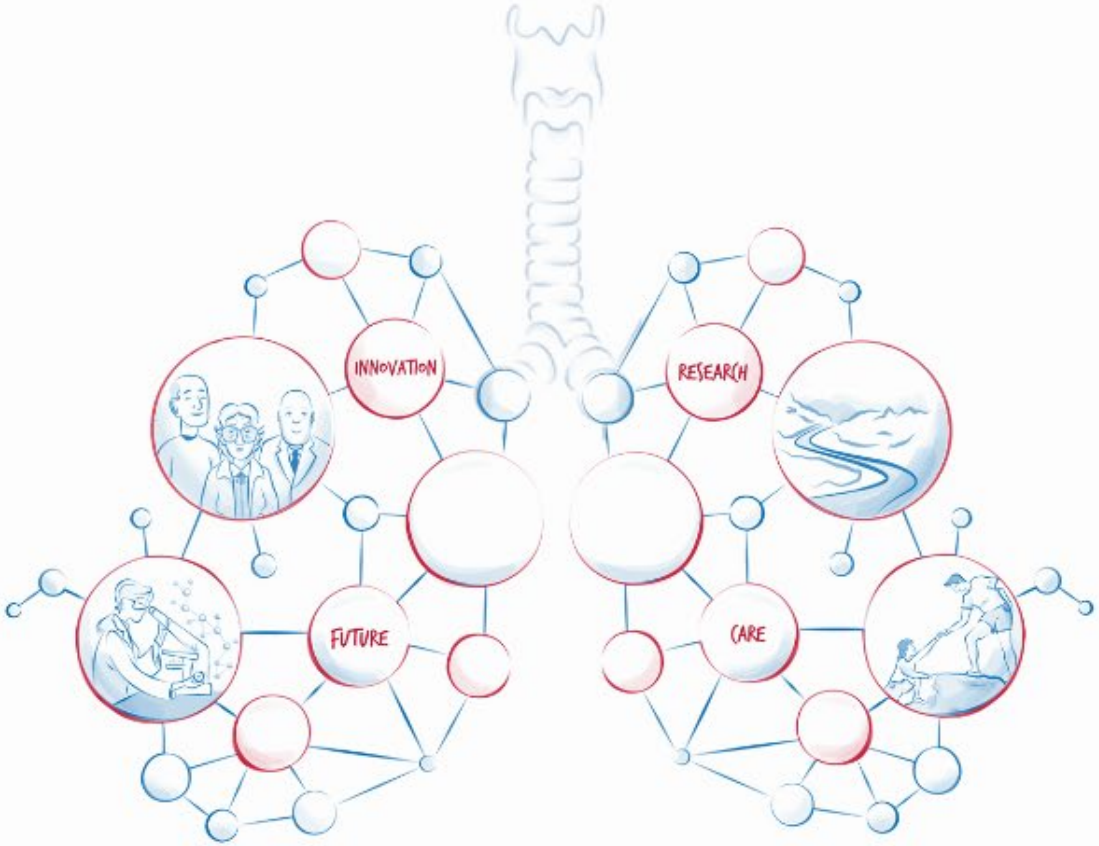
Otsuka



Otsuka TB Drug Development Update

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WGND Annual Meeting, 14 November 2023
Paris, France.

ONP-COP-2300002, Date of preparation: November 2023

FIGHTBACK

Disclosure

Simba Takuva, MD, MSc.

Otsuka Novel Products GmbH – Munich, Germany,

Otsuka Novel Products GmbH is an affiliate of Otsuka Pharmaceutical Co., Ltd.

Potential COI	Organization
Employment	Employee of Otsuka Novel Products GmbH, Munich, Germany.

OPC-167832 is currently in clinical development and not approved in any country.

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Otsuka's TB Development Program:
Addressing a Major Global Public Health Issue

1971

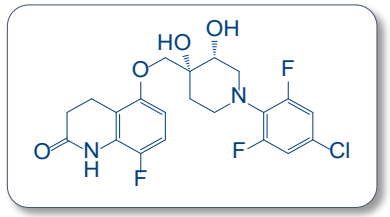
Development of a new TB drug was one of the first research areas that was undertaken by Otsuka Pharmaceutical.

2014

Delamanid
50mg film-coated tablets

approved for treatment of pulmonary MDR-TB in adults in Europe

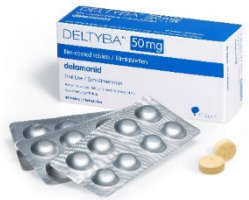
One of only two novel anti-TB drugs in past 40 years



OPC-167832

2016

Delamanid



OPC-167832:
DprE1 inhibitor
is a novel agent with potent anti-TB activity, enters early-phase clinical development

2021

Delamanid
25mg dispersible tablets

approved for treatment of pulmonary MDR-TB children weighing 10 to 30 kg

Present

OPC-167832:
DprE1 inhibitor
is in phase 2b/c trial in collaboration with Bill & Melinda Gates Foundation

MDR-TB = multi-drug resistant tuberculosis

References:

EU Summary of Product Characteristics: Delamanid 50mg film-coated tablets/ 25mg dispersible tablets (07/2023).

Hariguchi N, Chen X, Hayashi Y, *et al*. OPC-167832, a Novel Carbostyril Derivative with Potent Antituberculosis Activity as a DprE1 Inhibitor. *Antimicrob Agents Chemother*. 2020 May 21;64(6):e02020-19. doi: 10.1128/AAC.02020-19. Print 2020 May 21.

In vitro antimycobacterial activity of OPC-167832

Strain	Minimum inhibitory concentration (μg/mL)						
	OPC-167832	Delamanid	Rifampin	Bedaquiline	Levofloxacin	Moxifloxacin	Linezolid
M. tuberculosis							
ATCC 27294 (H37Rv)	0.0005	0.004	0.25	0.063	0.5	0.5	1
ATCC 35812 (Kurono)	0.0005	0.004	0.25	0.063	0.5	0.13	1
ATCC 35838 (H37Rv RIF-R)	0.0005	0.004	>16	0.063	0.5	0.25	0.5
ATCC 35822 (H37Rv INH-R)	0.00024	0.004	0.5	0.063	0.5	0.25	1
ATCC 35837 (H37Rv EMB-R)	0.002	0.004	0.25	0.063	0.5	0.25	0.5
ATCC 35820 (H37Rv SM-R)	0.001	0.004	0.25	0.063	0.5	0.5	0.5
ATCC 35828 (H37Rv PZA-R)	0.001	0.004	1	0.13	0.5	0.5	1
M. africanum ATCC 25420	0.002	0.001	0.25	0.25	0.25	0.25	0.5
M. bovis ATCC BAA-935	0.002	0.004	0.063	0.13	0.25	0.13	0.5
M. caprae ATCC BAA-824	0.001	0.002	0.13	0.13	0.25	0.063	0.25
M. microti ATCC 11152	0.001	0.002	0.13	0.063	0.25	0.063	0.5
M. pinnipedii ATCC BAA-688	0.0005	0.002	0.5	0.13	0.25	0.25	1

The minimum inhibitory concentrations against *M. tuberculosis* complex standard strains were determined by an agar proportion method (CLSI document M24-A2). The minimum inhibitory concentration was determined as the lowest concentration of a compound inhibiting at least 99% of bacterial growth.

RIF=Rifampin; INH=Isoniazid; EMB=Ethambutol; SM=Streptomycin; PZA=Pyrazinamide; -R=Resistant.

Reference: Hariguchi N, Chen X, Hayashi Y, *et al*. OPC-167832, a Novel Carbostyril Derivative with Potent Antituberculosis Activity as a DprE1 Inhibitor. *Antimicrob Agents Chemother*. 2020 May 21;64(6):e02020-19. doi: 10.1128/AAC.02020-19. Print 2020 May 21.

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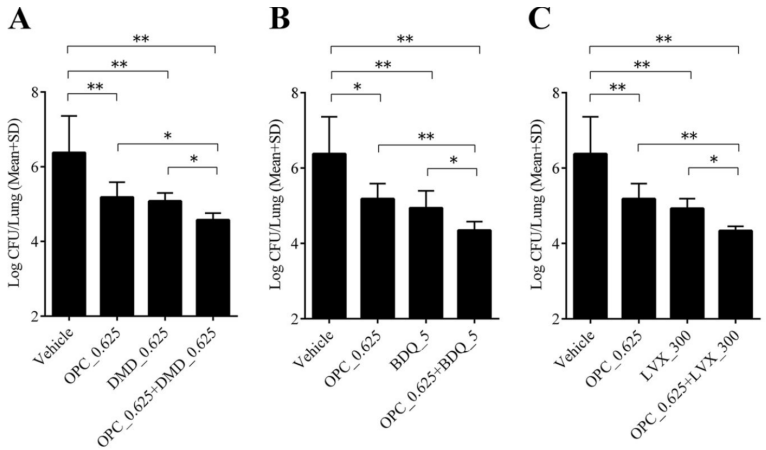
Single and Combination OPC-167832 in Murine Chronic TB Studies

Murine Chronic TB Studies

- Potent anti-mycobacterial activity in an experimental mouse model of chronic TB ICR mice infected with *M. tuberculosis* Kurono strain
- Several regimens combining OPC-167832 plus delamanid as core agents with other anti-TB drugs have the potential to shorten the treatment period.

***In vivo* combination effect of OPC-167832 (OPC) with delamanid (DLM), bedaquiline (BDQ), or levofloxacin (LVX).**



The significant differences between the combined treatment groups and their single-agent treatment groups were also determined by Dunnett's test. *, P < 0.05; **, P < 0.01; NS, not significant.

Mouse model of chronic TB evaluating the relapse rates

- Delamanid + OPC-167832 + Moxifloxacin + Bedaquiline (DOMB) regimen achieved excellent efficacy (0% relapse)
- Relapse rates of the other tested regimens were almost equivalent to those of the standard regimen RHEZ.

Regimen	Proportion (%) of Mice With Relapse After Treatment		
	10 Weeks	12 Weeks	14 Weeks
None	NT	NT	NT
Vehicle	NT	NT	NT
RHZE/RH[a]	12 of 15 (80)	4 of 14 (29)	1 of 14 (7)
DOMB	**0 of 15 (0)**	**0 of 14 (0)**	**0 of 5 (0)**

ICR mice infected by MTB Kurono via intratracheal route, started treatment after 2 weeks of the infection. B=bedaquiline (25 mg/kg). O=OPC-167832 (2.5 mg/kg). CFU=colony forming unit. D=delamanid (2.5 mg/kg). E=ethambutol (100 mg/kg). H=isoniazid (25 mg/kg). Lz=linezolid (100 mg/kg). M=moxifloxacin (100 mg/kg). NT=not tested. R=rifampicin (5 mg/kg). Z=pyrazinamide (150 mg/kg). [a]Z and E were administered only for the initial 8 weeks.

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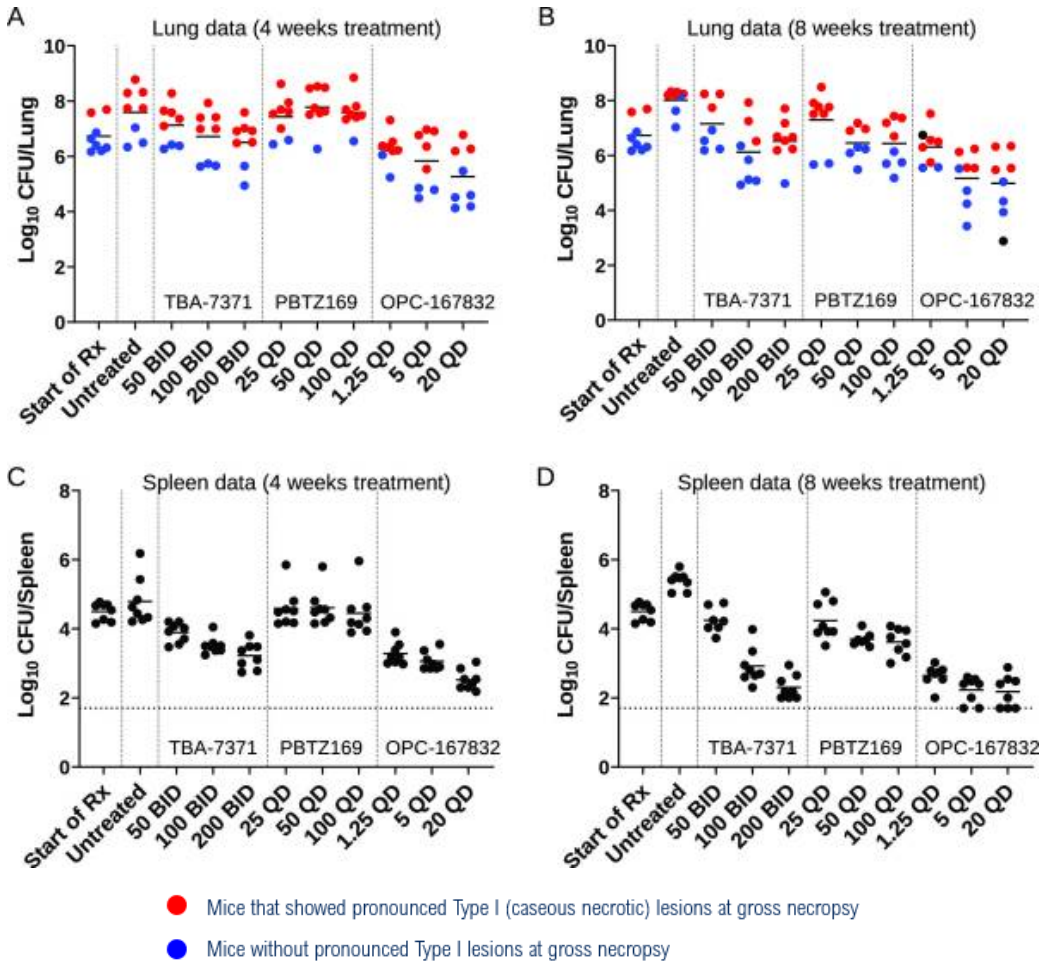
Reference: Hariguchi N, Chen X, Hayashi Y, *et al*. OPC-167832, a Novel Carbostyril Derivative with Potent Antituberculosis Activity as a DprE1 Inhibitor. *Antimicrob Agents Chemother*. 2020 May 21;64(6):e02020-19. doi: 10.1128/AAC.02020-19. Print 2020 May 21.

OPC-167832 Activity in the Kramnik Mouse Model

Comparison of DprE1 Inhibitor Activity in the Kramnik Mouse Model

- OPC-167832 showed superior efficacy compared to the two other DprE1 inhibitors (TBA-7371, PBTZ169), with the highest kill rate in the first month (4 weeks) of treatment, even at the low doses tested.

- At trough, only OPC-167832 showed adequate drug exposure above the MIC+huSA in the cellular-caseum interface and in caseum of type I lesions, which is where the majority of bacteria are located in C3HeB/FeJ lungs.



O: OPC-167832, D: delamanid, B: bedaquiline, Pa: pretomanid, S: sutezolid, M: moxifloxacin, Z: pyrazinamide,

References:
Robertson GT, Ramey ME, Massoudi LM, *et al*. Comparative Analysis of Pharmacodynamics in the C3HeB/FeJ Mouse Tuberculosis Model for DprE1 Inhibitors TBA-7371, PBTZ169, and OPC-167832. *Antimicrob Agents Chemother*. 2021 Oct 18;65(11):e0058321. doi: 10.1128/AAC.00583-21. Epub 2021 Aug 9.

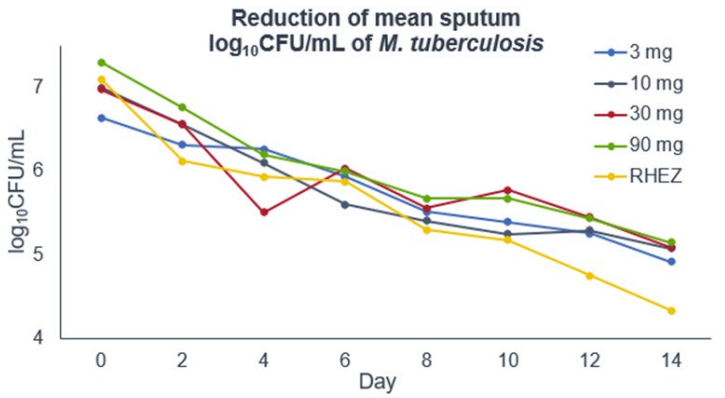
ONP-COP-2300002, Date of preparation: November 2023

Trial 323-201-00003: Phase 1b/2a (MAD/EBA) Study

A Phase 1/2, Active-controlled, Randomized, Open-label Trial to Evaluate the Safety, Tolerability, Pharmacokinetics, and Efficacy of Multiple Oral Doses of OPC-167832 Tablets in Subjects with Uncomplicated, Smear-positive, Drug-susceptible Pulmonary Tuberculosis (NCT03678688).

<u>Stage 1</u>: To evaluate the efficacy, PK, safety, and tolerability of multiple ascending oral doses of OPC-167832 (3 mg, 10 mg, 30 mg and 90 mg) compared with RHEZ

- OPC-167832 demonstrated potent bactericidal activity (65.7%-74.7% of RHEZ cohort)*
- QD doses of OPC-167832 in DS-TB subjects had similar PK parameters to healthy adults
- Daily dose of OPC-167832 for 14 days was well tolerated



CFU, colony forming units; RHEZ, rifampicin, isoniazid, ethambutol, and pyrazinamide; TEAEs, treatment emergent adverse event.

<u>Stage 2</u>: To evaluate the bactericidal activity and safety of OPC-167832 as part of combination therapy with delamanid (DLM), or bedaquiline (BDQ), or all three compounds compared to RHEZ in participants with drug-susceptible pulmonary tuberculosis

References:

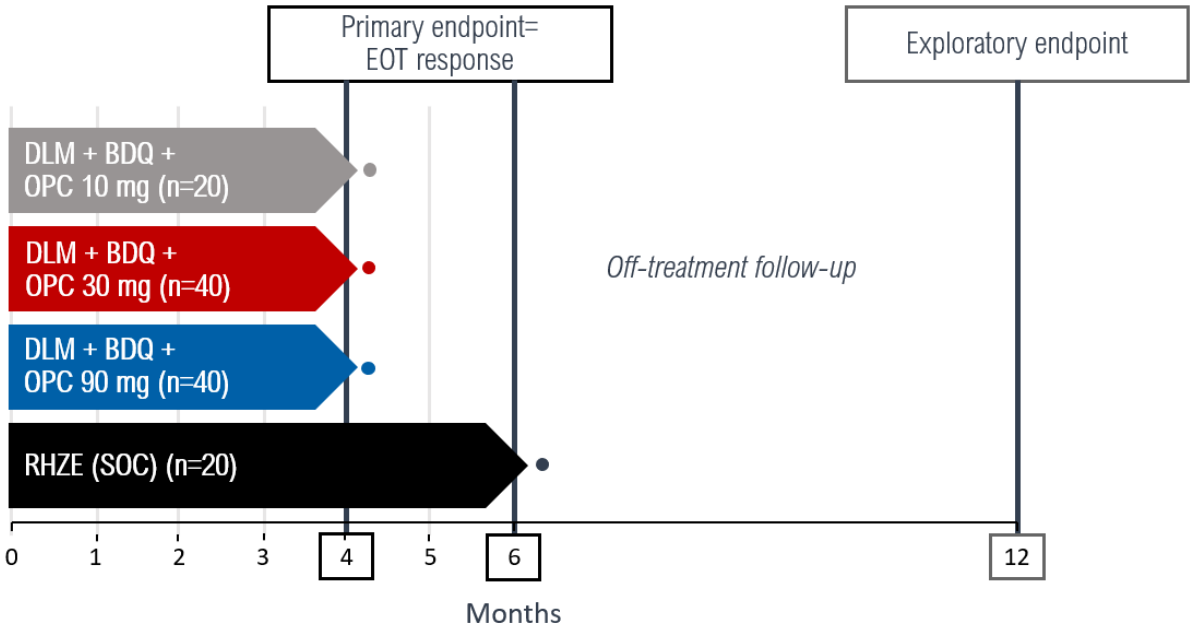
Dawson R, Diacon AH, Narunsky K, *et al*. Phase I Single Ascending Dose and Food Effect Study in Healthy Adults and Phase I/IIa Multiple Ascending Dose Study in Patients with Pulmonary Tuberculosis to Assess Pharmacokinetics, Bactericidal Activity, Tolerability, and Safety of OPC-167832. *Antimicrob Agents Chemother*. 2023;67(6):e0147722. doi: 10.1128/aac.01477-22. Epub 2023 May 23.

ONP-COP-2300002, Date of preparation: November 2023

Trial 323-201-00006: Phase 2b/c Study

A Multi-center, Phase 2b/c, Randomized, Dose-finding Trial to Evaluate the Safety and Efficacy of a 4-month Regimen of OPC-167832 in Combination with Delamanid (DLM) and Bedaquiline (BDQ) in Participants with Drug-susceptible Pulmonary Tuberculosis in Comparison with Standard Treatment (ClinicalTrials.gov Identifier: NCT05221502)

- To assess the safety and efficacy of OPC-167832 combined with DLM and BDQ in participants with DS-TB administered for 4 months compared to RHEZ administered for 6 months
- Ongoing trial at 7 sites in South Africa
- Randomization stratified by HIV status and presence of bilateral cavitation on screening CXR
- At the end of the treatment period, participants are followed until 12 months post-randomization
- Enrolment is complete (n=122), and all participants have completed the 4- and 6-month treatment
- Interim analysis expected early 2024



Looking into the Future

OPC-167832 as part of TB treatment regimens

- Regimens containing OPC-167832 with new or repurposed anti-TB drugs demonstrated better efficacy than current SoC regimen RHEZ in animal models
- This also included relapse prevention rates where OPC-167832 was a core drug of a regimen, suggesting its potential to contribute to treatment shortening.

Pan-TB Collaboration Trial

- OPC-167832 is included in the two-staged (Phase 2b/c), randomized duration-response efficacy and safety evaluation of two to four months of treatment with the combination regimens of DBQS and PBQS in adults with pulmonary TB (ClinicalTrials.gov Identifier: NCT05971602).

References:

Hariguchi N, Chen X, Hayashi Y, *et al*. OPC-167832, a Novel Carbostyril Derivative with Potent Antituberculosis Activity as a DprE1 Inhibitor. *Antimicrob Agents Chemother*. 2020 May 21;64(6):e02020-19. doi: 10.1128/AAC.02020-19. Print 2020 May 21.

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Otsuka remains committed to TB patients